Toward Intensity Modulated Treatment on the University of Washington Clinical Neutron Therapy System

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Disclosures

- This presentation does not constitute an endorsement of any product (for your neutron planning needs or otherwise).

- No funding sources or conflicts of interest to disclose.
Learner Outcomes

- Familiarity with the historical use and current indications for treatment with neutron therapy.
- Understand the design and function of the University of Washington Clinical Neutron Therapy System (CNTS).
- Awareness of different beam modeling approaches for the CNTS neutron beam.

CNTS History at University of Washington

- 1973-1984
  - Laboratory based neutron beam
  - 22 MeV deuterons incident on a beryllium target
  - Fixed horizontal beam
  - Magnetic rectangular collimation
  - No wedges
  - Resulting beam depth dose characteristics similar to Co-60
  - 604 Patient Treated
CNTS History at University of Washington

- **1979**
  - Installation of dedicated hospital based neutron treatment system begins as part of NIH grant.
  - Gantry with full range of rotational motion, collimator and built in wedges, flattening filter, MLCs.

- **1984**
  - October 19th: first patient treatment
  - >3000 patients treated since

Radiation Biology

- Neutrons are indirectly ionizing, and damage DNA through the secondary particles they produce.
  - Mostly low-energy, high-LET protons as well as some heavier ions.
  - Compare to photons/protons which primarily generate electrons.
- This affords neutrons unique radiobiological advantages.
  - Can overcome radiation resistance of hypoxic cells.
  - Dense ionization results in more fatal cellular damage per dose.
- Neutron RBE ~ 3-4 (compared to MV photon treatments)
  - Varies for different tissues and for fraction size.
- Useful for treatment of refractory tumors.
  - Sarcoma, salivary gland tumors, mucosal melanomas
Clinical Uses

Prospective randomized trials comparing photons vs neutrons for unresectable parotid gland tumors.

- 32 patients enrolled.
- Neutrons exhibit superior local control (56% vs 17%, p=0.009)
- No statistical difference in overall survival.


Clinical Uses

- 72 high-risk sarcoma patients treated with neutrons alone (73%) or a combination of neutrons and photons (27%) either curatively or palliatively.
- Curative group at 4 years
  - 68% local relapse free survival
  - 66% overall survival
- Palliative group at 1 year
  - 62% local relapse free survival
  - 78% effective clinical response

Case report for patient treated for merkel cell carcinoma.
- Extensive prior treatment including surgery, radiation, and systemic therapy.


Total radiotherapy dose (EQD2) prior to neutron treatment:
- 73.6 Gy to entire scalp
- 91.2 Gy to frontal scalp lesion
- 52 Gy to left/neck parotid

Clinical Uses

- Patient received ~18 neutron-Gray (nGy).
  - Scalp: 18 nGy in 12 fractions.
  - Parotids/cervical lymph nodes: 18 nGy in 10 fractions.
  - Smaller isolated scalp lesions: 16 nGy in 8 fractions.
- Complete clinical and radiologic response.
- No serious complications.
  - Mild telangiectasia
  - Moderate xerostomia
  - Decreased hearing on one side
- Disease is still controlled two years later.
  - Small out of field recurrences responded to immunotherapy.


Clinical Uses – Immune Response Trigger?

- Case report for patient treated for merkel cell carcinoma.
  - Patient with progressive merkel cell carcinoma with multiple tumors on the face
  - Surgery and two rounds of palliative radiation
  - Progressed through immunotherapy treatment
  - Most symptomatic lesions (circled in red) were treated with 6 Gy in 2 fractions separated by a week
  - Complete clinical resolution of treated lesions and out of field lesions (circled in blue) in two weeks
  - Serology suggests enhanced immune response
  - No clinical/radiologic evidence of disease 7 months later, patient remains on immunotherapy

Neutron Physics

- Neutrons are uncharged particles
- Interact through collisions with nuclei
  - Scatter off nuclei
    - Elastic/inelastic
      - Conservation of momentum means energy is transferred most efficiently to nuclei with similar mass. (e.g. Hydrogen)
  - Absorption by Nuclei
    - Gamma ray emission
    - Secondary neutron emission
    - Charged particle emission (Proton, Alpha Particle, etc.)


Neutron Physics – Production (CNTS)

- Proton beam incident on beryllium target
  - Most neutrons generated by (p,n) and (p,n+p) reactions.
    - 2 MeV Threshold for (p,n)
  - Some generated by (p,2n), (p,3n), (p,n+α).
  - Approximately 1 fast neutron generated for every 20 incident protons.
    - Only ~1/4 of these are traveling in the direction of the beam shaping collimation.
  - Maximum Neutron Energy – 50.5 MeV
  - Average Neutron Energy – 10-30 MeV (field size dependent)

Neutron Physics – Dosimetry (CNTS)

- Dose is primarily due to low energy protons
  - Absorption – \((n,p)\)
- 2%-10% of dose is from photons.
  - Bremsstrahlung of protons
  - Radiative absorption of neutrons
  - Photon component increases with depth and field size.


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Neutron Physics – Dosimetry (CNTS)

- Dose deposition depends on material in a very different way than photons.

<table>
<thead>
<tr>
<th>Material</th>
<th>Density (g cm(^{-3}))</th>
<th>Simulated output factor (x5 MU (^{-1}))</th>
<th>Percent difference from water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>1</td>
<td>0.984</td>
<td>0.00%</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>0.92</td>
<td>1</td>
<td>1.60%</td>
</tr>
<tr>
<td>Muscle</td>
<td>1.04</td>
<td>0.87</td>
<td>-11.60%</td>
</tr>
<tr>
<td>Bone</td>
<td>1.85</td>
<td>0.590</td>
<td>-39.10%</td>
</tr>
<tr>
<td>Solid water</td>
<td>1.039</td>
<td>0.940</td>
<td>-4.10%</td>
</tr>
<tr>
<td>Plastic water</td>
<td>1.039</td>
<td>1.325</td>
<td>55.00%</td>
</tr>
<tr>
<td>PMMA</td>
<td>1.19</td>
<td>0.908</td>
<td>-7.70%</td>
</tr>
<tr>
<td>Air</td>
<td>0.001 235</td>
<td>0.873</td>
<td>-11.50%</td>
</tr>
<tr>
<td>Water</td>
<td>0.92</td>
<td>0.937</td>
<td>-0.70%</td>
</tr>
<tr>
<td>Water</td>
<td>1.64</td>
<td>0.890</td>
<td>0.50%</td>
</tr>
<tr>
<td>Water</td>
<td>1.85</td>
<td>0.987</td>
<td>0.50%</td>
</tr>
</tbody>
</table>

CNTS Treatment Unit

- 50.5 MeV proton beam incident on a beryllium target.
  - Generated by a cyclotron.
- Primary collimation made of iron.
- Small/large flattening filter made of steel.
- Internal wedges
  - 30/45/60 degrees
  - Rotate independent of the collimator to each of the 4 cardinal angles
- Lead/polyethylene head shielding
- Dose rate of 60 MU/minute


Figure courtesy of Juergen Meyer.

CNTS vs Elekta Linac Profile Flatness at Dmax

Figure courtesy of Rob Stewart.
**CNTS Treatment Unit – Wedges**

28.8 x 28.8 cm² Wedged Profiles

**CNTS Treatment Unit – MLCs**

- Some of the first MLCs installed on a clinical treatment unit.
- 40 MLCs (20 per bank) of varying widths: 1.25 cm – 2 cm at isocenter.
- ~65 cm thick.
- Composed of iron with polyethylene inserts to scatter neutrons out of field.
- Double focused to match beam divergence across entire range of motion.
- Interdigitating, travel 3.5 cm past midline.
- Largest field size is 32.8 x 28.8 cm².
- 10x10 field is not possible due to leaf thicknesses, so reference field is 10.3x10.3 cm.
CNTS Treatment Unit – MLCs

2 cm Thickness

1.25 cm Thickness

1.4 cm Thickness

Maximum Overtravel

Maximum Retraction

Distances at isocentric plane.

Figure based on modification of Figure 1 in Moffitt et al. 2018.

CNTS Treatment Unit – MLCs

CNTS MLC vs Elekta Agility MLC (Approximately to Scale)

Figure based on modification of Figure 1 in Moffitt et al. 2018.
CNTS Treatment Unit - Gantry and Couch

- 150 cm SAD
- 360 degree gantry range
  - Floor opens to accommodate gantry head
- ~180+ degree collimator range.
  - Independent internal wedge rotation allows any wedge orientation.
- ‘Tennis-racket’ style couch.

CNTS Treatment Unit - Peripherals

- Minimal electronics in room
  - Neutrons are particularly destructive to electronics
- 4 treatment days/week
- Hydraulic treatment door
  - ~2.4m (8 feet) thick
  - 80 metric tons
Treatment Planning - Prism

- In-house software developed by Ira Kalet.
- Dose computation based on corrections to measured data in water phantom.

\[ D = C \cdot T \cdot C(w_c) \cdot \left( \frac{E}{P + m} \right)^2 \cdot D_b(x_c, y_c, z_c, d, w_d) \cdot I(x, y, z, x_s, y_s, z_s, A) \cdot W(x_w, d, w_e) \]  

- Well suited to neutrons.
  - Corrections for photon fields apply reasonably well to neutron fields.
  - No underlying assumptions about treatment machine.


Treatment Planning - Pinnacle

- CNTS planning was transitioned to Pinnacle along with photons.
- Pinnacle is **Model Based**
  - Models of the source and treatment head components are used to determine the intensity of radiation reaching the patient.
  - The patient dose due to incident radiation is determined using Monte Carlo simulated dose-deposition kernels.
  - Model parameters are tweaked to match calculated beams to measured data.

Treatment Planning - Pinnacle

- CNTS modeled with photon kernels
  - No neutron kernels available
  - Neutron dosimetry is similar to photon dosimetry.
- PDDs for all field sizes could not be modeled accurately
  - Broke CNTS into two models, one for small fields and one for large fields.
- Neutrons scatter significantly more than photons
  - Output factors could not be reproduced well with photon kernels
  - Pinnacle script to generate a uniform thickness compensator to correct the output factor is used as a workaround.
- Neutron dosimetry depends more on atomic composition and not electron density like photons
  - Override all tissue to water of a few different densities.

Monte Carlo Modeling

- Considerable effort invested in generating a Monte Carlo model of the CNTS system by Moffitt et al.
  - Monte Carlo is the gold standard for dose calculation.
    - Follow individual particle paths through treatment unit and patient and record dose from each interaction
    - Repeat billions of times
  - Can model treatment unit to desired level of detail.
  - Allows accurate accounting for heterogeneity and elemental composition.
    - Unlike megavoltage photons which are largely insensitive to parameters other than electron density, neutron dosimetry is greatly affected by elemental composition.
  - Independent check of TPS dose calculations.
  - Accurate dose estimation out of field

Monte Carlo Modeling

Target and Collimation Model Geometry

Measured vs Simulated Dose Profiles
Left: Open field, 28.8x28.8, 10.3x10.3, and 2.8x2.8 at Dmax
Right: 60 Degree Wedge, 28.8x28.8 and 10.3x10.3 at Dmax

RayStation Neutron Beam Modeling

- Initiated effort to commission neutron beam in RayStation
  - Photon treatment planning transitioning to RayStation
    - One treatment planning platform
  - Recent Pinnacle versions do not support extended SAD.
    - Neutrons -> planned with 9.0
    - Photons -> planned with most recent version (currently 9.10)
  - Multiple work arounds required for forward planning
    - Compensator to fix output factor
    - Multiple models depending on field size
  - Inverse optimization not possible in Pinnacle
    - Field specific compensator required for correct output factor.
    - CNTS violates Pinnacle machine logic
      - Fixed jaws can’t cover closed MLC pairs
- Goals
  - Reproduce or exceed current planning capabilities
  - Enable inverse planning (i.e. Intensity Modulated Neutron Therapy - IMNT)
RayStation Neutron Beam Modeling

- Machine Modeling
  - Initially used an Elekta Beam Modulator as a base machine.
    - Fixed jaws and MLC only collimation.
    - However, MLCs are able to cross entire field and reside beneath jaws when not used.
    - CNTS violates this machine logic.
  - Switched to an Elekta Agility as base machine.
    - MLCs replace jaws in one direction, jaws still present in other direction.
    - For commissioning, measurements may be indicated as ‘MLC only’.
    - For planning, jaws may be locked in place (at fixed jaw position for CNTS).
    - Machine logic is not violated, inverse planning is functional.
    - Other unique parameters (150 cm SAD, variable leaf width, etc.) did not pose problem.

RayStation – Modeling with Photon Kernels

Model targeting all field sizes
RayStation – Modeling with Photon Kernels

Model targeting all field sizes

Unable to reproduce PDDs

RayStation – Modeling with Photon Kernels

Model targeting small fields only (≤ 12.8x12.8)

Measured
Model – Small Fields
Model – All Fields
RayStation – Modeling with Photon Kernels

Model targeting large fields only (≥ 10.3x10.3)

Model targeting 2.8x2.8 Only
RayStation – Modeling with Photon Kernels

Model targeting 10.3x10.3 Only

Model targeting 28.8x28.8 Only
RayStation – Modeling with Photon Kernels

- Photon-kernel based model of CNTS not feasible.
  - Require more than 2 submodels for open fields alone.
    - With three wedge angles, more than 8 models required
    - Difficult for forward planning, very problematic for inverse planning.
  - Shallow depth dose not reproducible for even single field sizes.

- Alternatives
  - Direct incorporation of Monte Carlo?
    - Time consuming
    - From dose-to-water to dose-to-tissue
  - Neutron Based Kernels?
    - Fast calculation
    - Better capture neutron scatter than photon kernels
    - Neutron specific energy bins

Neutron Kernel Generation

- Kernels capture dose distribution resulting from interactions at a point
- Two sets of kernels required
  - Cylindrical for SVD Calculation
    - Pencil Beam
    - Simplified Collimation Modeling
    - Very fast approximate dose computation for inverse planning.
  - Spherical for CC Calculation
    - Collapsed Cone Convolution Superposition
    - More accurate but slower than SVD
Neutron Kernel Generation

- Kernel Generation
  - Monte Carlo to simulate:
    - Cylindrical dose distribution due to neutrons interacting at top of water column.
    - Spherical dose distribution due to neutrons interacting at a point in water.
  - Procedure Validation
    - Generated selected photon kernels first for comparison to existing kernels
  - Energy Bins
    - Generated 105 monoenergetic neutron kernels.
      - 1 keV
      - 10 keV
      - 100 keV
      - 0.5 Mev to 51.0 MeV in 0.5 MeV increments

Neutron Kernel Validation

- Neutron Kernel Validation
  - Compared monoenergetic dose calculations for open fields.

Embedding of images showing dose distribution and energy bins for 0.001 MeV, 20 MeV, and 45 MeV kernels.
Neutron Kernel Validation

- SVD vs CC for full spectrum.
  - PDD agrees to within 5%.
  - CC is generally hotter than SVD outside of shallow-depths in-field.

Neutron Kernel Validation

- Neutron Kernel Validation – SVD vs CC for complicated plans.
  - TG-119 ‘C-Shape’ Target
  - 90 Segments
  - Inverse Planning
  - Note: This is a far more intricate plan than would be delivered on the CNTS for practical reasons (e.g. time to deliver all 90 segments.
  - Reasonable agreement suggests inverse planning is feasible with generated kernels.
Beam Modeling – Depth Dose

Beam Modeling – Large Field Profile
Beam Modeling – Spectrum and Profile Corrections

- Low energy component is essential for shallow depth agreement.
- Arbitrary profile correction and off-axis softening allow matching of unique profile.

Beam Modeling – Output Factor Corrections

- Modeled and measured output factors agree reasonably well for large field sizes.
  - < 2% Correction
- Output factor corrections important for small field sizes.
  - Up to ~8% correction.
Conclusions

- Neutron treatment planning in RayStation appears highly feasible
  - Neutron specific kernels required
  - Some workarounds required to model machine geometry
    - Model has to have jaws, actual machine does not.
      - Jaws have to be locked to outer limits during planning.
  - One model for all field sizes
    - Straightforward planning
  - Wedge modeling (in progress) is promising
    - Match current planning capabilities
  - Small field agreement is good and inverse planning is functional
    - IMNT in some form is likely possible
      - Better target uniformity
      - Reduced dose to adjacent healthy tissue

Future Work

- Further refinement of beam models
- Beam model validation
- Hardware-software interface testing
- Determine beam model limits
  - What optimization constraints are necessary to remain within models limits?
    - Size and number of segments, number of MU, leaf separation, etc…
- IMNT QA tool development
  - Forward planned treatments are verified by a second MU calc and OSL measurements, not feasible for IMNT
Acknowledgements

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