Protons for Head and Neck Cancer

William M Mendenhall, M.D.
Protons for Head and Neck Cancer

**Potential Advantages:**

- Reduce late complications via more conformal dose distributions

- Likely to be the major advantage of protons for sites where they would be advantageous
Potential Advantages:

- Dose-escalation to improve local-regional control
  - Unlikely to occur because dose-escalation, even with more conformal treatment volumes, will likely result in increased late complications
Potential Disadvantages:

- Depending on daily variability, air cavities may cause dose distributions to be less predictable compared with photons.

- Increased skin reactions.

- Overly conformal dose distributions may result in marginal misses that would likely not be salvaged.
Protons for Head and Neck Cancer

Reduce Late Complications:

- Paranasal sinuses, nasal cavity, nasopharynx, minor salivary gland carcinomas involving skull base, skin cancer with clinical perineural invasion

- Protons alone or combined with IMRT to reduce risk of visual and CNS complications
Protons for Head and Neck Cancer

Reduce Late Xerostomia:

- Oropharynx
- IMRT plus proton boost
- Reduce dose to salivary gland(s) to ≤ 26 Gy
Protons for Head and Neck Cancer

Protons Unlikely to be Beneficial:
- Oral Cavity
- Larynx
- Hypopharynx
- Thyroid
Ca Oropharynx – Concomitant Boost
72 Gy
**Ca Oropharynx – Concomitant Boost 72 Gy**

95% PTV receives prescription dose, 99% PTV receives 93% of prescription dose, and 20% PTV receives <110% of prescription dose

<table>
<thead>
<tr>
<th>Tumor coverage</th>
<th>Photon IMRT</th>
<th>Protons</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% of PTV 5400/7200</td>
<td>7320 (101.6%)</td>
<td>7178 (99.7%)</td>
</tr>
<tr>
<td>99% of PTV 5400/7200</td>
<td>7221 (100.3%)</td>
<td>6975 (96.7%)</td>
</tr>
<tr>
<td>20% of PTV 5400/7200</td>
<td>7722 (107.3%)</td>
<td>7243 (106%)</td>
</tr>
<tr>
<td>Brain stem (0.1 c.c.)</td>
<td>5020</td>
<td>2685</td>
</tr>
<tr>
<td>Spinal cord (0.1 c.c.)</td>
<td>4400</td>
<td>546</td>
</tr>
<tr>
<td>Contralateral parotid (mean dose ≤ 2600)</td>
<td>2529</td>
<td>1482</td>
</tr>
<tr>
<td>Contralateral submandibular gland (mean dose ≤ 2600)</td>
<td>6928</td>
<td>6148</td>
</tr>
</tbody>
</table>
“Where’s the Beef?”

- Supposition that protons will be advantageous based on comparative dosimetry
- Limited long-term outcome data including variable primary sites, histologies, de novo vs. recurrent, etc...
- There’s not much “beef”!
Nasal Cavity and Paranasal Sinus Ca

University of Florida

• 1964 – 2005
• 109 patients
  • Definitive RT, 56 patients
  • Surgery and RT, 53 patients
  • Altered fractionation, 96 patients (88%)
• Median follow-up on living patients, 9.4 years (range, 2.0 to 35.9 years)
• 5 NED patients (5%) lost to follow-up from 4.9 years to 16.6 years
### Nasal Cavity and Paranasal Sinus Ca

#### University of Florida 5-yr Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>T1 – T3</th>
<th>T4</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local control</td>
<td>82%</td>
<td>50%</td>
<td>63%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>I-III</th>
<th>IV</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMFS</td>
<td>91%</td>
<td>75%</td>
<td>81%</td>
</tr>
<tr>
<td>CSS</td>
<td>81%</td>
<td>52%</td>
<td>62%</td>
</tr>
<tr>
<td>OS</td>
<td>71%</td>
<td>45%</td>
<td>55%</td>
</tr>
</tbody>
</table>

Mendenhall et al, unpublished
Nasal Cavity and Paranasal Sinus Ca

University of Florida - Severe Complications

- **Definitive RT** – 9 (16%) of 56 patients:
  - Ipsilateral blindness (6)
  - Bilateral blindness (1)
  - Maxillary ORN (1)
  - Fatal post-op meningitis after salvage CFR (1)

- **Surgery and RT** – 13 (25%) of 53 patients:
  - Ipsilateral blindness (3)
  - Post-op infection (1)
  - Graft failure (1)
  - Frontal bone ORN (1)
  - Frontal lobe necrosis (1)
  - Intracranial bleed (1)
  - Post-op meningitis (1)
  - Bilateral blindness (1)
  - Fatal infected bone flap (1)

Mendenhall et al, unpublished
Melanoma Maxillary Sinus
Paranasal Sinus Cancer

Massachusetts General Hospital

- 91 patients – carcinoma, 82 patients; sarcoma, 9 patients
  - Median dose – 73.6 Gy (range, 59.4 and 77.8 Gy)
  - Median proportion of proton dose – 49% (range, 23% to 84%)
  - 87% treated with accelerated hyperfractionated RT
  - 35% received adjuvant chemotherapy
  - Median follow-up, 45 months

Patel & Delaney, PPO Supplement, 2008
Paranasal Sinus Cancer

Massachusetts General Hospital
5-yr Outcomes (91 patients)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local control</td>
<td>82%</td>
</tr>
<tr>
<td>Ultimate local control</td>
<td>86%</td>
</tr>
<tr>
<td>DMFS</td>
<td>75%</td>
</tr>
<tr>
<td>DFS</td>
<td>52%</td>
</tr>
<tr>
<td>OS</td>
<td>58%</td>
</tr>
</tbody>
</table>

### Paranasal Sinus Cancer

Massachusetts General Hospital  
(91 patients)

<table>
<thead>
<tr>
<th>RT Complication</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal/temporal lobe injury on MR</td>
<td>4 patients</td>
</tr>
<tr>
<td>Soft tissue or bone necrosis</td>
<td>2 patients</td>
</tr>
</tbody>
</table>

Esthesioneuroblastoma

Proton Beam, NCI, Chiba, Japan

• 14 patients (1 previously irradiated)

• 1999 – 2005

• 65 $^{60}$Co Gy equivalent at 2.5 $Gy_E/Fx$

• Median follow-up, 40 months

Nishimura et al. IJROBP 68: 758, 2007
### Esthesioneuroblastoma

**NCI, Chiba, Japan**  
**N=14 patients**

<table>
<thead>
<tr>
<th>5-year outcomes</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local control</td>
<td>84%</td>
</tr>
<tr>
<td>RFS</td>
<td>71%</td>
</tr>
<tr>
<td>Overall survival</td>
<td>93%</td>
</tr>
</tbody>
</table>

Esthesioneuroblastoma

NCI, Chiba, Japan

N=14 patients

• 1 patient with Kadish stage C tumor – “liquorrhea” of skull base (STN?)

• No other grade 3 – 4 complications

Nishimura et al. IJROBP 68: 758, 2007
Adenoid Cystic Carcinoma
Head and Neck
University of Florida

• 101 de novo patients
• 1966 – 2001
• T<sub>1</sub> – T<sub>3</sub>, 57 patients; T<sub>4</sub>, 44 patients
• Surgery and RT, 59 patients; RT alone, 42 patients
• Median follow-up, 6.6 years (range, 0.4 – 30.6 years)

Mendenhall et al. Head Neck 26: 54, 2004
### Adenoid Cystic Carcinoma
#### Head and Neck

University of Florida

<table>
<thead>
<tr>
<th>Group</th>
<th>5-year local control</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_1$-$T_2$</td>
<td>92%</td>
</tr>
<tr>
<td>$T_3$-$T_4$</td>
<td>64%</td>
</tr>
<tr>
<td>Overall</td>
<td>77%</td>
</tr>
<tr>
<td>$T_4$ - RT alone</td>
<td>44%</td>
</tr>
<tr>
<td>$T_4$ - Surgery and RT</td>
<td>93%</td>
</tr>
</tbody>
</table>

Mendenhall et al. *Head Neck* 26: 54, 2004
### Adenoid Cystic Carcinoma

**Head and Neck**

**University of Florida**  \( (N=110\) patients)  

<table>
<thead>
<tr>
<th>Complications</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral blindness</td>
<td>6</td>
</tr>
<tr>
<td>Bilateral blindness</td>
<td>0</td>
</tr>
<tr>
<td>ORN requiring surgery</td>
<td>3</td>
</tr>
<tr>
<td>Permanent PEG</td>
<td>1</td>
</tr>
<tr>
<td>Oral antral fistula</td>
<td>1</td>
</tr>
<tr>
<td>Fatal meningitis after salvage surgery</td>
<td>1</td>
</tr>
<tr>
<td>Fatal hemorrhage after reconstructive surgery for tracheal stenosis</td>
<td>1</td>
</tr>
</tbody>
</table>

Mendenhall et al. *Head Neck* 26: 54, 2004
Skull Base Adenoid Cystic Ca

Massachusetts General Hospital

- 23 de novo patients
- 1991 – 2002
- Biopsy alone, 48%; subtotal resection, 39%; gross total resection, 13%
- Median follow-up on living patients, 64 months
- Median dose, 75.9 cobalt Gy equivalent

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year local control</td>
<td>93%</td>
</tr>
<tr>
<td>5-year DMFS</td>
<td>62%</td>
</tr>
<tr>
<td>5-year overall survival</td>
<td>77%</td>
</tr>
</tbody>
</table>

Skull Base Adenoid Cystic Ca

Massachusetts General Hospital

23 patients

- No grade 5 visual complications; 1 grade 4 retinopathy
- 7 chronic seizure disorders controlled with meds
- One fistula with CSF leak and meningitis

Oropharyngeal SCCA

Loma Linda

• 29 patients, stage II – IV

• 1991 – 2002

• 75.9 GyE / 45 FX / 5.5 weeks

• Follow-up, 2 to 90 months

Slater et al. IJROBP 62: 494, 2005
## Oropharyngeal SCCA

### Loma Linda

<table>
<thead>
<tr>
<th>5-year outcomes</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local control</td>
<td>88%</td>
</tr>
<tr>
<td>Neck control</td>
<td>96%</td>
</tr>
<tr>
<td>Local-regional control</td>
<td>84%</td>
</tr>
<tr>
<td>Late grade 3 toxicity</td>
<td>3/29 patients (10%)</td>
</tr>
<tr>
<td>No ORN</td>
<td></td>
</tr>
</tbody>
</table>

Slater et al. *IJROBP* 62: 494, 2005
### Oropharyngeal SCCA

<table>
<thead>
<tr>
<th>Series</th>
<th>No. of patients</th>
<th>% T4</th>
<th>% St IV</th>
<th>5-year local control</th>
<th>5-year local regional control</th>
<th>Late complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loma Linda</td>
<td>29</td>
<td>21%</td>
<td>62%</td>
<td>88%</td>
<td>84%</td>
<td>10%</td>
</tr>
<tr>
<td>UF - Tonsil</td>
<td>503</td>
<td>17%</td>
<td>61%</td>
<td>79%</td>
<td>73%</td>
<td>12%</td>
</tr>
<tr>
<td>UF - BOT</td>
<td>333</td>
<td>21%</td>
<td>75%</td>
<td>82%</td>
<td>77%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Slater et al. *IJROBP* 62: 494, 2005
Mendenhall et al. *AJCO* 29: 32, 2006
Mendenhall et al. *AJCO* 29: 290, 2006
Conclusions

• Protons probably most useful for tumors involving skull base to reduce CNS and visual complications and possibly improve local control
• Hyperfractionated to reduce visual complications
• May be useful in oropharyngeal cancer to reduce late effects, particularly xerostomia – decrease parotid dose to less than median 26 Gy
Caution

Do not be too conformal!

If you can miss with IMRT, you can miss with protons!

RAPID COMMUNICATION

RECURRENCE IN REGION OF SPARED PAROTID GLAND AFTER DEFINITIVE INTENSITY-MODULATED RADIOTHERAPY FOR HEAD AND NECK CANCER

DONALD M. CANNON, B.S., * AND NANCY Y. LEE, M.D. †

*Weill-Cornell Medical College, New York, NY; and †Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY