Learning objectives

• Identify which treatment sites benefit from proton therapy.

• Delineate the difference between proton and photon therapy dose distributions between different treatment sites.

• Describe considerations when determining if a patient is an eligible candidate for proton therapy, or when photon therapy may be a safer option.

• Discuss the cost/benefit analysis done by payers.
State of the Union

25 proton centers in operation in the United States, with 12 under construction

http://www.proton-therapy.org/map.htm
NIH-Sponsored Clinical Trials

- Cholangiocarcinoma: NRG - GI001
- Hepatocellular: RTOG 1112
NIH-Sponsored Clinical Trials

- Brain: NRG BN001 (GBM), NRG BN005 (low-grade glioma), NRG BN003 (atypical meningioma)

- Prostate: PARTIQOL

- Pediatrics: COG

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**ClinicalTrials.gov Identifier: NCT01617161**

- **11-497 Proton Therapy vs. IMRT for Low or Intermediate Risk Prostate Cancer (PARTIQoL):** In this research study, we are comparing IMRT to proton beam therapy to determine which therapy best minimizes the side effects of treatment for men being treated for prostate cancer.

**Table:**

<table>
<thead>
<tr>
<th>Description</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Risk Medulloblastoma</td>
<td>ACNS0331</td>
</tr>
<tr>
<td>High-Risk Medulloblastoma or SPNET</td>
<td>ACNS0332</td>
</tr>
<tr>
<td>Phase III Randomized Trial of Post-Radiation Chemo</td>
<td>ACNS0831</td>
</tr>
<tr>
<td>CNS Germ Cell Tumors</td>
<td>ACNS1123</td>
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<tr>
<td>Non-Metastatic Extracranial Ewing Sarcoma</td>
<td>AEWS1031</td>
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<tr>
<td>Metastatic Ewings Sarcoma</td>
<td>AEWS1221</td>
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<tr>
<td>High-Risk Neuroblastoma</td>
<td>ANBL09P1</td>
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<tr>
<td>Non-Rhabdomyosarcoma Soft Tissue Sarcoma study</td>
<td>ARST1321</td>
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<tr>
<td>High Risk Rhabdomyosarcoma</td>
<td>ARST08P1</td>
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<tr>
<td>Medulloblastoma</td>
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<td>Ependymoma</td>
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<td>CNS</td>
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<tr>
<td>Ewing Sarcoma</td>
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<tr>
<td>All</td>
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<tr>
<td>All</td>
<td></td>
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<tr>
<td>Trunk/Extremities</td>
<td></td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td></td>
</tr>
</tbody>
</table>

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0 Gy RBE 18-21 Gy RBE
NIH-Sponsored Clinical Trials

- NCTO2603341 Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients With Non-Metastatic Breast Cancer: A Radiotherapy Comparative Effectiveness (RADCOMP) Consortium Trial: A pragmatic randomized clinical trial of patients with locally advanced breast cancer randomized to either proton or photon therapy and followed longitudinally for cardiovascular morbidity and mortality, health-related quality of life and cancer control outcomes. Quality of life is the outcome measure for the estimated primary completion date of November, 2020.

- RTOG 13O8 Comparing Photon Therapy To Proton Therapy To Treat Patients With Lung Cancer: This randomized phase III trial studies proton chemoradiotherapy to see how well it works compared to photon chemoradiotherapy in treating patients with stage II-III non-small cell lung cancer that cannot be removed by surgery. ClinicalTrials.gov Identifier: NCTO1993810
Institution-sponsored clinical trials

- Pediatrics: PPCR
  - PPCR 12-1O3 PPCR-Registry for Pedi Patients Treated With Proton RT: The goal of the Pediatric Proton Consortium Registry (PPCR) is to enroll children treated with proton radiation in the United States in order to describe the population that currently receives protons and better evaluate its benefits over other therapies. The data collected from this study will help facilitate research on proton beam radiation therapy and allow for collaborative research.
  - ClinicalTrials.gov Identifier: NCT01696721

- PCG: Prostate, Breast, and Lung

- Ovarian preservation for lumbosacral tumors– coming soon!

0 Gy\textsubscript{RBE} 50.4 Gy\textsubscript{RBE}
Institution-sponsored clinical trials

• Oropharyngeal: New Trial from MD Anderson


Clinical Investigation

Intensity Modulated Proton Therapy Versus Intensity Modulated Photon Radiation Therapy for Oropharyngeal Cancer: First Comparative Results of Patient-Reported Outcomes

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C. David Fuller, MD, PhD, * Tito R. Mendoza, PhD, ‡ Radhe Mohan, PhD, * Xin Shelley Wang, MD, MPH, ‡ and Steven J. Frank, MD *

Departments of *Radiation Oncology, †Symptom Research, and §Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas; and ‡Department of Radiation Oncology, Mayo Clinic, Scottsdale, Arizona

*Image from SCCA Proton Therapy home page
Evolution of new technologies into the healthcare landscape
Evolution of the introduction of Proton Therapy to different disease types

• The development of hospital-based systems starting in 1990 reached more disease sites, provided multi-institutional database development, and the development of clinical trial protocols

• These centers were capable of conducting comparative effectiveness studies, but there did not exist at that time the same level of scrutiny that new technologies face today

• Study methods need to be tailored to each disease site, and randomized controlled trials may not be appropriate for every diagnosis
## Evolution of New Technology

### A comparison between the introduction of Gamma Knife and Proton Therapy

<table>
<thead>
<tr>
<th><strong>Gamma Knife</strong></th>
<th><strong>Proton Therapy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st patient treated in 1968</strong></td>
<td><strong>1st patient treated in 1955</strong></td>
</tr>
<tr>
<td><strong>Cautious introduction with treatment of brain metastasis</strong></td>
<td><strong>Cautious introduction with treatment of ocular tumors, pediatric patients, and clival tumors</strong></td>
</tr>
<tr>
<td><strong>Innovation into benign tumors (acoustics, meningiomas, pituitary adenomas), benign diseases (AVMs, trigeminal neuralgia)</strong></td>
<td><strong>Innovation into prostate Ca, CNS tumors (low-grade glioma, ependymoma), lung cancer, pancreatic cancer, nasopharyngeal</strong></td>
</tr>
<tr>
<td><strong>Emerging research: Treat &gt;10 brain mets, Parkinsonian tremor, GBMs</strong></td>
<td><strong>Emerging research: Breast cancer, oropharyngeal cancer, anal cancer</strong></td>
</tr>
</tbody>
</table>

Introduction of Pencil Beam Scanning PT

Broadened the landscape of what can be treated with protons

Key advantages of PBS*: conformality, homogeneity, planning with robustness

Specific Anatomical Sites treated with Proton Therapy and Photon Therapy
Historically Recognized Disease Sites Treated with Protons

- Pediatric tumors of the CNS or elsewhere
- Brain tumors
- Spinal cord tumors
- Base of skull chordomas or chondrosarcomas
- Prostate cancer
- Ocular melanomas

PBS planning allows the possibility to treat additional disease sites that were once too cumbersome to deliver optimally with traditional proton technology.
Additional Disease Sites Commonly Treated with Protons Present Day

- Lung cancer
- Pancreatic cancer
- Esophageal cancer
- Nasopharyngeal cancer
- Breast cancer
- Sites that have previously been irradiated
Disease Sites Historically Treated with Photons, that generally are not treated with Protons

- Wilms Tumor
- Bilateral eyes for Graves disease
- Prophylactic Whole Brain RT for Leukemia patients

*For pediatrics cases such as Wilms tumor, IMRT treats too much of the contralateral side of the body unnecessarily, and for those patients 3D photon plans are preferred.*

*Ermoian May 2017 AAMD Webinar*
Disease Sites Historically Treated with Photons, that generally are not treated with Protons

- Skin cancer
- Keloids
- GYN Pelvic Tumors
- Most Palliative Sites

Differences in Dose Distributions between Protons and Photons
Why Use Protons?

Spread Out Bragg Peak (SOBP)

- **Advantages:**
  - Sparing integral dose to surrounding normal tissue structures
Protons vs Photons – Depth Dose Curves

- Protons have a finite range and controllable penetration in tissue
Protons vs Photons – the penumbra reality

Hemangioendothelioma Spinal Tumor

0 Gy RBE - 50.4 Gy RBE

Proton
Photon

Solid Line = Photons
Dashed Line = Protons

Solid Line = Photons
Dashed Line = Protons

CTV

Spinal Cord
Heart
Lungs
Esophagus

Graph showing dosimetry with different radiation types for Hemangioendothelioma Spinal Tumor.
Sinonasal Adenocarcinoma

0 Gy RBE

Proton

Photon

Solid Line = Photons

Dashed Line = Protons

Brainstem

L Retina

L Optic Nerve

R Lens

R Parotid

Brainstem

L Parotid

R Retina

R Optic Nerve

Brainstem

Retina
Adenocarcinoma of the Lung, previous MI

0 Gy\textsubscript{RBE} - 60.0 Gy\textsubscript{RBE}

Proton

Photon

Solid Line = Photons
Dashed Line = Protons

CTV
Lungs
Spinal Cord
Esophagus
Heart
Intermediate Risk Prostate

0 Gy RBE to 70.0 Gy RBE

Proton vs. Photon treatment plans:
- Solid Line = Photons
- Dashed Line = Protons

Anatomical regions:
- Rectum
- Sigmoid
- Bladder
- Penile Bulb

CTV (Clinical Target Volume) coverage analysis:
- Graph showing dose distribution across different structures.
Post Prostatectomy

0 Gy$_{\text{RBE}}$ - 70.2 Gy$_{\text{RBE}}$

Proton

Photon

Solid Line = Photons
Dashed Line = Protons

PTV

Rectum

Bladder

L Femur

R Femur
Retreat Squamous Carcinoma of the Tonsils

0 Gy\textsubscript{RBE} to 70.0 Gy\textsubscript{RBE}

Proton

Photon

Solid Line = Photons
Dashed Line = Protons

PTV 7000
PTV 6000

R Optic Nerve
L Optic Nerve
Brain
Optic Chiasm
L Parotid
L Cochlea
R Optic Nerve
Mediastinal Liposarcoma

0 Gy RBE

60.0 Gy RBE

Proton

Photon

PTV

Solid Line = Photons

Dashed Line = Protons

Heart

Esophagus

L Lung

R Lung

Spinal Cord
Locally Advanced Comprehensive Nodal Breast

0 Gy$_{\text{RBE}}$ to 50.4 Gy$_{\text{RBE}}$

Proton

Photon

Solid Line = Photons
Dashed Line = Protons

CTV
L Lung
Heart
Distal Esophagus

0 Gy RBE

Proton

Photon

Solid Line = Photons

Dashed Line = Protons

PTV 4500

PTV 5040

Heart Lungs-PTV
Cholangiocarcinoma

Proton

Photon

0 Gy RBE 45.0 Gy RBE

Solid Line = Photons
Dashed Line = Protons

PTV

Spinal Cord
Liver
R Kidney
L Kidney
Considerations when determining if a patient is eligible for Proton Therapy
Are there high Z materials in the treatment area?

• Tumors surrounded by significant metal can be problematic
Is there significant motion in the target area?

- Generally, target areas with more than 5 mm of breathing motion are not recommended to be treated with PBS proton therapy.

- For Uniform Scanning, it is recommended to not have more than 1 cm of breathing motion.
Challenges with Proton Therapy

- Less forgiving than photons for changes in tissue densities
  - Bone/Mucosa/Air interfaces
  - Fluid/Mucus changes
  - Weight changes

- Energy, or range, in tissue is strongly influenced by tissue heterogeneities
When would Photon Therapy be a safer option?

• Depends on location and size of tumor

• Depends on performance status of patient and therapeutic intent
Graves disease – Benign condition

Proton arrangement not feasible due to distal ends being too close
Concerns with higher RBE on Distal End

- Proton RBE generally thought to be between 1.1-1.4
- Requires careful beam selection to avoid overlap at the distal end
- Despite best efforts to mitigate this, a small percentage of CNS proton patients have developed radiation necrosis
Cost Benefit Analysis
What is Required for Insurance Company Approval?

• Up to Financial Counselors to learn all the major payers' company policies:
  − BCBS, Humana, Cigna, United Health Care, etc.
  − All companies have different exclusions

• Having previous treatment helps with getting approval

• Medicare covers most indications for protons, but varies by region
  − There is no national Medicare policy

  − Evicore is a third party reviewer that many insurance companies use to review patient cases to determine eligibility for proton therapy

Here is an example from Evicore's criteria

Proton Beam Radiation Therapy

POLICY
Proton Beam Therapy (PBT) is medically necessary for the treatment of the following tumors:

I. Chordomas and chondrosarcomas of the base of the skull, localized and in the postoperative setting

II. Uveal melanoma, when PBT is considered preferential compared to brachytherapy

III. Localized unresectable hepatocellular carcinoma, when considered preferential to Stereotactic Body Radiation Therapy (SBRT) or radiofrequency ablation

IV. Stage II A seminoma

Prostate Cancer

I. For prostate cancer where no prostatectomy was performed, PBT is not medically necessary

II. For adjuvant or salvage treatment of prostate cancer where prostatectomy was performed, PBT is experimental, investigational, and/or unproven (EIU)
What is Required for Insurance Company Approval?

• When a patient is determined as qualified for a proton consult, then financial benefits are reviewed

• Pre Consult: *Passport* - software that checks patient insurance eligibility, out-of-pocket expense, deductible

  – Financial approval is sought prior to initiating the TPCT to prevent unnecessary imaging

  - Prior authorizations are sometimes needed for additional diagnostic imaging needed for planning, but not planning CTs. (Except HMOs)
What is Required for Insurance Company Approval?

• Time of Consult: Finance initiates a letter of Medical Necessity for MD to submit to insurance
• Patient is medically approved during an in-house review
• Financial Counselor will call the insurance company or Evicore regarding need for prior authorization or pre-determination approval
  • Pre-D: does the patient meet criteria for protons per policy
  • This ‘approval’ can take 3-15 days, average is 10
• Insurance/Evicore will notify if Peer to Peer meeting is needed
What is Required for Insurance Company Approval?

- If the patient is denied, then a Peer to Peer is initiated, which is usually an MD to MD discussion about the request for proton therapy.
- Proton vs Photon planning comparisons may be needed if there is a denial.
With more proton centers opening, is insurance approval getting better or worse?

• Getting worse before getting better

• Payer policies becoming more restrictive

• Insurance companies may be underestimating and/or undervaluing the cost of side effects and toxicities.
Overall Cost decrease with Protons, due to decrease in long term side effects

“Reducing fatalities, improving patient post-treatment quality of life, and diminishing the frequency of side effects, are all breakthroughs that would justify the expense of proton therapy, and the continued advancements promoting affordability and accessibility. Defining those benefits is an intrinsic part of the scientific process, and an essential step in the responsible adoption of the treatment. With every completed study and every randomized trial, physicians and patients alike become better equipped to weigh the benefits of proton therapy against the cost.”

Insurance companies need data! Proton centers need to deliver

• This is what we’re up against:

In addition to the excellent American Society for Radiation Oncology (ASTRO) evidence-based review of PBT, there are other systematic reviews of PBT which also conclude that rationale for PBT is often associated with a low level of evidence according to standard heath technology assessment and evidence-based medicine criteria (Brada et al., 2007; Olsen et al., 2007).

− from the Evicore Policy

• Problem is that randomized, controlled trials are not the solution for all case types, nor are educated patients always willing to participate
Why not Randomized Controlled Trials for all sites?

- Cost
- Ethics
- Long term follow-up
Conclusions

• Both protons and photons have their place in the world of radiation oncology

• The use of protons continues to grow for a variety of disease types, thanks to advanced PBS technology

• Which modality is better is largely dependent on the tumor type, size, stage, location, and intent
Conclusions

• Adoption of new technologies has evolved over time and payers demand more evidence now than before

• Patients are more educated about options more than ever before
Conclusion

Now that you know more based on these disease site comparisons, which would you choose???
Acknowledgements

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