Proton Therapy for Head and Neck Cancer: The Future is Now

Michael Chuong, MD
Radiation Oncologist

Disclosures

- None

Overview

- Physical limitations of photons
- Dosimetric/clinical proton data for HNC
- Proton patient selection
- Practical proton considerations
Proton therapy

The physical characteristics of protons provide the rationale for its use—THIS IS NOT NEW!

“The proton proceeds through the tissue in very nearly a straight line, and the tissue is ionized at the expense of energy of the proton until the proton is stopped... These properties make it possible to irradiate internally a strictly localized region within the body.”

Robert Wilson, 1946

X-ray | Proton
--- | ---
No mass | Large mass
No charge | + charge

Apisarnthanarax et al, 2018
Courtesy of Varian

Passive scattering (OLD)

Pencil beam scanning (NEW)

MCI Exclusively Has Pencil Beam Scanning
Why protons?

- Superior dose-distribution
- Lower normal tissue doses
- Lower toxicities
- Higher tumor doses
- Higher local control and maybe survival

PARSPORT – IMRT vs. 3DCRT

| Grade 2+ xerostomia | 12 months: 3D 75% vs. IMRT 38%, p=.003 | 24 months: 3D 83% vs. IMRT 29%, p<.0001 |

- Rosenthal et al, IJROBP, 2008
- 3D IMRT
- Grade 2+ xerostomia
- 12 months: 3D 75% vs. IMRT 38%, p=.003
- 24 months: 3D 83% vs. IMRT 29%, p<.0001
CHORDOMA/CHONDROSARCOMA

Adapted from Hug PTCOG 2012

Where can protons improve the therapeutic ratio?

46 year old female

- T4N0 spindle cell carcinoma right maxillary sinus
- Involvement of infraorbital nerve, orbit, infratemporal fossa
- s/p endoscopic maxillectomy, rhinotomy, orbital decompression
- 74.4 Gy in 1.2 Gy fractions BID (optic structures in target volume)
Therapeutic ratio w/ protons

- Selected sinonasal/paranasal sinus, NPC patients
  - Optic, cranial nerves, salivary gland, anterior oral cavity sparing
  - Brainstem/spinal cord avoidance
  - Dose intensification

- Selected OPC patients
  - Salivary gland, pharyngeal constrictor, anterior oral cavity sparing

- Ipsilateral target

- Reirradiation
Primary goal to evaluate parotid and submandibular gland
Patient selection for protons should be done on an individual patient basis through comparing x-ray vs. proton treatment plans.

Distance between target and normal tissue matters.

The same reduction in mean dose to salivary glands will not always result in similar toxicity risk reductions. 
- Dependent on baseline value obtained with reference technique 
- Dependent on the shape of NTCP curve
Clinical evidence for protons

- Early limited data suggest protons can achieve superior dose escalation and/or reduce toxicity.
- Predominantly passive scattering.
- IMPT is expected to further reduce toxicities.
- Largely retrospective data.
- Several prospective trials currently underway.

Sinonasal/Paranasal sinus

- Local failure is common (~50-60% LC).
- Improved LC w/ dose escalation (>65 Gy) is limited w/ photons.
- Close proximity of brainstem, brain, optic structures, oral cavity, larynx, salivary glands.
- High rate of severe acute/late toxicity (brain necrosis, blindness, mucositis, etc.).


3DCRT IMRT Proton

MGH experience

- Resto et al. (Head Neck, 2008)
  - 102 pts. treated 1991-2002
  - Proton-photon; median 71.6 Gy(RBE)
  - 5 yr LRC ~90%
- Pommier et al. (AOHNS, 2006)
  - 23 pts. w/ ACC, BOS
  - 87% had gross residual disease, 48% only had biopsy
  - Proton-photon; median 75.9 Gy(RBE)
  - 5 yr LRC 95%, 5 yr OS 71%
- Fitzek et al. (Cancer, 2002)
  - 19 pts. w/ neuroblastoma, neuroendocrine tumors
  - Proton-photon; median 62.2 Gy(RBE)
  - 5 yr LC 88%, 5 yr OS 74%

Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis

- 5 yr OS and DFS significantly higher for CPT
- Why better outcomes for CPT?
  - Higher dose?
  - Higher RBE?
- Phase II trial IMRT or proton (NCT01586767)

Nasopharynx

- IMRT is standard of care, reduces xerostomia
- Target is in challenging anatomic location
- Few clinical proton reports
- OAR sparing w/ protons suggested by in silico studies
Reduced oral cavity dose

Matched IMPT and IMRT pts

Mean oral cavity dose:
17.3 Gy IMPT vs. 40.6 Gy IMRT; p<.001

GT tube rates:
20% IMPT vs. 65% IMRT; p=.02

No patient with mean oral cavity dose <26 Gy(RBE) required feeding tube.

Acute toxicity in comprehensive head and neck radiation for nasopharynx and paranasal sinus cancers: cohort comparison of 3D conformal proton therapy and intensity modulated radiation therapy

40 patients
26 IMRT, 14 proton
17 NPC, 23 nasal/paranasal

MGH Phase II Trial (NCT00592501)

- Preliminary results from 23 patients
- Stage III/IV (T3/4 60%, N2/3 65%)
- 70 Gy(RBE) + cis-q3 wk + cis/5FU
- Photons for low neck, protons for NPX + upper neck
- At median FU 28 months, LRC 100%
- 2 yr DFS 91% (2 patients w/ DM)
- 2 yr OS 100%
- G3 hearing loss (29%), G tube (48%), weight loss (38%)
- No G3+ xerostomia

Chan et al. IJROBP, 2012.
First 9 NPC patients treated at MDACC w/ IMPT
- T1-2 66%, N1-2 89%
- Induction 78%, concurrent 100%, adjuvant chemo 22%
- Median 70 Gy(RBE) in 33 fx

Mean dose to 29 OARs

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<th>OAR</th>
<th>IMRT (Gy)</th>
<th>IMPT (Gy)</th>
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<td>Area postrema</td>
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Favorable early clinical outcomes
- Median FU 24.5 mo
- 2-yr LRC 100%
- 2-yr DMFS 88.9%
- 2-yr OS 88.9%
- Grade 3 acute toxicity
  - Mucositis 11%
  - Dysphagia 22%
  - Dermatitis 44%
- Grade 3 late toxicity
  - None but longer follow up needed
**Oropharynx**

- Increasing incidence of HPV+ OPC
- Dosimetric studies suggest proton therapy can further reduce xerostomia and dysphagia
- Limited clinical data

**MD Anderson**

- Initial 50 OPC patients treated w/ IMPT
- Stage IV 80%, p16+ 88%, 50% never smoker
- Simultaneous integrated boost
  - GTV 66-70 Gy(RBE)
  - CTV 54-63 Gy(RBE)
- Bilateral neck 80%
- Induction chemo 40%, concurrent chemo 64%

**Median follow up 29 months**

- 2 yr OS 94.5%
- 2 yr PFS 88.6%
- Overall Survival
- Progression Free Survival
Acute G3 toxicities
- 46% dermatitis
- 24% dysphagia
- 58% oral mucositis
- 2% xerostomia

Late G3 toxicities
- 12% dysphagia
- 2% xerostomia
- 2% mucositis

Frank et al, IJROBP, 2014

Unilateral target

For bilateral targets, OAR overlap by TV limits benefit of sharp dose gradients achieved w/ protons

For unilateral targets, larger separation between target and normal tissue
- Lower mean parotid dose results in better function, even for doses <10 Gy (Rancati et al, IJROBP, 2010)
- Submandibular gland and oral cavity sparing may also reduce xerostomia
**Comparison IMRT plans generated**

**Immediate shift in practice from IMRT to PBRT** once PBRT become available

- Treated w/ 7-beam IMRT
- Primary + ipsilateral neck
- Comparison IMRT plans generated
Reirradiation

- Up to ~1/3 of HNC patients w/ have LRR
- Many are not surgical candidates
- Chemotherapy outcomes are dismal
  - Median survival 5-10 months
- LR progression is the major cause of death
  - Re-RT can cure some, improve QOL
  - Significant toxicity from re-RT, potentially limiting prescription dose
  - Improved outcomes w/ modern RT techniques (Watkins et al, Head Neck, 2009)

Memorial Sloan Kettering

- Largest published HNC re-RT experience
- Most treated w/ modern RT techniques
- LRC: 2 yr 47%, 5 yr 34%
- OS: 2 yr 43%, 5 yr 29%
- 35 patients alive >5 years
- Grade 3+ toxicity 31%
Proton Beam Re-Irradiation for Recurrent Head and Neck Cancer: Multi-Institutional Report on Feasibility and Early Outcomes

Paul Romesser, Oren Cahlon, Eli Reiter, Eugen Hug, Kevin Sino, Carl Overholt, James Fun, Dennis Mah, Madhur Garg, John Hans-Chih Chang, Nancy Lee

Methods

- Retrospective analysis of prospective registries from 2 hybrid community-academic proton centers
- 92 patients w/ recurrent HNC s/p prior definitive intent EBRT
  - 65% had OPC primary
  - 83% had 1 prior RT course, median 61.4 Gy
  - 39% salvage surgery

Median 34.4 months to re-RT
Median 65.6 Gy(RBE)
~50% concurrent chemo
A Phase II Study of Proton Re-Irradiation for Recurrent Head and Neck Cancer

Primary Endpoint: Incidence of Grade 3 complications at 3 months
Practical considerations

Proton dose distribution is sensitive to changes in tissue density. Planned and delivered doses can differ significantly.

- Setup
  - Inadequate immobilization
  - Weight loss
  - Anatomic changes
    - Tumor regression
    - Changes in air cavities
    - Tumors
  - Range uncertainties
    - Calculating CT Hounsfield units
    - Converting HU to stopping power
    - Reconstruction artifacts

Conclusions

- Proton therapy has undeniable dosimetric advantages (no exit dose)
  - But are they clinically meaningful?
    - Very likely yes for selected patients!
  - Mostly retrospective clinical evidence is encouraging
  - Results of prospective studies are eagerly awaited, need to enroll to these trials
  - Patient selection should be done on an individual patient basis

Thank you