PROTON PLAN EVALUATION: HOW TO ‘BRAGG’ ABOUT A PERFECT PLAN

Dr Sapna Nangia
## DOSE RESPONSE RELATIONSHIP

### Established
- Medulloblastoma
- Nasopharynx
- Head neck cancer – dose intensity of chemotherapy, acceleration of treatment
- Adding a boost for breast cancer
- Liver
- Cervix
- Prostate

### Controversial / Absent / Under investigation
- Lung
- Oesophagus
- Rectum
- Pancreas
## Influence of Late Side-Effects Upon Daily Life After Radiotherapy for Laryngeal and Pharyngeal Cancer

Anders B. Jensen, Olfred Hansen, Karsten Jørgensen & Lars Bastholt

### Pre IMRT era 1994, Odense

*All experienced side-effects during the treatment period, spontaneously mentioned by the patient. Number of patients with percentages in parentheses*

<table>
<thead>
<tr>
<th>Problem</th>
<th>Laryngeal cancer</th>
<th>Pharyngeal cancer</th>
<th>Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xerostomia</td>
<td>6 (22)</td>
<td>12 (75)</td>
<td>18 (42)</td>
</tr>
<tr>
<td>Tiredness</td>
<td>6 (22)</td>
<td>10 (63)</td>
<td>16 (37)</td>
</tr>
<tr>
<td>Taste change</td>
<td>2 (7)</td>
<td>12 (75)</td>
<td>14 (33)</td>
</tr>
<tr>
<td>Psychological problems</td>
<td>6 (22)</td>
<td>4 (25)</td>
<td>10 (24)</td>
</tr>
<tr>
<td>Pain</td>
<td>5 (19)</td>
<td>5 (31)</td>
<td>10 (23)</td>
</tr>
<tr>
<td>Skin problems</td>
<td>1 (4)</td>
<td>2 (13)</td>
<td>10 (23)</td>
</tr>
<tr>
<td>Weightloss</td>
<td>0</td>
<td>8 (50)</td>
<td>1 (19)</td>
</tr>
<tr>
<td>Voice problems</td>
<td>5 (19)</td>
<td>2 (13)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Loathing for food</td>
<td>1 (4)</td>
<td>1 (6)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Problems with swallowing</td>
<td>4 (15)</td>
<td>1 (6)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>3 (19)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Problems with teeth</td>
<td>1 (4)</td>
<td>2 (13)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Hearing</td>
<td>0</td>
<td>3 (7)</td>
<td></td>
</tr>
<tr>
<td>Problems with swallowing</td>
<td>1 (4)</td>
<td>2 (13)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>the trial medicine</td>
<td>1 (4)</td>
<td>2 (13)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Transport to hospital</td>
<td>2 (7)</td>
<td>2 (13)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Other**</td>
<td>6 (22)</td>
<td>8 (50)</td>
<td>14 (23)</td>
</tr>
</tbody>
</table>

### All late side-effects related to treatment at follow-up, spontaneously mentioned by the patients. Number of patients with percentages in parentheses

<table>
<thead>
<tr>
<th>Problem</th>
<th>Laryngeal cancer</th>
<th>Pharyngeal cancer</th>
<th>Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xerostomia</td>
<td>4 (15)</td>
<td>15 (94)</td>
<td>19 (44)</td>
</tr>
<tr>
<td>Voice</td>
<td>10 (37)</td>
<td>1 (6)</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Taste change</td>
<td>1 (4)</td>
<td>3 (19)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Teeth</td>
<td>0</td>
<td>4 (25)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Pain</td>
<td>2 (7)</td>
<td>1 (6)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Eating problems</td>
<td>3 (11)</td>
<td>0</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Others**</td>
<td>3 (11)</td>
<td>2 (13)</td>
<td>5 (12)</td>
</tr>
</tbody>
</table>

* p < 0.05 for the group with laryngeal cancer vs pharyngeal cancer.

** Psychological problems, balance, coughing, skin problems, hairloss
Dose to tumour impacts control rates
Dose to OARs impacts physical functioning, and symptoms, cognitive, social and role function, and global QOL.
Heart Dose Is an Independent Dosimetric Predictor of Overall Survival in Locally Advanced Non-Small Cell Lung Cancer

Christina K. Speirs, MD, PhD, Todd A. DeWees, PhD, Sana Rehman, MD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;15 y</td>
<td>13.58</td>
<td>0.041 (1.1–166.42)</td>
</tr>
<tr>
<td>13% temporal lobe receiving &gt;43.2 Gy (80% of the prescribed dose)</td>
<td>7.57</td>
<td>0.048 (1.02–56.16)</td>
</tr>
</tbody>
</table>

Fig. 1. Intelligence quotient (IQ) decline with respect to radiotherapy doses to left temporal lobe.

<23% left temporal lobe to receive 27 Gy
IMPACT OF DOSE TO OAR

Heart Dose Is an Independent Dosimetric Predictor of Overall Survival in Locally Advanced Non-Small Cell Lung Cancer

Christina K. Speirs, MD, PhD, a Todd A. DeWees, PhD, a Sana Rehman, MD, a

Journal of Thoracic Oncology Vol. 12 No. 2: 293-301

OS @ 1 yr 61%, @ 2 yrs 38%

OS @ 1 yr if V50 Gy < 25% - 70.2% vs 46.8% if V50 Gy > 25%
The Bragg peak

- Spread-out Bragg peak
- Depth
- LET
- Distal fall-off
- Tumour
DNA damage & repair,

NASOPHARYNGEAL CANCER

• 41 years/ Male,
• No co-morbidities, No addictions, No significant family history
• Decreased hearing in the right year since last 6 months, insidious in onset and gradually progressive.
• Heaviness in the right eye gradually progressing and hindering in movement of the eye and causing diplopia since last 2 months.
• History of occasional nasal bleeding

• MRI Brain (19.02.20) – Moderately enhancing altered signal intensity in the right cavernous sinus and meckel’s cave with infratemporal extension via foramen ovale / lacerum and into pteryo-palatine fossa, right parapharyngeal space and nasopharynx.
• Biopsy from the cavernous sinus lesion (27.02.20) - Nasopharyngeal carcinoma, Raygau pattern.
• PET CT scan (28.02.20) – FDG avid thickening in the posterior and right lateral wall of the nasopharynx effacing the fossa of rosenmuller with extension into the right medial pterygoid muscle.extension into the carotid canal and right cavernous sinus region encasing the intrapetrous and the intracavernosal segments of the right ICA. Prominent right retropharyngeal LN. enlarged bilateral cervical level II LN
• Visual Peripheral field analysis revealed constriction of vision on the right temporal side.
• Started on neoadjuvant chemotherapy (NACT) (TPF based), received 3 cycles LD 22.04.20
IMPT VS IMRT PLAN COMPARISON (HIGHER ISO-DOSE)
IMPT VS IMRT PLAN COMPARISON (LOWER ISO-DOSE)
## IMPT VS IMRT PLAN - DOSE STATISTICS

<table>
<thead>
<tr>
<th>OAR doses</th>
<th>IMPT dose in GyE</th>
<th>IMRT dose in Gy</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem (Dmax)</td>
<td>51.77</td>
<td>55.30</td>
<td>6.3 % decrease in dose</td>
</tr>
<tr>
<td>Temporal Lobe (Dmean)</td>
<td>9.23 (Left) 19.85 (Right)</td>
<td>15.68 (Left) 25.52 (Right)</td>
<td>41.1 % decrease in dose 22.2% decrease in dose</td>
</tr>
<tr>
<td>Hippocampus (Dmean)</td>
<td>3.20 (Left) 13.11 (Right)</td>
<td>8.45 (Left) 19.13 (Right)</td>
<td>62.1% decrease in dose 31.4% decrease in dose</td>
</tr>
<tr>
<td>Hippocampus (Dmax)</td>
<td>17.22 (Left) 48.75 (Right)</td>
<td>18.37 (Left) 55.71 (Right)</td>
<td>6.2% decrease in dose 12.4% decrease in dose</td>
</tr>
<tr>
<td>Eye (Dmean)</td>
<td>7.20 (Left) 6.85 (Right)</td>
<td>7.45 (Left) 6.67 (Right)</td>
<td>3.3% decrease in dose 2.6 % increase in dose</td>
</tr>
<tr>
<td>Optic nerve Rt (Dmax)</td>
<td>44.91</td>
<td>52.58</td>
<td>14.5 % decrease in dose</td>
</tr>
<tr>
<td>Optic Chaim (Dmax)</td>
<td>48.27</td>
<td>48.09</td>
<td>0.3 % increase in dose</td>
</tr>
</tbody>
</table>
### IMPT VS IMRT PLAN - DOSE STATISTICS

<table>
<thead>
<tr>
<th>OAR doses</th>
<th>IMPT (GyE)</th>
<th>IMRT (Gy)</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parotid (Dmean)</td>
<td>21.99 (Left)</td>
<td>30.67 (Left)</td>
<td>28.3 % decrease in dose</td>
</tr>
<tr>
<td></td>
<td>21.40 (Right)</td>
<td>31.45 (Right)</td>
<td>31.9 % decrease in dose</td>
</tr>
<tr>
<td>Oral cavity (Dmean)</td>
<td>33.14</td>
<td>47.15</td>
<td>29.7 % decrease in dose</td>
</tr>
<tr>
<td>Mandible (Dmean)</td>
<td>40.28</td>
<td>45.19</td>
<td>10.8 % decrease in dose</td>
</tr>
<tr>
<td>Larynx (Dmean)</td>
<td>27.73</td>
<td>43.89</td>
<td>36.8 % decrease in dose</td>
</tr>
<tr>
<td>Midline mucosa (Dmean)</td>
<td>35.23</td>
<td>46.24</td>
<td>23.8 % decrease in dose</td>
</tr>
<tr>
<td>Spinal Cord (Dmax)</td>
<td>23.36</td>
<td>37.56</td>
<td>37.8 % decrease in dose</td>
</tr>
</tbody>
</table>
PATIENT REPORTED OUTCOMES – BETTER IN OROPHARYNGEAL CANCER

• 39 years, Male complaints of foreign body sensation for 3 weeks and difficulty in swallowing & swelling over left upper neck of one week duration

• FNAC from left cervical lymph node - Atypical cells, suggestive of squamous cell carcinoma.

• Left tonsillar biopsy - Moderately differentiated Squamous cell carcinoma, keratinizing type (IHC for p16-Positive).

• PETCT done showed increased uptake in left tonsil and left lateral wall of oropharynx of size 3x2.8x4cm (SUV 13) with minimal extension into left parapharyngeal space. Left level II node seen 2.6x2.4cm (SUV 12)

• On examination - Proliferative growth seen over tonsillar bed, anterior tonsillar pillar and posterior tonsillar pillar and superiorly extending short of the base of uvula. Neck-Mobile left level II node 2x2 cm.
<table>
<thead>
<tr>
<th>OAR</th>
<th>Proton (GyE)</th>
<th>Tomo (Gy)</th>
<th>Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain stem D1cc</td>
<td>39.1</td>
<td>45.2</td>
<td>13.5</td>
</tr>
<tr>
<td>Spinal cord D1cc</td>
<td>16.8</td>
<td>36.6</td>
<td>54.1</td>
</tr>
<tr>
<td>Lips Mean dose</td>
<td>21.8</td>
<td>43.2</td>
<td>49.5</td>
</tr>
<tr>
<td>Oral cavity Mean dose</td>
<td>40.1</td>
<td>49.0</td>
<td>18.2</td>
</tr>
<tr>
<td>Larynx Mean dose</td>
<td>41.2</td>
<td>46.6</td>
<td>13.1</td>
</tr>
<tr>
<td>Mandible Mean dose</td>
<td>34.9</td>
<td>44.8</td>
<td>22.1</td>
</tr>
<tr>
<td>Midline mucosa mean dose</td>
<td>47.8</td>
<td>53.1</td>
<td>9.9</td>
</tr>
<tr>
<td>Constrictors mean dose (Outside PTV)</td>
<td>38.4</td>
<td>43.8</td>
<td>12.3</td>
</tr>
<tr>
<td>Prescription dose covering 98% of the volume (D98) in CTV 70</td>
<td>69.3</td>
<td>69.3</td>
<td></td>
</tr>
<tr>
<td>Prescription dose covering 98% of the volume (D98) in CTV 56</td>
<td>55.8</td>
<td>55.5</td>
<td></td>
</tr>
</tbody>
</table>
STEPS FOR PLANNING – SALIENT DIFFERENCES

• Account for uncertainties
• The concept of robust optimization
• Difference in motion management strategies
• Close monitoring
STEPS FOR PLANNING – WHAT IS DIFFERENT - I

• Immobilisation
  • Attention to beam path/length/number
  • Attention to replicability
  • Attention to CT stopping power of accessories
  • Attention to proximity of nozzle & range shifter
  • Requirement of respiratory management
  • Standard delineation of scars, drain sites etc.

• Imaging
  • Avoid contrast
  • Pay attention to artefacts
    • SEMAR (Single Energy Metal Artifact Reduction)
    • MVCT
    • OPG
  • Motion management
    • 4DCT
    • Abdominal compression

• Target delineation
  • No change in GTV/CTV delineation
  • Attention to skin
  • Contour metal/High HU material/variable tissue (gut, sinuses)
STEPS FOR PLANNING – WHAT IS DIFFERENT - II

- Preplanning audit
  - Motion
  - Beam path and length
  - Avoiding encroaching on critical structure

- Dose Prescription
  - In GyE incorporating RBE.
  - Higher prescription?
  - Tighter constraints
  - Often in close proximity of critical structures
  - Often in reirradiation setting
• Plan evaluation
  • Tighter prescription parameters
  • Avoid hot spots on OARs
  • Check for OAR doses
  • Check beam path
  • Assess End of Range
  • Ensure coverage of all targets by at least two beams
  • Identify location of hotspots.

• Robust optimisation
STEPS FOR PLANNING – EVALUATION OF QACT

- Change in beam path
- Change in target
- Change in OAR
- Impact on target coverage
- Impact on OAR doses
- Impact of unspecified tissue
COMPARATIVE EVALUATION - THE MODEL BASED APPROACH
Another form of evaluation: The model-based approach for selection of patients for proton therapy

- Patient rated moderate to severe xerostomia
- Physician rated ≥ Grade II dysphagia
- Tube feeding dependance

Standard coverage requirements
Sparing of bilat parotids, swallowing structures (SPC, IPC, CP)
Oral cavity

Preselection tool. Compare clinically prepared VMAT plan with IMPT plan assuming 0 dose to all OARs. Put patient through the IMPT process if one threshold is reached.

Target Δ NTCP thresholds

- Patient rated moderate to severe xerostomia ≥ 10%
- Physician rated ≥ Grade II dysphagia ≥ 10%
- Tube feeding dependance ≥ 5%

Σ Δ NTCP ≥ 15%

Create SIB based IMPT plan. Robustness earlier 5mm later 3mm
The model based approach for selection of patients for proton therapy

Who did not get preselected

Outcome after selection

Patients qualifying for proton significantly related to
- Treatment modality
- Overlap of OAR with PTV

Synchronous tumour
- Higher T stage
- Higher N stage
- Tumour location (OP vs others)
- Baseline xerostomia
- Baseline dysphagia
- Baseline weight loss > 10%

Rapid progression
- Metal implants
- Unsuitable immobilisation
The model based approach for selection of patients for proton therapy

Outcome of IMPT planning
- Did not qualify: 57%
- Qualified: 43%

Reasons for qualifying for protons
- Dysphagia: 22%
- Xerostomia: 18%
- Dysphagia + Xeostomia: 11%
- Tube dependence: 6%
- Did not qualify: 43%