Model-based clinical validation of proton therapy in head and neck cancer

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Why is this relevant?

• New delivery modality (proton therapy)
  • Unique physical characteristics → improved normal tissue sparing
  • Improved dosimetry = better outcomes?
  • Comparative, prospective data lacking

• Changing demographics/outcomes in HNC
  • Outcomes and long-term challenges are increasingly divergent/distinct
Challenges

• Proton therapy
  • Limited resource/access
  • Lack of level I evidence

• Prospective RCT
  • Challenges:
    • Time
    • Cost
    • Equipoise
    • Relevance (changing treatment paradigms)
Rationale

- Impact of PBT difficult to quantify in the absence of prospective, randomized data.

- A model-based approach may be an alternative method to quantify potential clinical gains, helping guide appropriate patient selection.

- The aim of this study was to generate and clinically validate a NTCP model for PBT for oropharynx cancer, and to compare results vs IMRT.
Left Submandibular: IMRT (40 Gy), PBS (33 Gy)
Left parotid: IMRT (18 Gy), PBS (9 Gy)
Oral cavity: IMRT (13.5 Gy), PBS (1.3 Gy)
Quality of Life of Postoperative Photon versus Proton Radiation Therapy for Oropharynx Cancer

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Abstract

Purpose: Quality of life (QOL) for patients with oropharyngeal squamous cell cancer is negatively affected by conventional radiation (RT) owing to radiation exposure to normal tissues. Proton therapy, via pencil beam scanning (PBS), can better spare many of these tissues, and may thereby improve QOL.

Patients and Methods: Patient-reported outcomes were prospectively collected from patients treated from April 2013 to April 2015. Patients were treated with PBS or intensity-modulated radiation therapy (IMRT) via volumetric arc therapy after transoral robotic surgery. Validated QOL questionnaires were collected before RT, and 3, 6, and 12 months post RT.

Results: Sixty-four patients were treated with adjuvant RT after transoral robotic surgery, 33 (52%) with volumetric arc therapy, and 31 (48%) with PBS. Both groups were similar in terms of age, site, stage, and dose delivered. Patients receiving PBS had significantly less dose to many normal structures than those receiving IMRT. These dosimetric advantages with PBS were reflected in higher scores in head and neck specific, as well as general, QOL measures. Most notable was significantly less xerostomia with PBS, on multiple patient-reported outcomes at multiple timepoints (6 and 12 months).

Conclusion: Pencil beam scanning, when compared to IMRT, confers a significant dosimetric advantage to many normal organs at risk, with a corresponding benefit in multiple patient-reported QOL parameters in patients receiving adjuvant RT for oropharyngeal squamous cell cancer.

Keywords: oropharyngeal cancer; quality of life; proton therapy; intensity-modulated radiation therapy
**Parotid**

![Bar chart showing mean dose comparison between Ipsilateral and Contralateral Parotid for VMAT and PBS techniques.](image)

**Submandibular**

![Bar chart showing mean dose comparison between Ipsilateral and Contralateral Submandibular for VMAT and PBS techniques.](image)
**Ipsilateral Buccal** (p<0.0001)

**Contralateral Buccal** (p<0.0001)

**VMAT**

<table>
<thead>
<tr>
<th></th>
<th>PBS</th>
<th>VMAT</th>
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<tbody>
<tr>
<td>Ipsilateral</td>
<td>10</td>
<td>27</td>
</tr>
<tr>
<td>Contralateral</td>
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**Sublingual**

**Buccal**

**PBS**

<table>
<thead>
<tr>
<th></th>
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<th>VMAT</th>
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<tbody>
<tr>
<td>Ipsilateral</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>Contralateral</td>
<td>2</td>
<td>44</td>
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</table>
Hard Palate (p<0.0001)
Soft Palate (p=0.0209)
Tongue (p<0.0001)
Upper Lip (p<0.0001)
Lower Lip (p<0.0001)

<table>
<thead>
<tr>
<th></th>
<th>VMAT</th>
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<tr>
<td>Hard Palate</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Soft Palate</td>
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<td>31</td>
</tr>
<tr>
<td>Tongue</td>
<td>41</td>
<td>26</td>
</tr>
<tr>
<td>Upper Lip</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Lower Lip</td>
<td>20</td>
<td>3</td>
</tr>
</tbody>
</table>

Mean Dose (Gy)
Moderate-Severe Xerostomia (p=0.002)

Mild-Severe Appetite Changes (p=0.015)

Mild-Severe Sticky Saliva (p=0.853)

Normal Taste (p=0.10)
Can we use these results to generate a predictive model?
Methods

• Advanced-stage oropharynx cancer treated with curative intent (PBT, n=30; IMRT, n=175). All patients had patient-reported and physician-reported toxicity at 3 and 6 mos.

• Multivariable NTCP models developed using multivariable logistic regression analysis with backward selection.

• The models were then applied to the PBT treated pts to compare predicted and observed clinical outcomes (calibration-in-the large).

• Five binary endpoints were analyzed at 6 months post-treatment: dysphagia ≥ grade 2, dysphagia ≥ grade 3, xerostomia ≥ grade 2, salivary duct inflammation ≥ grade 2, and feeding tube dependence.
Comparing PBT vs IMRT

• For each PBT treated pt, a treatment-approved IMRT plan was available for backup, in case of unplanned proton unavailability.
• Therefore, each patient receiving PBT served as an internal control for purposes of comparison.
Results

• The NTCP models developed based on outcomes from all pts were applied to those receiving PBT.

• For pts receiving PBT, no significant differences were observed between the expected and observed prevalences.

• In addition, the NTCP-values were calculated for the equivalent IMRT plans for all PBT treated pts, revealing significantly higher NTCP-values for the IMRT plans.

• PBT associated with statistically significant reductions in the mean NTCP values for each endpoint at 6 months post treatment, with the largest absolute differences in rates of ≥ grade 2 dysphagia and xerostomia
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Observed prevalence (%)</th>
<th>% NTCP (Protons)</th>
<th>%NTCP (Photons)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Dysphagia ≥grade 2</td>
<td>6.7</td>
<td>6.7</td>
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<td>&lt;0.001</td>
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<td>Dysphagia ≥grade 3</td>
<td>3.3</td>
<td>4.9</td>
<td>7.6</td>
<td>&lt;0.001</td>
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<tr>
<td>Xerostomia ≥Grade 2</td>
<td>0.0</td>
<td>10.0</td>
<td>19.0</td>
<td>&lt;0.001</td>
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<tr>
<td>Salivary duct inflammation ≥ grade 2</td>
<td>3.3</td>
<td>4.7</td>
<td>7.6</td>
<td>&lt;0.001</td>
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<tr>
<td>Feeding tube dependence</td>
<td>0.0</td>
<td>1.3</td>
<td>1.7</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Dysphagia ≥ Grade 2 at 6 months
NTCP XRAYs minus NTCP PROTONS

Δ NTCP

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
Xerostomia ≥ Grade 2 at 6 months
NTCP XRAYS minus NTCP PROTONS

Δ NTCP

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
Conclusions

• Model is accurate in predicting toxicity in pts receiving PBT for OPC, and allows for comparisons between treatment modalities for patients.

• Findings suggest significant gains in treatment-related toxicity (at 6 months) with PBT compared to IMRT.

• Demonstrates the value of NTCP model-based approaches in comparing predicted patient outcomes when randomized data are not available.
Oropharynx RCT (PI: Frank, MDACC)
Applications/Future Directions

• Model-based approach
  • More robust to potential future changes in treatment paradigms
    • HPV+: reduced dose, volume, omission of chemotherapy

• Can be used either by itself (where RCT is infeasible or unavailable)

• Can be used within a RCT
  • As part of patient selection
  • As a treatment biomarker
  • Opportunity for prospective validation of the model

• Can be applied as part of a ‘personalized’ approach to cancer therapy