Intensity Modulated Proton Therapy (IMPT) for Head and Neck Tumors – Hype or Hope?

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Disclosure

State employee of Texas
No financial interest in protons
NCI/NIH P01 Co-Investigator H-N PNS Trial
PI of Phase II/III IMPT vs. IMRT OPSCC
Patient advocate – IMPT is important technology
Clinical advantages
The future for proton therapy is IMPT

‘Current state-of-art is passively scattered proton therapy’ – [2008]

‘Current state-of-art is active scanning proton therapy’ – [2010]

‘Current state-of-art is intensity modulated proton therapy’ – [2011]
Proton Therapy for Head and Neck Malignancies

- IMPT is the future of head and neck treatment
- Clinical feasibility has been established
- IMPT can reduce beam path toxicities of IMRT
  - We must test this hypothesis in a Phase III Trial
- VALUE proposition of HN proton therapy
  - Hospitalization, Emergency Center, Ambulatory Center, Feeding Tubes
HYPE or HOPE
The Current Epidemic of Oropharyngeal Cancer

Ramqvist and Dalianis *Lancet* 2012
Most patients with HPV+ disease will live following treatment

Ramqvist and Dalianis *Lancet* 2012
Benefits of IMRT

2000

2010
Disadvantages of IMRT
Beam Path Toxicities

Rosenthal et al. *IJROBP* 2008
### IMRT and Beam Path Toxicity

Table 3. Rates (%) of toxicities by treatment group: IMRT with or without concurrent cisplatin (100 mg/m²)

<table>
<thead>
<tr>
<th>Incidence of toxicities by treatment group (%)</th>
<th>IMRT alone</th>
<th>Concurrent cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>76</td>
<td>98</td>
</tr>
<tr>
<td>Vomiting</td>
<td>38</td>
<td>68</td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Occipital scalp epilation</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>Moist skin desquamation</td>
<td>28</td>
<td>35</td>
</tr>
<tr>
<td>Anterior oral mucositis</td>
<td>9</td>
<td>22</td>
</tr>
</tbody>
</table>

*IMRT non-target beam path toxicity (D. I. Rosenthal et al.)*
Optimizing H-N Outcomes
Acute and Chronic Morbidity

- Corneal ulceration
- Vision Loss
- Nausea and vomiting
- Xerostomia
- Mucositis
- Dysphagia
- Odynophagia
- Loss of smell
- Cranial neuropathy
- Motor/sensory function
- Memory loss
- Aphasia
- Tinnitus
- Dysguesia
- Feeding Tube
- Aspiration
- Xerostomia
- Death
Base of Tongue – IMRT (3 wks concurrent CRT)
Anterior Oral Mucositis

‘Out of field’
What Causes Decreased Oral Intake?

• Altered taste (metallic/cardboard)
• Loss of taste (dysguesia)
• Dry mouth (xerostomia)
• Thick saliva
• Nausea
• Vomiting
• Mouth ulcers (mucositis)
• Pain swallowing (odynophagia)
• Fatigue (narcotics)
• Constipation
• Difficulty swallowing (dysphagia)
Dysgeusia
Dysphagia
Nausea
Vomiting
Mucositis
Pain
Decreased Oral Intake
Weight Loss
Feeding Tube

Radiation Therapy IMRT
We can try supportive care to slow this progression
Radiation Therapy

- Fatigue
- Nausea
- Vomiting
- Dysgeusia
- Dysphagia
- Mucositis
- Pain
- Xerostomia

Decreased Oral Intake

Symptom Relief

Nutritional Prescription

Weight Loss

Feeding Tube
What if we could act a step before and prevent or decrease the incidence of side effects?
50 yo M
T1N0
Base of Tongue
SCC HPV+

3 weeks

6 weeks
66 Gy/30 fx

3 month follow-up
HOPE
MD Anderson Proton Facility
Spot Scanning Nozzle

Performance

- Range 4.0 – 30.6 cm
- Adjustability: 0.1 cm
- Max field size: 30x30 cm
- Beam size: 5-14 mm $\sigma$ (in air)
- 94 energies w/wo energy absorber (range shifter)
Depth doses and lateral profiles

- Monte Carlo simulated data

Sawakuchi et al. Med Phys 2010

Zhu et al. Med Phys 2013
### MDACC - Head and Neck Proton Treatment by Site (n-120)

<table>
<thead>
<tr>
<th>Location</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oropharynx</td>
<td>40</td>
</tr>
<tr>
<td>Periorbital</td>
<td>25</td>
</tr>
<tr>
<td>Parotid</td>
<td>15</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>14</td>
</tr>
<tr>
<td>Paranasal Sinus</td>
<td>12</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>8</td>
</tr>
<tr>
<td>Larynx</td>
<td>3</td>
</tr>
<tr>
<td>Skin</td>
<td>3</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>3</td>
</tr>
<tr>
<td>Base of skull</td>
<td>2</td>
</tr>
</tbody>
</table>
The First IMPT H-N Patient at MDA

T4N0M0 ACC of the Nasopharynx

• 33 yo female
• 2008: Presented with left pupillary constriction
  – MRI negative
• 2010: Progressive symptoms
  – Dysphagia, headaches, bilateral fullness in ears
  – MRI showed a mass in the nasopharynx
    • Involved paravertebral musculature
    • Invaded carotid space
    • Extends circumferentially around left lateral C1
    • Epidural extension at level of occipital condyles
    • PNI – left hypoglossal canal, left vidian canal, left foramen
      rotundrum and foramen ovale
    • Dura of left middle cranial fossa enhancing
  – Biopsy – Adenoid cystic carcinoma with PNI

Gillin et al. 2010
Adenoid Cystic Carcinoma of the Nasopharynx

Frank SJ et al., *IJROBP* (Submitted)
IMRT could not be delivered safely
IMRT could not be delivered safely

Brainstem with IMPT ~ 54 Gy and IMRT ~ 60 Gy
Less dose with IMPT: Optic nerves, Oral cavity, Cochleas
Nasopharyngeal Tumors
Adenoid Cystic Carcinoma

Protons - IMPT

Photons - IMRT
Nasopharyngeal Tumors
Adenoid Cystic Carcinoma
Complete Response
24 months

Completed treatment:
January 21, 2011
Periorbital Tumors
Basaloid Squamous Cell

Protons - IMPT
Photons - IMRT
Periorbital Tumors
Basaloid Squamous Cell
HOPE
Oropharynx (Base of Tongue) Squamous Cell Carcinoma

Completed treatment: May 7, 2011
IMPT with SIB
66 Gy/30 Fx concurrent with Cetuximab

1. Decrease Mucositis
2. Decrease odynophagia
3. Decrease N/V
4. Decrease weight loss
5. No PEG tube
6. Decrease xerostomia
7. Maintain taste
8. Decrease dysphagia
Excellent Early Clinical Outcomes with IMPT + Cetuximab

Frank SJ et al., Head and Neck (Submitted)
Oropharyngeal Cancer – Local Regional Control
T1N2aM0 (Stage IVA) – HPV+
Base of Tongue – Squamous Cell Carcinoma
MFO-IMPT - Dose: 66 Gy in 30 fx

PET/CT at Diagnosis

PET/CT at 10 week follow-up

There is no metabolically active disease in the mucosal surfaces, and no FDG-avid neck disease.
Oropharynx Tumors
Base of Tongue SCC

Protons - IMPT

Photons - IMRT
Oropharynx Tumors
Base of Tongue SCC
Oropharyngeal Cancer - Skin Toxicity
T1N2aM0 (Stage IVA) – HPV+
Base of Tongue – Squamous Cell Carcinoma
MFO-IMPT - Dose: 66 Gy in 30 fx

Grade 2 = moderate erytherma
Grade 3 = dry desquamation
Oropharyngeal Cancer - Skin Toxicity
T1N2aM0 (Stage IVA) – HPV+
Base of Tongue – Squamous Cell Carcinoma
MFO-IMPT - Dose: 66 Gy in 30 fx

Grade 1 = faint erytherma

End of Treatment
Oropharyngeal Cancer - Skin Toxicity
T1N2aN0 (Stage IVA) – HPV+
Base of Tongue – Squamous Cell Carcinoma
MFO-IMPT - Dose: 66 Gy in 30 fx

Grade 2 = Moderate Erythema
Grade 3 = Dry desquamation

End of Treatment
Oropharyngeal Cancer - Mucositis
T1N2aM0 (Stage IVA) – HPV+
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End of Treatment
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MFO-IMPT - Dose: 66 Gy in 30 fx

10 week follow-up
Head and Neck
Oropharynx (40 pts)

• Tonsil (25 pts)
• Base of Tongue (15 pts)
• Reirradiation (4 pts - BOT)
• Follow-up
  – Max (24 mo)
  – Mean (10 mo)
IMPT - Oropharynx (25 pts)
Swallowing-related Outcomes
(Symptomatic aspiration/stricture – Modified barium swallow and/or EGD)

- Median age: 62 yrs (38-83)
- Primary tumors
  - Tonsil (18 pts)
  - Base of Tongue (8 pts)
- HPV/p16+ (100%)
- Dose: 66-70 Gy in 30-33 fx
- Chemotherapy: 77%
- G-Tubes (5 pts – 19%)
  - All removed - median duration: 4.2 mo

Hutcheson and Frank (ASTRO 2013)
IMPT - Oropharynx (26 pts)
Swallowing-related Outcomes
(Symptomatic aspiration/stricture – Modified barium swallow and/or EGD)

• Pre-IMPT
  – 77% evaluated (speech pathologist)

• Post-IMPT
  – 65% evaluated with MBS and/or EGD
  – No patient had aspiration/stricture
  – 16 pts had minimum 6 mo follow-up
    • 15 pts (94%) tolerated regular diet
    • 1 pt (4%) restricts dry foods due to xerostomia

Hutcheson and Frank (ASTRO 2013)
Oropharynx (50 pts)
Case-Match Control Study
IMPT (2011-2012) vs. IMRT (2000-2009)

- Unilateral (10) vs Bilateral (42)
- Tonsil (36) vs. BOT (16)
- T-category (T1-10, T2-34, T3-4, T4-4)
- N-category (N0-2, N1-10, N2a-4, N2b-20, N2c-12, N3-4)
- Concurrent chemoradiation (50% vs 58%)
- Induction chemotherapy (65% vs 58%)
- Smoking status (NS-26, Q-26)
- Sex (male-48, female-4)
- Age (mean yrs - 61 vs 56) (p<0.001)

Frank and Garden (ASTRO 2013)
Oropharynx (50 pts)
Case-Match Control Study
IMPT (2011-2012) vs. IMRT (2000-2009)

• Technique:
  – IMRT: 85% had mono-isocentric/larynx block
  – IMPT: 100% whole field [base of skull – clavicle]

• Simultaneous integrated boost (SIB)
  – 66-70 Gy in 30-33 fx

• Gastrostomy feeding tubes
  – IMRT: 48%
  – IMPT: 20% (p=0.039)

Frank and Garden (ASTRO 2013)
## Swallowing related structures

<table>
<thead>
<tr>
<th>Structures</th>
<th>IMPT Mean ± SD(cGy)</th>
<th>IMRT Mean ± SD(cGy)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOC-mean</td>
<td>829 ± 590</td>
<td>3047 ± 789</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>POC-mean</td>
<td>4054 ± 1530</td>
<td>5060 ± 804</td>
<td>0.0001</td>
</tr>
<tr>
<td>BOT-mean</td>
<td>3896 ± 1692</td>
<td>5145 ± 1012</td>
<td>0.0169</td>
</tr>
<tr>
<td>IPC-mean</td>
<td>3276 ± 1071</td>
<td>2879 ± 1584</td>
<td>0.0667</td>
</tr>
<tr>
<td>SPC-mean</td>
<td>5525 ± 1300</td>
<td>5795 ± 1127</td>
<td>0.5434</td>
</tr>
<tr>
<td>MPC-mean</td>
<td>4818 ± 1782</td>
<td>5463 ± 936</td>
<td>0.5364</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Structures</th>
<th>IMPT Mean ± SD(cGy)</th>
<th>IMRT Mean ± SD(cGy)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem-mean</td>
<td>770 ± 373</td>
<td>1860 ± 879</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cerebellum-mean</td>
<td>1255 ± 427</td>
<td>1891 ± 760</td>
<td>0.0006</td>
</tr>
<tr>
<td>WB-mean</td>
<td>230 ± 105</td>
<td>438 ± 381</td>
<td>0.0026</td>
</tr>
<tr>
<td>AP-mean</td>
<td>1457 ± 899</td>
<td>3072 ± 650</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DVC-mean</td>
<td>1751 ± 869</td>
<td>3148 ± 630</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NA-mean</td>
<td>1912 ± 986</td>
<td>3327 ± 628</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SN-mean</td>
<td>1545 ± 850</td>
<td>3116 ± 872</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MO-mean</td>
<td>1963 ± 980</td>
<td>3235 ± 685</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PONS-mean</td>
<td>584 ± 364</td>
<td>1268 ± 653</td>
<td>0.0002</td>
</tr>
<tr>
<td>LV-mean</td>
<td>755 ± 652</td>
<td>1638 ± 1038</td>
<td>0.0035</td>
</tr>
<tr>
<td>FV-mean</td>
<td>683 ± 845</td>
<td>1762 ± 860</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV-mean</td>
<td>738 ± 407</td>
<td>1179 ± 682</td>
<td>0.0134</td>
</tr>
</tbody>
</table>

AP: Area Postrema; WB: Whole Brain; DVC: Dorsal Vagal Complex; NA: Nucleus Ambigues; SN: Solitary nucleus; MO: Medulla Oblangata; PONS; LV: Left Vestibule; RV: Right Vestibule; FV: Forth Venticule.
## Organ at Risks

<table>
<thead>
<tr>
<th>Structures</th>
<th>IMPT Mean ± SD(cGy)</th>
<th>IMRT Mean ± SD(cGy)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hard_Palate-mean</td>
<td>1197 ± 908</td>
<td>2632 ± 1036</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Larynx-mean</td>
<td>2952 ± 910</td>
<td>2645 ± 1517</td>
<td>0.036</td>
</tr>
<tr>
<td>Lt_Ant_Digastric_M-mean</td>
<td>2965 ± 1901</td>
<td>4817 ± 1540</td>
<td>0.0017</td>
</tr>
<tr>
<td>Mandible-mean</td>
<td>2658 ± 932</td>
<td>3811 ± 913</td>
<td>&lt;0.0004</td>
</tr>
<tr>
<td>Mylohyoid_M-mean</td>
<td>3202 ± 1769</td>
<td>4570 ± 1702</td>
<td>0.0156</td>
</tr>
<tr>
<td>Rt_Buccinator_M-mean</td>
<td>1405 ± 916</td>
<td>3395 ± 1206</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lt_Buccinator_M-mean</td>
<td>1197 ± 1000</td>
<td>4264 ± 1108</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lt_Lateral_Pterygoid_M-mean</td>
<td>3383 ± 1729</td>
<td>5460 ± 1547</td>
<td>0.01</td>
</tr>
<tr>
<td>Lt_Masseter_M-mean</td>
<td>2189 ± 1400</td>
<td>3381 ± 1079</td>
<td>0.004</td>
</tr>
<tr>
<td>Lt_Medial_Pterygoid_M-mean</td>
<td>3991 ± 2352</td>
<td>5460 ± 1547</td>
<td>0.004</td>
</tr>
</tbody>
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## Swallow Examinations

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Dysphagia per SLP</td>
<td>2</td>
<td>8%</td>
</tr>
<tr>
<td>Abnormal MBS</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>Aspiration (per MBS)</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Stricture (per MBS/EGD)</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>
Figure 2. Dietary outcomes (n=25)

Diet (last follow-up)

- NPO: 0%
- Liquid/Pureed: 4%
- Soft: 17%
- Regular: 75%
Feeding Tube Duration and Incidence

- For the IMPT group:
  - Median duration was 4.2 (2.6-11.3) months
- For the IMRT matched case control group:
  - Median duration was 4.7 (1.4-20) months

<table>
<thead>
<tr>
<th></th>
<th>Entire IMRT Cohort (N = 998)</th>
<th>IMPT (N = 25)</th>
<th>Matched IMRT (N = 25)</th>
<th>p-value (IMPT v. Matched IMRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeding Tube Incidence</td>
<td>475 (48%)</td>
<td>5 (20%)</td>
<td>12 (48%)</td>
<td>0.037</td>
</tr>
</tbody>
</table>
Eligibility
1) Stage III-IV oropharyngeal cancer
2) Squamous cell carcinoma
3) ECOG≤2
4) Target volume delineation

Randomization

**IMPT (70 Gy[RBE])**
Chemotherapy (locally advanced disease)

**IMRT (70 Gy)**
Chemotherapy (locally advanced disease)

Treatment 33 days
Recovery 10 wks

PROs

Restaging
No Surgery

Follow-up

Surgery

Follow-up
PROs Q3 mo

PROs Q3 mo

Frank – PI
Trial Activated – Sept 2013
Randomized Phase II/III Trial
Advanced Stage Oropharynx Cancer

• 360 patients (180 in each arm)
• Current proposed primary endpoint:
  – CTC-AE G3+ toxicity rate at 90 days – 2 years
• Prospectively examined secondary endpoints:
  – Local/Regional control
  – Disease specific survival
  – Overall Survival
  – PRO (MDASI, MDADI, QOL, XQ)
  – Functional swallowing outcomes
  – Sialography
  – Serum biomarkers
  – Imaging biomarkers
  – Cost analysis

Trial Activated – Sept 2013
Phase II/III Trial of IMPT vs IMRT for Advanced Stage Oropharyngeal Tumors

Signed Informed Consent
\( N_{ic} = 20 \)

Number Randomized
20

IMRT (Photons)
10

\( N_{IMRT} = 9 \)

Withdraw IC
\( N_{IMRT WD} = 1 \)

IMPT (Protons)
10

\( N_{Protons TX} = 9 \)

Insurance Denied/Withdrew IC
\( N_{Protons Denied} = 1 \)
HOPE
MD Anderson Proton Facility
Acknowledgments

• Proton Physics Team
  – Michael Gillin
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  – William Morrison
  – Adam Garden
  – Brandon Gunn
  – Beth Beadle
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  – Dave Fuller

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• H-N Surgery
• Dieticians