Perfecting Cancer Care Together

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ASTRO 2016
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# Table of content

Click on the picture to go directly to the presentation

<table>
<thead>
<tr>
<th>Speaker</th>
<th>Title</th>
</tr>
</thead>
</table>
| Thomas E. Merchant, DO, Ph.D | Chair of Radiation Oncology  
St. Jude Children’s Research Hospital  
Proton Therapy in the treatment of pediatric cancers. Insights from the Stockholm clinical focus group |
| Minesh P. Mehta, M.B.Ch.B. | Chair of Radiation Oncology  
Miami Cancer Institute  
Cost effectiveness of Proton Therapy |
| Andrew K. Lee, MD, MPH | Medical Director  
Texas Center for Proton Therapy  
The future of Proton Therapy |
| Kevin Teo, PhD | Associate Professor  
University of Pennsylvania, Perelman school of medicine  
CBCT and adaptive proton therapy |
| Alexander Lin, MD | Medical Director  
Roberts Proton Therapy Center  
University of Pennsylvania,  
Selecting the patients who could most benefit from proton therapy |
The best in proton therapy today and tomorrow

- 100% Committed to clinical innovation
- 65% of PT patients are treated on IBA systems
- 20% of RT patients could benefit from Proton Therapy
- 30 years leading innovation in proton therapy
- 40 Institutions perfecting cancer care together
IBA Leadership Position in Proton Therapy

40 facilities
102 treatment rooms
Growing recognition of Proton Therapy clinical advantages

PERSPECTIVE ON RADIATION THERAPY PATIENTS RECEIVING PROTON THERAPY AS PART OF THEIR TREATMENT

1% Today
20% Following reports & policies
45% Following clients’ experiences

Proton Therapy Typical Cancer Indication Mix (% patients)

- Brain: 10%
- Head & Neck: 10%
- Pediatrics: 15%
- Gastro-Intestinal: 20%
- Lung: 20%
- Genitourinary: 15%
- Sarcoma: 5%
- Retreatment: 5%
The best in proton therapy today and tomorrow

One or Multi-room Solution; Always at the cutting edge

Proteus® ONE
Compact Single-Room IMPT solution

Proteus® PLUS
Multi-room custom solution

One Platform
Simultaneous development
Advanced Imaging Technology Continuum
Perfecting Cancer Care Together

Thomas E. Merchant, DO, Ph.D
Chair of Radiation Oncology
St. Jude Children’s Research Hospital

Proton Therapy in the treatment of pediatric cancers. Insights from the Stockholm clinical focus group
Proton Therapy in the treatment of pediatric cancers

Insights from the Stockholm clinical focus group

Thomas E. Merchant, DO, Ph.D

Chair of Radiation Oncology
St. Jude Children’s Research Hospital
Pediatric Radiation Oncology – Clinical Focus Group

Goals

- To better define the role of proton therapy in the management of pediatric cancers
- To reach group consensus on clinical situations where proton therapy provides the most benefit in pediatric cancers
- To prioritize innovation and development necessary for further advancement within the subspecialty area of pediatric oncology

Format

- 24 international leaders in pediatric radiation oncology, pediatric oncology, medical physics, and radiobiology
- Exchange of knowledge via interactive presentations, group breakout sessions, and treatment planning comparisons
Early Consensus

- Delivery of radiation to children requires extra caution:
  - the radiosensitive nature of developing tissue and organs
  - the long natural life expectancy of survivors

- The goal for pediatric radiation oncologists remains constant: reduce radiation dose and volume as much as possible without compromising cure

- There are many paths to success
  - Refine indications for irradiation
  - Reduce radiation dose and volume through clinical trials
  - Harness advancements in radiation therapy → Proton therapy
100% of participants considered “access to a proton therapy system a complement to their pediatric program”

58% of participants thought that >50% of pediatric tumors should be treated with proton therapy

No participant thought that proton therapy was appropriate for every pediatric case

There were “no bright lines” about which tumors should be treated

“What is the treatment of choice for the following pediatric tumors?”
Plan Comparisons: Ependymoma

- Most common tumor treated with proton therapy

- Risks associated with dose outside PTV are low using IMRT

- Risks associated with dose within and near to CTV/PTV are low but very consequential

- Proton pencil-beam scanning
  - Reduce risk of secondary tumors
  - Reduce risk of necrosis
  - Reduce risk of hearing loss
Plan Comparisons: Craniopharyngioma

- Risk of toxicity to organs within the target volume will not be improved with proton therapy
- Advantage in low-moderate dose delivered to supratentorial brain outside the target volume
- Modeling would suggest clear neurocognitive benefit
- RT2CR (St. Jude-University of Florida Collaborative Clinical Trial) will provide evidence
- Reducing the target volume will be important, regardless of modality, to decrease the risk of severe complications
Plan Comparisons: Medulloblastoma

- Proton therapy dosimetry for medulloblastoma is regarded as the signature model to demonstrate the benefit of proton therapy over photon therapy.
- Objective benefit of proton therapy may be realized through the assessment of extra-CNS effects as well as CNS effects.

Images Courtesy of B. Timmermann and S. Constine
Plan Comparisons: Medulloblastoma

- Proton therapy reduces dose to the face, neck (thyroid), and organs of the heart, lungs, and abdomen

- Delivers higher dose to the scalp and para-spinal soft tissue in many cases

- Mixed impact with regard to brain exposure

Images Courtesy of B. Timmermann and S. Constine
Plan Comparisons: Parameningeal Rhabdomyosarcoma

- Most common non-CNS tumor treated with proton therapy
- These patients receive multi-agent chemotherapy concurrent with irradiation
Plan Comparisons: Parameningeal Rhabdomyosarcoma

- Proton therapy reduces dose to the hypothalamus-pituitary axis, cochlea, oral cavity, facial structures, and infratentorial brain
- In some cases may deliver higher doses to the frontal lobe and larynx
- Normal tissue irradiation depends on optimization goals and priorities

Images Courtesy of M. Pankuch and N. Laperriere
Prioritization and Magnitude of Benefit

- Questionable value in total body irradiation, whole abdomen irradiation, whole lung irradiation, whole brain irradiation

- Are marginal benefits of “cardiac- and breast-sparing whole lung radiation” outweighed by the technical uncertainty of proton delivery?

- Are marginal benefits of “lens-sparing whole brain radiation” outweighed by the radiobiological uncertainty of proton interactions?

- MD Anderson data demonstrates a 46% / 54% split between protons and photons among 1600 pediatric patients treated since 2006
Prioritization and Magnitude of Benefit

- In cases where there is a probable benefit but magnitude is small, the selection of patients for proton therapy is a matter of prioritization

  - Q: for a child with advanced-stage or incurable cancer, should we use protons to simply reduce acute effects of irradiation or combined modality therapy?
  - Q: Should we use proton therapy to further reduce the risk of rare complications? (high-frequency hearing loss - 7% → 5%; SMN 5% →2%)

- Do we have models that accurately predict late effect risk? Are photon models useful to estimate the benefits of proton therapy? How confident are we that treatment planning comparisons provide sufficient evidence of benefit?

- Decisions regarding patient prioritization are inextricably tied to availability, access and treatment efficiency; these considerations are inextricable tied to healthcare resources and cultural expectations
Prioritization and Magnitude of Benefit

Long term

- Further work is needed in the development of pediatric dose-effect models, independent of technology
  - Accurate modeling will permit detailed, patient-specific “virtual trials” which can then be placed into context of healthcare resources
- The use of proton therapy to increase tumor dose (and cure) is promising but should be explored within a clinical trial

Short term

- The ideal proton candidate is a young child with a curable tumor requiring moderate to high dose irradiation and normal tissue sparing
- The goal is to optimize the magnitude of risk reduction and durable benefit
Beyond Dosimetry

- There are many unknowns concerning proton radiobiology, LET, and RBE
  - Only 1/3 of participants felt that RBE uncertainty was an “obstacle for broad adoption of proton therapy” yet there was widespread acceptance that this area requires more research
- Limits to treatment capacity exist, particularly at the high-volume, experienced pediatric proton therapy centers
- Referral barriers
  - Participants did not regard neutron dose in treatment room to be an obstacle to implementation
  - Participants did not consider randomized studies or a “model based approach” mandatory before broad acceptance.
Referral Barriers

- “These doctors bought a proton machine and now think they are pediatric radiation oncologists.”
  - Treating a pediatric patient is complex, independent of technology
  - Anesthesia/immobilization, setup imaging, multi-agent concurrent chemotherapy, cooperative group protocols, family dynamics, decision making (in)capacity

- “It is too expensive for my state/country to refer every child for proton therapy. We have higher healthcare priorities and less resources.”
  - What happens when your role as an individual patient fiduciary conflicts with role as societal fiduciary?

- “If I refer this child for proton therapy, I will not meet my salary revenue goals. I have been treating children for decades and I am very good at what I do.”
  - Ego and personal reimbursement are uncomfortable topics to confront
Pediatric Needs

#5 Treatment room age-appropriate entertainment/distraction options

#4 Treatment table integration with anesthesia unit

#3 Safe volumetric image-guidance including low-dose CBCT with collimation and variable field-of-view

#2 Formal national or international registry

#1 Lower cost system development - 100% of participants agreed that cost was the main barrier to broad adoption of proton therapy for children
Impressions

- The technology of proton therapy represents an incremental and non-exclusive advancement, consistent with long-standing goals of pediatric radiation oncologists.

- Significant questions remain regarding the magnitude of benefit, patient prioritization, and radiobiology.

- There is a relative consensus among pediatric radiation oncologists on technological and research needs.

- These are not conclusions but rather starting points and common themes to generate global discussion around the use of proton therapy in children.

Contributions

Thank you

Questions?
Minesh P. Mehta, M.B.Ch.B.
Chair of Radiation Oncology
Miami Cancer Institute

Cost effectiveness of Proton Therapy
Cost effectiveness of proton therapy

Minesh P. Mehta, M.B.Ch.B.
Chief of Radiation Oncology
Miami Cancer Institute
Objectives/Background

- In the absence of randomized data, the clinical value of proton therapy (PBT) is consistently questioned.

- Because of its higher initial relative cost, 3rd party payor’s raise significant questions regarding the cost-effectiveness of PBT

- We performed a systematic review of the cost-effectiveness of PBT, and this talk will focus on the findings
A Systematic Review of the Cost and Cost-Effectiveness Studies of Proton Radiotherapy

Vivek Verma MD¹; Mark V. Mishra MD²; and Minesh P. Mehta MBChB²
Approach

- In the absence of randomized data, the clinical value of proton therapy (PBT) is consistently questioned.

- Because of its higher initial relative cost, 3rd party payor’s raise significant questions regarding the cost-effectiveness (CE) of PBT.

- We performed a systematic review of the cost-effectiveness of PBT, and this talk will focus on the findings.
General Definitions

- Cost–benefit analysis: Assigns a monetary value to the measure of effect.

- Cost-effectiveness analysis (CEA) is frequently used in health services, where it may be inappropriate to monetize health effect.

- This compares relative costs and outcomes of 2 or more therapies.

- It is expressed as a ratio; the denominator is the “gain in health”, and the numerator is the cost.

- The most commonly used outcome measure is quality-adjusted life years (QALY).
The best in proton therapy today and tomorrow

Cost-effectiveness Plane

<table>
<thead>
<tr>
<th>More Effective</th>
<th>More Effective</th>
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<tbody>
<tr>
<td>Lower cost</td>
<td>Higher Cost</td>
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<table>
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<td>Lower Cost</td>
<td>Higher Cost</td>
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</table>
Definitions Used in This Study

- 2 types of studies: Non-modeling, and modeling; the latter use probabilistic inputs, data and models, the former only uses “costs”.

- 2 modeling methods: Population based (Markov) and individual based (Monte Carlo).

- Whenever possible, costs of managing toxicities are accounted for and sensitivity analysis are performed.
Definitions Used in This Study

- **Endpoints**: QALYs (Quality-adjusted life years), ICER (incremental cost-effectiveness ratio), set at $50,000/QALY, WTP (willingness to pay) threshold.

- Based on a 1995 study that found the median cost-effectiveness of >500 life-saving medical interventions = $42,000 per life-year saved.
  - At 4% inflation, in 2016, this would translate to $95,708.

PRISMA Searches


- Key searches: protons, proton facility, proton radiation, cost, cost-effectiveness, value, economics, policy, monetary, reimbursement, and medical insurance.
Excluded:
No assessment of PBT costs.
Editorials/commentaries

30 review articles (cited, but not included)
7 articles + 3 abstracts addressed PBT CE
but did not directly assess monetary aspects (cited but not discussed in depth)
Prostate Cancer: Markov Analysis

- Konski: Markov modeling analysis:

- PBT not as cost effective as IMRT.

- In a man aged 70 years, mean costs were $63,511 vs. $36,808, with 8.54 and 8.12 QALYs gained. In a man aged 60, the costs were $64,989, and $39,355, with 9.91 and 9.45 QALYs gained.

Prostate Cancer: Low Risk and SBRT

- Aizer: For low-risk CAP, the costs were $42,772 for PBT, $29,616 for IMRT, $14,000 for prostatectomy, $16,883 for brachytherapy, and $2,766 for watchful waiting.

- Parthan: Markov analysis compared IMRT, SBRT, and PBT in men aged 65. By using RTOG toxicity criteria and systematic searches of acute/late toxicity data, payer’s perspective costs were
  - $24,873 and 8.11 QALYs gained for SBRT,
  - $33,068 and 8.05 QALYs for IMRT, and
  - $69,412 with 8.06 QALYs for PBT.

- However, these data failed to take into account that PBT can be used to deliver SBRT—another technique by which PBT costs could decrease.

Prostate Cancer: How can PBT become Cost-Effective?

- Yu: 2008-09 Medicare data; identified 27,647 pts who received prostate RT (553 PBT and rest IMRT).
  - At 12-month median F/U, no differences in GU (IMRT vs PBT: 17.5 vs 18.8%), GI (10.2 vs 9.9%), or other (5.6 vs 4.5%) toxicities.
  - Median Medicare reimbursement: $32,428 for PBT and $18,575 for IMRT.
- Goyal: Markov data estimate a need to decrease composite toxicity by 41% for PBT to be as cost effective as IMRT.

Breast Cancer: Unselected Populations

- A Swedish Markov modeling study analyzed 2 groups of breast cancer patients, either PBT or tangents. Costs were $13,610 for PBT and $6,051 for tangents, with 12.35 and 12.25 QALYs, i.e. no significant gain.

- Consistent with another Markov analysis by the same group demonstrating an increase of $7,163 and only 0.17 QALYs gained for PBT.

Breast Cancer: Selected Populations

- When examining a specific population with twice the estimated risk of nonRT-related cardiac disease, the average cost for PBT per QALY gained was nearly halved from $80,596 to $41,491.

- The applicability of this study is uncertain in light of the modern techniques used for cardiac dose sparing in photon-based RT. In addition, the assumption of a 14% risk of severe RT pneumonitis is too high for the modern era.

Lundkvist J, Radiother Oncol. 2005;75:179-185
Breast Cancer: APBI

- A recent CE analysis for APBI (methodological details unavailable), was presented at PTCOG NA 2015, using 2014 Medicare charges.

- IMRT was the most expensive treatment; 3DCRT APBI was the least expensive ($6,771).

- Medicare allowable for PBT APBI were $13,883, only marginally greater than for conventional WBI ($13,149).

- PBT APBI was less expensive than strut adjusted volume implant applicators ($14,859) and only slightly more expensive than MammoSite ($12,245).

- Current research examining APBI versus WBI could have implications for the potential incorporation of PBT.
Early Stage NSCLC

- Grutters: Inoperable stage I NSCLC analyzed:
  - PBT, carbon-ion RT, 3DCRT, and SBRT
  - which cost $33,356, $23,250, $27,462, and $16,784, respectively;
  - corresponding QALYs gained were 2.33, 2.67, 1.98, and 2.59.
  - Thus, the costs per QALY gained were lowest for SBRT.
  - A critique of that report included large assumptions of similar utility figures for acute and chronic aftereffects as well as lack of assessment beyond 5 years.
  - Did not segregate central versus peripheral locations and, thus, could not identify possible subsets that could benefit.

Head and Neck Cancers

- A Markov report specifically examined stage III and IV oral cavity, laryngeal, and pharyngeal cancers.

- Cohorts were divided into 3 groups: IMRT for all, IMPT for all, and mixed IMPT/IMRT with IMPT only if “expected to be cost-effective” (based on the estimated 6-month risk of xerostomia).

- 1 year xerostomia and dysphagia rates: 22 and 18%, with IMPT; 36 and 21%, with mixed IMPT/IMRT; 44 and 23%, with IMRT.

- All groups had similar gains in QALYs (6.52-6.62), costs were $61,697 for IMPT, $49,656 for IMRT, and $52,816 for mixed.

- This is the strongest evidence to date suggesting that select patients with head/neck cancer may have decreased side effects with PBT, with similar RT costs as IMRT.

Head and Neck Cancers: Clinical Trials

- Frank: Recent data in oropharyngeal and nasopharyngeal ca using matched-cohorts (PBT vs IMRT) have demonstrated ~50% reduction in the use of gastrostomy tubes with PBT.

- The potential of PBT for improving CER and QALYs for this event would be considerable; a randomized trial is currently underway.

- This group has also conducted a modeling study, evaluating episodic costs of care, including acute toxicities, and the data favorably support PBT.

Thaker NG, Particle Therapy Co-Operative Group, Annual Meeting; May 18-23, 2015
Medulloblastoma: Markov Analysis

- Markov modeling of a cohort of children (aged 5 years) with medulloblastoma comparing PBT versus IMRT.

- Initial costs of PBT were estimated at $12,364 compared with $5,129 for conventional RT (2.4-fold increase), total costs of adverse effects were estimated at $5,121 and $40,967, respectively (8-fold difference in favor of PBT), yielding total costs of $17,484 and $46,096 (2.6-fold decrease with PBT).

- The greatest factors contributing to adverse event costs were IQ, hearing loss, and growth hormone deficiency.

Using Monte Carlo methodology, children aged 5 years were analyzed for PBT or IMRT.

Whereas the lifetime (including morbidity management) IMRT cost was estimated at $112,790, the PBT cost was estimated at $80,211.

Total QALYs gained favored the PBT treated patients (17.37 vs 13.91, respectively).

Cancer of the Esophagus

- Currently no data examining PBT CE in esophageal ca.

- Data from a multi-institutional, cohort of neoadjuvant chemoradiotherapy (chemoRT) followed by resection in 582 pts treated with photons (471) or protons (111) revealed that postoperative length of stay was shorter for PBT (9 vs 12 days; P<.0001), largely attributable to fewer cardiopulmonary and wound toxicities.

- 90-day mortality rates were also lower for PBT.

- A detailed analysis is underway, including CE.

Uveal Melanoma

- Markov model compared PBT, enucleation, and brachy.

- Similar costs of $22,772 for enucleation, $24,894 for PBT, and $28,662 for plaque brachytherapy.

- QALYs gained were identical at 2.918, 2.938, and 2.994.

- Analysis did not stratify by tumor size; did not use recent data indicating that particle therapy produces superior survival vs. enucleation and improved eye preservation compared with plaque brachytherapy.

Limitations

- There are no perfect PBT CE studies.
- There are too few comparative randomized trials.
- Few studies prospectively collected all cost-elements, or QOL (necessary for QALYs).
- No study accounted for all possible side-effects and complications, and most models are relatively sparse in terms of possible outcomes; mortality costs not included.
- Older RT and PBT techniques considered by most; compact proton system upfront costs lower.
- Transcontinental interpretations are limiting; “WTP” thresholds are now closer to $100K per QALY.
Conclusions

- PBT for unselected populations with early-stage lung and prostate cancer is economically suboptimal.
  - Historical PBT for CAP have used opposed lats, which do not spare the ant rectal wall; recent developments, such as spacers and in vivo Bragg-peak range verification, would allow the use of dosimetrically superior ant or ant-oblique beams, which could improve PBT CE.
  - Hypofx studies not addressed

- PBT is likely the economic standard of care for a significant proportion of pediatric patients, although CE evidence only exists for pediatric brain tumors.
Conclusions

- Others with the potential for significant reduction of RT-induced toxicities, such as head/neck ca, esophageal ca, advanced NSCLC, brain tumors, skull base neoplasms ocular cancers, and certain left-sided breast cancers as well as certain soft tissue sarcomas are all potential candidates for cost-effective PBT.

- Data for these indications and also for re-irradiation in multiple anatomic sites are rapidly emerging and will likely result in radical revision of many current conclusions.
Minesh P. Mehta, M.B.Ch.B.
Chief of Radiation Oncology
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Perfecting Cancer Care Together

Andrew K. Lee, MD, MPH
Medical Director
Texas Center for Proton Therapy

The future of Proton Therapy
The future of proton therapy

Andrew K. Lee, MD, MPH
Medical Director
Texas Center for Proton Therapy
What is “new” in proton therapy?

- Proton therapy has improved as technology has advanced (just like X-ray therapy)
- Imaging (OBI and CBCT)
- Treatment planning (software)
- Treatment delivery systems
- Intensity modulation
- Immobilization
Special Planning Considerations

- Proton planning is dependent upon high-fidelity CT scans

- CT number $\rightarrow$ Tissue Density $\rightarrow$ Proton stopping power

- Water and Air CT number assignment provides a patient-specific correction

- CT image artifacts must be “edited”
Dual energy CT

80 kV
Attenuation B

140 kV
Attenuation A
Dual energy CT may improve tissue density characterization
Metal artifacts degrade fidelity of planning CT
First CBCT on full PBS gantry in N. America  (04/06/2016)
Why do you need CBCT with protons

- Volumetric targeting
  - Lung tumor
  - Liver
- Improve fine 6-degree corrections
  - Brain
  - Skull base
  - Brain stem
- Image and validate PROXIMAL anatomy in beam path
  - External contour (e.g. breast)
  - Image changing anatomy (HN, pleural effusion)
50GyE/4 fx with layer and volumetric repainting
CBCT for targeting
PROTON (3 FIELD) HCC
Two field breast + lymph nodes w/ pencil-beam proton therapy
Postop MFO-IMPT chordoma w/ metal instrumentation
The best in proton therapy today and tomorrow
Auto activation detected by PET

- Protons can produce nuclear reactions in target tissue
  - $^{11}\text{C}$, $^{15}\text{O}$, $^{13}\text{N}$
  - Positron emission of these isotopes can be detected via PET
  - Half-life is short (~2 min to 20 min)
  - Can be used for validation of beam path and distal edge
“Solid water” irradiated with proton beam

Proton beam

Solid water
Proton path as imaged by PET scan, Calculated depth (10 cm) \( \cong \) PET depth (9.9 cm)
Prompt gamma imaging concept

- Prompt Gamma Ray Emission
- Occurs within $10^{-9}$ seconds of interaction
- Virtually “real-time” signal
- Each element emits unique characteristic gamma-rays with different energies
- Gamma rays only emitted where protons interact in the patient (i.e. where dose is deposited)
Proton range validation with prompt gamma
Prompt Gamma “Slit” Camera
Proton radiography

T. Plautz et al. IEEE Transactions on Medical Imaging 2014;33
First proton radiograph of hand phantom

Relief map of WET from summed stopping power of hand phantom

T. Plautz et al. IEEE Transactions on Medical Imaging 2014;33
Thank you

Andrew K. Lee, MD, MPH
Medical Director
Texas Center for Proton Therapy
Meet the experts

Kevin Teo, PhD
Associate Professor
University of Pennsylvania, Perelman school of medicine

CBCT and adaptive proton therapy
CBCT and Adaptive Proton Therapy

Kevin Teo, PhD
Assistant Professor of Radiation Oncology
Hospital of the University of Pennsylvania
The Rational for CBCT in Proton Therapy

All the advantages of CBCT in photon therapy:
- Visualization of soft tissue
- 3D anatomy matching/patient alignment
- Assessment of tumor motion, size or location

AND Beyond Image Guided Radiation Therapy (IGRT):
- Assessment of dose delivery deviations due to anatomical change and setup variations
- Dose calculation using CBCT
- Adaptive proton therapy
Why is CBCT needed for Proton Therapy?

Impact on dose distribution to target and organs at risk needs to be assessed

Tumor regression

Tumor growth
Complex Anatomical Change

- **Planning CT**
  - **Pleural effusion**
  - **Tumor density change**

- **CBCT**
Other Types of Anatomical Change

Atelectasis

Lung reinflation
Dynamics of Pleural Effusion and Atelectasis

Anatomical change will impact proton range, periodic assessment during treatment is necessary.
Head and Neck Anatomical Change During Therapy

Oropharyngeal cancer
Impact of Anatomical Change

- Less optimal dose distribution - degrades with time
- OAR doses may increase eg oral cavity
- Worse with IMPT compared with SFO with integrated boost
Limitations of CBCT for Dose Calculation

Proton dose calculation is more sensitive to HU uncertainties than photon therapy.

CBCT cannot be used directly for dose calculation unless HU accuracy is verified.

If CT number is off by 100 HU:
Stopping power is different by 5%.
For a 10cm range, error is 5 mm.

Need error in water equivalent depth $\ll$
Range uncertainty of 3.5%
Limitations of CBCT for Dose Calculation

Beam hardening and scatter artifacts (dark streaks between high density structures, cupping artifacts)

Motion artifacts (streaking)
Improving Accuracy of CBCT HUs for Dose Calculation

1) Deformable Image Registration (DIR) approach - Deform planning CT to geometry of CBCT
   
   C Veiga et al, IJROBP 95 549 (2016)

2) A priori CT based scatter correction


CBCT with uniform scatter correction

CBCT with a priori CT based scatter correction
From CBCT to a Virtual CT (vCT)

Deform planning CT to geometry of CBCT

Method works in most cases

Limitations:
(1) Complex anatomical change not handled correctly by deformable image registration (DIR) software
(2) Subtle changes in lung/tumor density not accounted for

C Veiga et al, IJROBP 95 549 (2016)
Correction for Large Tumor Regression

Identify gross DIR errors between CBCT and vCT and replace HU with lung or tissue density

Large tumor regression
Correction for Lung Changes

Atelectasis: Not handled correctly by deformable image registration

![CBCT](image1)
![vCT](image2)
![Corrected vCT](image3)

Lung reinflation
Comparison of Virtual CT with Rescan CT

WET:
Water Equivalent Thickness from entrance of beam to target

Results of 20 patient study:

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>WET_{mean} (mm)</th>
<th>WET_{RMS} (mm)</th>
<th>WET_{95%} (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal surface</td>
<td>0.5±2.2</td>
<td>3.7±1.9</td>
<td>8±4</td>
</tr>
<tr>
<td>Proximal surface</td>
<td>0.1±1.9</td>
<td>2.3±1.5</td>
<td>4±3</td>
</tr>
<tr>
<td>PTV</td>
<td>0.4±2.1</td>
<td>3.4±2.0</td>
<td>7±4</td>
</tr>
</tbody>
</table>

- Mean difference in WET is about 1mm
- Possible to estimate shifts in range with 2 to 3 mm accuracy

C Veiga et al, IJROBP 95 549 (2016)
Fast Online Dose Estimation

Deform TPS dose for each field based on change in WET

Over-ranging
Under-ranging
No Change

C Veiga et al, IJROBP 95 549 (2016)
Traditional Analysis with vCT

Feasible to replace evaluation CTs with CBCT

IJROBP  Veiga et al 2016
Quantitative Tools for Assessment of CBCT

Projection Depth Radiograph

Digitally Reconstructed Radiograph (DRR) = simulated projection of X-rays

Projection Depth Radiograph (PDR) = simulated projection of water equivalent thickness (WET) for protons
Projection Depth Radiograph

Conceptual illustration of a virtual PDR calculated using WETs of patient onto a virtual plane. Unit is in mm.

The difference between two PDRs. Unit is in mm.
Serial CBCT PDR Difference Trending

\[ \text{PDR}_{\text{cCBCT}} - \text{PDR}_{\text{pCT}} \text{ will highlight the errors of both anatomical change and setup error} \]

Week 1

Week 2

Week 3

Right lateral, parallel beam path, to the middle plane. Criteria: 3mm (difference), 3mm (radius)
WET Analysis

Beam’s eye view of WET map to PTV distal surface

Difference map indicates over/under ranges
Prototype Software: REGGUI*

Image/Geometric indicators

WET analysis

* Guillaume Janssens, IBA
The best in proton therapy today and tomorrow

CBCT Triggered Adaptive Therapy

With CBCT and WET analysis tools, the need for evaluation CTs can be patient specific

**Therapist**
- Weekly CBCT
  - Image Analysis OK?
    - Yes: Treat
    - No: vCT Dose Calculation OK?
      - Yes: No Replan but Monitor
      - No: Verification CT or repeat CBCT OK?
        - Yes: Replan
        - No: Offline Analysis
          - vCT Dose Calculation OK?
            - Yes: Replan
            - No: No Replan but Monitor

**Physics**

**Physician**
Summary

- CBCT may be used for triggering adaptive therapy
- Most adaptive therapy will be in Lung and Head and Neck
- Offline adaptation is feasible
- Online plan adaption is more challenging- need fast re-optimization tools and advanced proton range verification and QA tools
Thank you

Kevin Teo, PhD
Assistant Professor of Radiation Oncology
Hospital of the University of Pennsylvania
Meet the experts

Alexander Lin, MD
Medical Director
Roberts Proton Therapy Center

Selecting the patients who could most benefit from proton therapy
Selecting patients who could most benefit from PT

Alexander Lin, MD
Assistant Professor
Medical Director, Roberts Proton Center
University of Pennsylvania
X-rays deliver a greater dose outside the target for the same dose within the target volume as protons.
Rationale: Which patients may benefit most?

- Suboptimal outcomes with photon-based approaches
  - Current options yield cure, but with significant toxicity (proton therapy to improve side effects and QOL)
    - Pediatrics
    - Head and Neck
  - Suboptimal locoregional control with current treatment options (proton therapy to improve disease outcomes and toxicity)
    - Central Nervous System/Base of Skull
      - Chordoma/Chondrosarcoma
    - Thoracic
    - GI
    - Reirradiation
- Others
  - Prostate
  - Breast
Which Patients Would Benefit Most?

- Limited Resource
- High Demand
- Lack of randomized evidence
- Systems are needed to best select/identify patients
Principles of Proton Prioritization

- Incremental Benefit

- Equity

- Transparency

- Age

- Contribution to Medical Knowledge
PENN Proton Priority System (PROPS)

- **Diagnosis**: certain diagnoses given priority
- **Site**: 
- **Stage**: local, regional, metastatic
- **Performance Status/Comorbidities**
- **Age**
- **Urgency**: gross disease with symptoms
- **Clinical trial**
Proton Therapy Decision Matrix

- **“Yes”**
  - Will proton therapy likely lead to incrementally better outcomes for the patient?
    - “No” or “Not sure”
      - Will proton therapy likely lead to materially worse outcomes for the patient?
        - “Yes”
          - Alternative approach
        - “No” or “Not sure”
          - Will providing proton therapy to the patient under consideration take a treatment spot from another more suitable patient?
            - “Yes”
              - Alternative approach
            - “No”
              - Is proton therapy planning and delivery technically feasible under our current program?
                - “Yes”
                  - Proton therapy
                - “No”
                  - Alternative approach
Scenario 1: Significant long-term toxicity with standard photon-based approaches.

Treatment with proton therapy is the preferred method. Randomization away from proton therapy infeasible/unethical.
The best in proton therapy today and tomorrow
Scenario 2: level 1 evidence suggesting significant morbidity/mortality with photon-based approaches.

Treatment with proton therapy should be strongly considered, on a clinical trial if possible.
A RANDOMIZED PHASE III COMPARISON OF STANDARD-DOSE (60 Gy) VERSUS HIGH-DOSE (74 Gy) CONFORMAL RADIOTHERAPY WITH CONCURRENT AND CONSOLIDATION CARBOPLATIN/PACLITAXEL IN PATIENTS WITH STAGE IIIA/IIB NON-SMALL CELL LUNG CANCER

<table>
<thead>
<tr>
<th></th>
<th>60 Gy</th>
<th>74 Gy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥3 Pulmonary</td>
<td>20%</td>
<td>19%</td>
<td>0.71</td>
</tr>
<tr>
<td>Grade ≥3 Pneumonitis</td>
<td>7%</td>
<td>4%</td>
<td>0.25</td>
</tr>
<tr>
<td>Grade ≥3 Esophagitis</td>
<td>7%</td>
<td>21%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade ≥3 Any</td>
<td>76%</td>
<td>79%</td>
<td>NS</td>
</tr>
<tr>
<td>Grade 5 Toxicity</td>
<td>N=3</td>
<td>N=8</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Median overall survival: 28.7 months (60 Gy) vs. 20.3 months (74 Gy), p=0.0042

RTOG 9410 concurrent daily arm median overall survival: 17.0 months

### RTOG 0617 Multivariate Cox Model - Survival

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Comparison</th>
<th>Dead/Total</th>
<th>Dead/Total</th>
<th>HR (95% CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RL Group 1</td>
<td>Group 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation Level</td>
<td>Standard Dose (RL) vs. High Dose</td>
<td>121/208</td>
<td>136/199</td>
<td>1.34 (1.04, 1.73)</td>
<td>0.0213</td>
</tr>
<tr>
<td>Maximum related esophagitis/dysphagia grade</td>
<td>Maximum grade &lt; 3 (RL) vs. Maximum grade ≥ 3</td>
<td>210/349</td>
<td>47/58</td>
<td>1.54 (1.11, 2.15)</td>
<td>0.0102</td>
</tr>
<tr>
<td>Volume of PTV</td>
<td>Continuous</td>
<td>257/407</td>
<td>1.000 (1.000, 1.001)</td>
<td>0.0729</td>
<td></td>
</tr>
<tr>
<td>Heart V5</td>
<td>Continuous</td>
<td>257/407</td>
<td>1.007 (1.002, 1.011)</td>
<td>0.0035</td>
<td></td>
</tr>
<tr>
<td>Zubrod PS</td>
<td>0 (RL) vs. 1</td>
<td>151/240</td>
<td>106/167</td>
<td>1.14 (0.89, 1.47)</td>
<td>0.3045</td>
</tr>
<tr>
<td>PET Staging</td>
<td>No (RL) vs. Yes</td>
<td>30/39</td>
<td>227/368</td>
<td>0.77 (0.52, 1.13)</td>
<td>0.1766</td>
</tr>
<tr>
<td>Gender</td>
<td>Male (RL) vs. Female</td>
<td>153/240</td>
<td>104/167</td>
<td>0.97 (0.74, 1.26)</td>
<td>0.7975</td>
</tr>
<tr>
<td>Histology</td>
<td>Non-squamous (RL) vs. Squamous</td>
<td>146/228</td>
<td>111/179</td>
<td>1.01 (0.78, 1.31)</td>
<td>0.9380</td>
</tr>
<tr>
<td>Smoking History</td>
<td>Non-smoker/former light smoker</td>
<td>39/60</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Former heavy/current smoker vs. unknown</td>
<td>206/328</td>
<td>12/19</td>
<td>1.14 (0.80, 1.63)</td>
<td>0.4617</td>
</tr>
</tbody>
</table>

RL = reference level, HR = hazard ratio, CI = confidence interval

*Two-sided log-rank p-value

**Authors:** “heart dose might best explain why patients given 74 Gy did worse than patients given the 60 Gy”

- Did increased heart dose in the 74 Gy arm (V50 – 11% vs. 7%) lead to an increase in intercurrent cardiac deaths?
NRG ONCOLOGY
RTOG 1308

Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradiotherapy for Inoperable Stage II-IIIB NSCLC

SCHEMA

Stage
1. II
2. IIIA
3. IIIB

Histology
1. Squamous
2. Non-Squamous

Concurrent Chemotherapy
Doublet Type
1. Carboplatin/paclitaxel
2. Cisplatin/etoposide

Randomize

Arm 1: Photon dose—70 Gy*(RBE), at 2 Gy (RBE) once daily plus platinum-based doublet chemotherapy**

Arm 2: Proton dose—70 Gy (RBE), at 2 Gy (RBE) once daily plus platinum-based doublet chemotherapy**

Both Arms:
Consolidation chemotherapy x 2 cycles required for patients who receive concurrent carboplatin and paclitaxel***

- Treatment with proton therapy should be strongly considered, on a clinical trial if possible.

- Otherwise, selection of patients from a model-based approach, prioritizing patients for whom protons would provide the most benefit.
Submandibular Gland Sparing

Stage 4a, T1N2b, HPV+, R tonsil SCCA

PBS  Rapid Arc IMRT: Backup plan
Submandibular Gland Sparing

Mean Doses: IMRT (40 Gy), PBS (33 Gy)
Parotid Sparing
Parotid Sparing

Mean Doses: IMRT (18 Gy), PBS (9 Gy)
Oral Cavity Sparing
Oral Cavity Sparing

Mean Doses: IMRT (19 Gy), PBS (3 Gy)
Patient-reported toxicity/QOL

1. Have you experienced a change in taste? Check all of the following statements that apply to you now:

<table>
<thead>
<tr>
<th>My sense of taste is:</th>
<th>Normal</th>
<th>Diminished</th>
<th>Absent</th>
<th>Distorted</th>
<th>Heightened</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. I sometimes experience a taste when nothing is there (PHANTOM TASTE) [ ] YES [ ] NO

3. For each of the following taste qualities, indicate with a check whether your perception of it is currently normal, diminished, absent, distorted, heightened, or present when nothing is there (phantom taste):

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Diminished</th>
<th>Absent</th>
<th>Distorted</th>
<th>Heightened</th>
<th>Phantom Taste</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWEET</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SALTY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOUR (e.g., lemon, vinegar)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BITTER (e.g., tonic water, medicine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROTTEN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BURNING</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TINGLING</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OTHER</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(if other, specify)

4. If you have PHANTOM TASTE (taste when nothing is there), indicate with a check where your perception of it is (check all that apply):

<table>
<thead>
<tr>
<th>FRONT OF TONGUE</th>
<th>BACK OF TONGUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROOF OF MOUTH</td>
<td>SALIVA</td>
</tr>
<tr>
<td>THROAT</td>
<td>WHOLE MOUTH</td>
</tr>
<tr>
<td>GUMS</td>
<td>DENTURES OR CAPS</td>
</tr>
<tr>
<td>OTHER (specify)</td>
<td></td>
</tr>
</tbody>
</table>

5. My sense of smell is:

If phantom smell (smell when nothing is there), please describe

6. My changes in taste or smell have resulted in my eating (check all that apply):

<table>
<thead>
<tr>
<th>The same amount of food</th>
<th>Less</th>
<th>More</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different types of food (Specify the change)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
UPenn Experience, Adjuvant RT (n=51)

### Parotid

- **Ipsilateral Parotid (p=0.759)**
  - VMAT: 33 Gy
  - PBS: 34 Gy

- **Contralateral Parotid (p<0.0001)**
  - VMAT: 21 Gy
  - PBS: 12 Gy

### Submandibular

- **Ipsilateral Submandibular (p=0.941)**
  - VMAT: 60 Gy
  - PBS: 60 Gy

- **Contralateral Submandibular (p=0.0236)**
  - VMAT: 38 Gy
  - PBS: 29 Gy
The best in proton therapy today and tomorrow

**Ipsilateral Buccal (p<0.0001)**

**Contralateral Buccal (p<0.0001)**

**VMAT**

<table>
<thead>
<tr>
<th></th>
<th>Ipsilateral</th>
<th>Contralateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>VMAT</td>
<td>44</td>
<td>38</td>
</tr>
<tr>
<td>PBS</td>
<td>32</td>
<td>8</td>
</tr>
</tbody>
</table>

**Sublingual**

**Ipsilateral Sublingual (p=0.0007)**

**Contralateral Sublingual (p<0.0001)**

**VMAT**

<table>
<thead>
<tr>
<th></th>
<th>Ipsilateral</th>
<th>Contralateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>VMAT</td>
<td>44</td>
<td>38</td>
</tr>
<tr>
<td>PBS</td>
<td>32</td>
<td>8</td>
</tr>
</tbody>
</table>

**Buccal**

**Ipsilateral Buccal (p<0.0001)**

**Contralateral Buccal (p<0.0001)**

**VMAT**

<table>
<thead>
<tr>
<th></th>
<th>Ipsilateral</th>
<th>Contralateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>VMAT</td>
<td>27</td>
<td>19</td>
</tr>
<tr>
<td>PBS</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>
The best in proton therapy today and tomorrow

Hard Palate
(p<0.0001)

Soft Palate
(p=0.0209)

Tongue
(p<0.0001)

Upper Lip
(p<0.0001)

Lower Lip
(p<0.0001)

Mean Dose (Gy)

<table>
<thead>
<tr>
<th></th>
<th>VMAT</th>
<th>PBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hard Palate</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Soft Palate</td>
<td>37</td>
<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>
The best in proton therapy today and tomorrow

- Normal Taste (p=0.10)
  - PBS: 63%
  - VMAT: 33%

- Mild-Severe Appetite Changes (p=0.015)
  - PBS: 13%
  - VMAT: 53%

- Mild-Severe Sticky Saliva (p=0.853)
  - PBS: 50%
  - VMAT: 53%

- Moderate-Severe Xerostomia (p=0.002)
  - PBS: 19%
  - VMAT: 73%
UPenn: “AVOID” Trial

- Phase II study (60 pts)
  - TORS → SND → RT (+/- chemo)
  - Stage IVa OPC
    - HPV+
    - T1/T2
    - Negative margin
    - No PNI or LVI

- RT to nodal regions only
  - Protons or IMRT

- Omission of primary tumor bed from RT field

- Rationale
  - Improve toxicity profile, while maintaining high LC
    - Operative site breakdown
    - Mucositis
    - Dysphagia/Odynophagia

- Primary outcome: local control

- Secondary outcome: toxicity/QOL (proton vs IMRT)
Conclusions

- Proton therapy: unique modality that offers potential significant improvements for our patients, especially in those who have suboptimal outcomes (toxicity, cure) with photon-based approaches.

- Limited (but expanding) resource.

- Patient selection, using existing comparative data or model-based approaches, will allow us to maximize the benefits of proton therapy for our patients.

- Continued medical and technical advances (pencil beam-scanning, imaging, adaptation, dose verification) will continue to advance the field and improve outcomes.
Thank you

Alexander Lin, MD
Assistant Professor
Medical Director, Roberts Proton Center
University of Pennsylvania
One or Multi-room Solution; Always at the cutting edge

One Platform
Simultaneous development
Advanced Imaging
Technology Continuum

Proteus®ONE
Compact Single-Room IMPT solution

Proteus®PLUS
Multi-room custom solution

The best in proton therapy today and tomorrow
The best in proton therapy today and tomorrow

Protect, enhance and save lives

IBA