The Current & Future State of Particle Therapy

The MD Anderson Proton Therapy Center- Houston

Matthew Palmer, MBA, CMD
Chief Operating Officer
mpalmer@mdanderson.org
The Challenge

PlanIQ™, Courtesy of Ben Nelms, PhD
The Challenge
LUNG:  - 56%
HEART:  - 67%
Technology Advances

1980’s
3D-CRT X-RAYS

1990’s
IMRT X-RAYS

2000’s
VMAT X-RAYS

2005+
PASSIVE PROTONS

2010+
IMPT PROTONS

HEART DOSE (cGy):

2833 1933 2200 1301
943

LUNG DOSE (cGy):

1747 1324 1103 966
775

LIVER DOSE (cGy):

1184 1141 986 218
235
Goals of Radiation Therapy

- Maximize disease control
- Minimize both early and late side effects
- Preserve organ function
- Preserve quality of life
- Minimize extraneous radiation dose to the patient

“One cannot have a radiation-induced side effect in tissue that does not receive radiation.”

-H. Suit
ELIMINATION OF UNNECESSARY RADIATION

Proton Therapy (IMPT)  X-Ray Therapy (IMRT)  Added Radiation w/ IMRT (X-Rays)

*25 Gy (25 Sv) of Unnecessary Radiation
**ELIMINATION OF UNNECESSARY RADIATION**

*25 Gy (25 Sv) of Unnecessary Radiation =

- 12,500 H&N CTs (2 mSv)
- 5,000,000 Intraoral X-Rays (0.002 mSv)
- 25,000x General Public Annual Limit (1.0 mSv)

**Added Radiation w/ IMRT (X-Rays)**
Proton Therapy for Nasopharynx Ca
60% reduction in feeding tubes

Frank SJ et al. IJROBP 2014
Frank SJ et al. ASTRO 2013
Technology Advances

1900’s
←Brachytherapy

1952
←Cobalt Teletherapy

1954
←Proton Therapy

1960’s
←Radiosurgery

1970’s
←CT planning

1980’s
←BEV planning

1990’s
←3D planning

1990’s
←IMRT

2000’s
←IGRT

←VMAT

←IMPT

2010+

- Particle accelerators (1920s) constructed.

- Linear Accelerator (1927)- Developed by Widerøe

- Supervoltage X-ray tubes (1929)- for Linac developed by Coolidge

- Cyclotron (1930)- Lawrence’s laboratories (UC Berkeley)

- Synchrotron (1944–1945)- Veksler (Soviet Union) & McMillan [US]

- Electron Beam Therapy (1940)- Kerst developed the Betatron

- Concept of Proton Therapy (1946)- Robert R. Wilson proposed protons for medical purposes

- Proton Therapy (1954)- first clinical use at Berkeley in 1954.
Technology Advances

- 1900’s: Brachytherapy
- 1952: Cobalt Teletherapy
- 1954: Proton Therapy
- 1960’s: Radiosurgery
- 1960’s: CT planning
- 1970’s: Radiosurgery
- 1980’s: BEV planning
- 1980’s: CT-Based Treatment Planning (1978)
- 1990’s: 3D planning
- 1990’s: IMRT
- 1990’s: 1,000 Medical Photon Linacs in US (1986)
- 1990’s: Virtual Simulation (1987) at UNC
- 2000’s: IGRT
- 2000’s: VMAT
- 2010+: IMPT
Technology Advances

- **CyberKnife** developed by J. Adler at Stanford University (1990).
- World’s first **Hospital-based Proton Facility** opened at LLUMC (1990)
- **First commercial TPS** developed in (1990)
- **MLC developed** (3D-planning) which allows first dose escalation trials. (1990s)
- **CT Simulations** first used (1990s)
- **IMRT** developed (1994)
- **KV Imaging & CBCT** (1990-2000)
- **Tomotherapy** clinically developed (2003).
- **Intensity Modulated Proton Therapy** delivered at MDACC (2008)
Future Potential of Proton Therapy

Proton Therapy Development Lag = ~17 Yrs.

Photons vs Protons Development

- 1st Linac (1960)
- 2-D Planning & MV Port Films (1970)
- 3-D Planning (1990)
- CT-Based Planning (1987)
- IMRT Implementation (1992)
- 75% of RO using IMRT (2002)
- kV Imaging VMAT Implementation (2006)
- CBCT & VMAT Growth (2010)
- 1st USA IMPT (MDACC)* (2009)
- UCSF (#2) (1994)
- LLUMC (#1) (1990)
- MGH (#3) (2001)
- MDACC (#5) (2006)

- 1st USA Spot Scanning (2008)
- 39 New PT Centers (45%) (2014 - 2018)
- Single Room PT Growth (2018)
- VMAT Maturation (2014 →)
- 7 w/ Spot Scanning & 0 w/ CBCT (2014)

Proton Therapy Development Lag = ~17 Yrs.
Technology Development Lifecycle

- **On the Rise**
  - Expectations rise
  - Supplier proliferation
  - Mass media hype begins
  - Early adopters investigate
  - First-generation products, high price, lots of customization needed
  - Startup companies first round of venture capital funding

- **Peak of Inflated Expectations**
  - Activity beyond early adopters
  - Supplier consolidation and failures
  - Second/third rounds of venture capital funding

- **Trough of Disillusionment**
  - Negative press begins
  - Second/third products, some services
  - Less than 5 percent of the potential audience has adopted fully

- **Slope of Enlightenment**
  - Methodologies and best practices developing
  - Third-generation products, out of the box, product suites

- **Plateau of Productivity**
  - High-growth adoption phase starts: 20% to 30% of the potential audience has adopted the innovation
Roadblocks for Proton Therapy

1. Required resources and cost of treatment
2. A limited number (25) of proton therapy centers to publish data and average time to publication
3. Insurance Companies Medical Policies are outdated
4. Only a few randomized studies
Barriers for Rapid Proton Therapy Adoption

1) Large gantry designs
2) Infrastructure requirements
3) Shielding requirements
4) Large equipment technology
5) Power and cooling requirements
6) Old accelerator technology
7) Time to First Treatment (3+ years)
Technology Advancements

Size

Technology & Functionality

Smartphone Image Courtesy MIM Vista
Website
PT Industry Developments

Gantry Design

-28%

IBA/Varian
Full 360 deg
115/220 tons

Sumitomo
Full 360 deg
240 tons

IBA/Proteus ONE
210 deg
90 tons

Mevion
190 deg
60 tons

Protom/Hitachi
220 deg
50 tons

ProNova
Full 360
25 tons

Courtesy of ProNova
PT Industry Developments

Floor Plan Design
-46%

Vault Design (Maze)
-33%

 Courtesy of VOA Associates
PT Industry Developments

Shielding Design

-36%

Modular Shielding

-27%

36% Reduction in Shielding

Courtesy of VOA Associates & Veritas Shielding
PT Industry Developments

Accelerator Design
-20%

Power Supply
-59%

Images Courtesy of Hitachi Medical & ProTom
PT Industry Developments

Superconducting Accelerators & Magnets

Reduced Footprint

Images Courtesy of ProNova & Mevion
PT Industry Developments

Proton Source (Nanotechnology)

Reduced Footprint

LASER ACCELERATOR TECHNOLOGY CAN MAKE A SMALL AND CHEAP PROTON THERAPY SOLUTION

*Note: Gantry not drawn to scale; likely to be ~5m in diameter


Images Courtesy of HIL Applied Medical
Rapid Adoption of Proton Therapy is Close

Collective Industry Developments will Break the Financial-Viability Threshold with Support!

- Gantry Design -28%
- Floor Plan Design -46%
- Vault Design -33%
- Shielding Design -36%
- Accelerator Design -20%
- System Design
- Proton Source -59%
- Power Supply
- Construction Time -10-12 months

Image Courtesy of HIL Applied Medical

$17-18M Single-room financial-viability Threshold

$150M to $250M PT Facility
$5M X-ray Room
< $12M
$25M
$30M
$40M
$40M
# Proton Therapy Operational Cost

**Protons/Photon Cost = 3.2**

<table>
<thead>
<tr>
<th>Operation</th>
<th>Particle facility</th>
<th>Proton-only</th>
<th>Photon facility</th>
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<tbody>
<tr>
<td></td>
<td>Combined (carbon-ion and proton)</td>
<td>3 rooms (^a)</td>
<td>3 rooms (^b)</td>
</tr>
</tbody>
</table>

## Costs (€)

### Capital costs
- **Medical equipment and IT**
  - Combined: 13,750,000
  - Proton-only: 11,250,000
  - Photon: 14,250,000
- **Particle therapy equipment**
  - Combined: 90,000,000
  - Proton-only: 60,000,000
  - Photon: –
- **Building**
  - Combined: 34,850,000
  - Proton-only: 23,680,000
  - Photon: 9,180,000
- **Total capital costs**
  - Combined: 138,600,000
  - Proton-only: 94,930,000
  - Photon: 23,430,000
- **Assumed lifecycle**
  - Combined: 30 years
  - Proton-only: 30 years
  - Photon: 30 years
- **Capital costs/year**
  - Combined: 4,620,000
  - Proton-only: 3,164,333
  - Photon: 781,000

### Operational costs
- **Cost of operation/year**
  - Combined: 10,952,350
  - Proton-only: 5,736,450
  - Photon: 2,758,350
- **Cost of renewal/year**
  - Combined: 3,697,750
  - Proton-only: 2,080,200
  - Photon: 1,562,700
- **Cost of staff/year**
  - Combined: 6,366,304
  - Proton-only: 6,366,304
  - Photon: 2,599,716
- **Yearly interest for financing (5% over 20 years)**
  - Combined: 11,121,623
  - Proton-only: 7,617,429
  - Photon: 1,880,084
- **Operational cost/year**
  - Combined: 32,138,027
  - Proton-only: 21,800,383
  - Photon: 8,800,850

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<th>Combined (carbon-ion and proton)</th>
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<td>36,758,027</td>
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<td><strong>Cost/fraction</strong></td>
<td>1128</td>
<td>743</td>
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<td><strong>Ratio to photon</strong></td>
<td>4.8</td>
<td>3.2</td>
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*Peeters et al, Radiotherapy and Oncology, 2010, “How Costly is Particle Therapy? Cost Analysis of EBRT with C-ions, protons, & photons”*
Particle Therapy Facility Worldwide

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**Grand Total**: 138 Rooms
Particle Therapy Centers

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Proton Therapy Market Forecast

Proton Therapy

- Demand will grow at a moderate rate in the near-term
- Single-room systems, targeting (eg, IMPT) and expanded clinical applications will drive later growth.
- Pediatrics is prime opportunity
  - Clinically validated
  - Strong 10-year growth (>200%) over low baseline volume

Challenges

- Clinical necessity for some tumors has been questioned (eg, prostate)
- Increased payer scrutiny
- Determining patient demand is key

Proton Therapy Forecast
US Market, 2015–2025

<table>
<thead>
<tr>
<th>Volumes</th>
<th>5-Year</th>
<th>10-Year</th>
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<tr>
<td>Thousands</td>
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- +19%
- +18%
- +55%
- +35%

Note: Pediatric cases represent an important application of proton therapy. Radiation therapy volumes shown representtrations (not patients). IMPT = Intensity-modulated proton therapy. Sources: Impact of Change® v15.0; IMS LifeLink® Pharmetrics Health Plan Claims Database, 2011, 2013; The following 2013 CMS Limited Data Sets (LDS): Carrier, Denominator, Home Health Agency, Hospice, Outpatient, Skilled Nursing Facility; The Nielsen Company, LLC, 2015; Sg2 Analysis, 2015.

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Proton Therapy Support

- White House
- Medicare (LCDs)
- NCI/NIH
- NCCN (prostate, lung, esophagus, HN)
- ASTRO
- California state government
- Washington state government
- Oklahoma state government
- University of Texas System
- Louisiana state government – mandate for clinical trials
- Institute for Clinical and Economic Review (ICER)
In that report, only 28% of men with normal erectile function maintained normal erectile function after therapy. A prospective quality of life comparison of patient-reported outcomes using the EPIC instrument between IMRT (204 patients) and proton therapy (1234 patients) concluded that "No differences were

believes there is no clear evidence supporting a benefit or decrement to proton therapy over IMRT for either treatment efficacy or long-term toxicity. Conventionally fractionated prostate proton therapy can be considered a reasonable alternative to X-ray based regimens at clinics with appropriate technology, physics, and clinical expertise.

PRINCIPLES OF RADIATION THERAPY (1 of 9)

General Principles (see Table 1. Commonly Used Abbreviations in Radiation Therapy)

- Determination of the appropriateness of radiation therapy (RT) should be made by board-certified radiation oncologists who perform lung cancer RT as a prominent part of their practice.
- RT has a potential role in all stages of NSCLC, as either definitive or palliative therapy. Radiation oncology input as part of a multidisciplinary evaluation or discussion should be provided for all patients with NSCLC.
- The critical goals of modern RT are to maximize tumor control and to minimize treatment toxicity. A minimum technologic standard is CT-planned 3D-CRT.
- More advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include (but are not limited to) 4D-CT and/or PET/CT simulation, IMRT/VMAT, IGRT, motion management, and proton therapy (https://www.astro.org/Practice-Management/Reimbursement/Model-Policies.aspx). Nonrandomized comparisons of using advanced technologies versus older techniques demonstrate reduced toxicity and improved survival."
NCI Supported PT RCT Studies

Nine (9) NCI-Funded ($19M) projected to accrue 2,500 patients, half protons and half photons

1. Trial #11-497 (Active, Accrual Goal- 400): “PARTIQoL: PIII RCT for Low or Intermediate Risk Prostate Cancer”

1. NCI-2013-01850 (Active, Accrual Goal- 560): “PIII RCT for Inoperable Stage II-IIIIB Non-Small-Cell Lung Cancer”

1. Trial #12-100 (Active, Accrual Goal- 80): “PII RCT with SIB to the High Risk Margin for Retroperitoneal Sarcomas”

1. NCI-2012-00071 (Active, Accrual Goal- 120): “PII RCT for centrally located Stage I, selected stage II & recurrent NSCLC”

1. Trial #10-308 (2P01CA021239-29) (Active, Accrual Goal- 90): “A PII RCT for Locally Advanced Sinonasal Malignancy”


1. NCI-2012-00078 (Active, Accrual Goal- 180): “PIII RCT for the Treatment of Esophageal Cancer”

1. NCI-2014-01072 (Active, Accrual Goal- 576): “PII RCT for Patients With Newly Diagnosed Glioblastoma”

1. NCI-2011-01094 (Completed, Accrue- 275): “Phase II Bayesian RCT for locally Advanced NSCLC”
Where is the evidence?

World’s first Hospital-based Proton Facility opened at LLUMC. (1990) [already 1,000+ photon linacs by this time]

World’s first Proton Facility at a Comprehensive Cancer Center opened at MDACC. (2006)

Only 14 proton therapy centers in the US to-date (2015)

Average time to publication is 6.75 years (61 – 99 mo. or 5.1 – 8.3 yrs)

- Treatment: 24 – 36 months
- Follow Up: 24 – 36 months
- Data Analysis: 1 – 3 months
- Time to Publication: 12 – 24 months
Cumulative MDA PTC Publications

Total = 313
Advanced technologies improve perioperative pulmonary complications

- 444 patients who had surgery after Chemo Radiation Therapy (CRT)

- 3D (n=208, 1998-2008); IMRT (N=164, 2004-2011), and PBT (n=72, 2006-2011)

- Evaluated Pulmonary, GI, cardiac, wound healing within 30 days of surgery

- **Pulmonary complications** (ARDS, pleural effusion, RI, PNA) most predictive based on radiation type
  - IMRT vs 3D (OR 0.50, 95% CI 0.27-0.91)
  - PBT vs 3D (OR 0.32, 95%CI 0.14-0.73)
  - IMRT vs PBT (OR 1.56, 95%CI 0.68-3.60)

Pulmonary Complications

33.7% (69/205) 23% (41/178) 14% (7/50)

Wang J and Lin SH et al, IJROBP 2013
Value Proposition - Esophagus

Protons reduces hospital stay by > 2 days

Lin SH et al., ASTRO 2015
Protons one of the least costly options for ABPI

Additional costs of applicator placement by surgeon and prophylactic antibiotics not included

Strom, et al, IJROBP, 2014
Value Proposition - H&N

\[
\text{Value} = \frac{\sum \text{(Outcomes)}}{\sum \text{(Costs)}}
\]

Cumulative Cost of Care During Radiation Therapy

Equivalent at 21 Days

Protons just 6% more at end
IMRT loses 3x more body weight
Re-planning due to weight loss
Feeding tube

0 10 20 33

Number of patient treatments

Thaker N et al. Oncology Payers 2014
Levels of Evidence per Medical Policy

<table>
<thead>
<tr>
<th>Level of Evidence/Type of Study</th>
<th>PTCOG</th>
<th>Aetna</th>
<th>BCBS</th>
<th>UnitedHealthcare</th>
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</thead>
<tbody>
<tr>
<td>Level 1</td>
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<tr>
<td>Large multi-institutional prospective randomized clinical trials</td>
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<td>Level 2</td>
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<td>Single institution randomized controlled studies</td>
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<td>Well-conducted single arms studies</td>
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<td>Level 4</td>
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<td>Prospective registries</td>
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<td>Level 5</td>
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<td>Well-structured retrospective studies and systematic review of lower level evidence</td>
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<td>Level 6</td>
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<td>Population or claims-based studies, and smaller case-series</td>
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<td>Level 7</td>
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<td>Anecdotal patient case reports, dosimetric studies, mechanism-based</td>
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<td>Level 8</td>
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<td>Clinical reviews</td>
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The Future of Proton Therapy Development
Diversity & Complexity

Case
Complexity-
Nasopharynx (IMPT)

Case
Complexity-
Mesothelioma (IMPT)
MDACC’s Proton Therapy Development - Dose Response Evaluation with Advanced Imaging

Protons Stop where they should!

Image Courtesy of Anita Mahajan, MD
The Future of Proton Therapy Development

MDACC’s Proton Therapy Development-Dose Response Evaluation with Advanced Imaging
(Patient with Complete Response)

Image Courtesy of Clifton Fuller, MD, PhD & Abdallah S.R. Mohamed, MD, Msc.
The Upside!

* Newer technology is more compact, efficient, & IMPT development
* Gating, painting, redirection to minimize effects of motion
* Real-time tumor tracking
* Dual Energy (DE) to reduce uncertainties
* Advanced IGRT w/ DE CBCT
* Robust Optimization to reduce uncertainties & margins
* TPS Developments
* RBE plan optimization
* Image Response Analysis

Image Courtesy of Anita Mahajan, MD

Image Courtesy of Clifton Fuller, MD, PhD & Abdallah S.R. Mohamed, MD, Msc
Can Technology Achieve the Impossible?

Impossible = 100% Tumor Coverage
Impossible = 0% Normal Tissue Dose

FICIONAL/IMPOSSIBLE* DOSE?
— Yes, that’s the point!
— Impossible = Inarguable
— Impossible can remain constant.
— Impossible leaves “growing room.”
— Impossible allows inter-modality comparisons when a new one claims greatness.

* Kinda sorta

Courtesy of Ben Nelms, PhD
WHAT TREATMENT PLAN WOULD YOU SELECT? (MODALITY UNKNOWN)
• Rapid Technology Changes in Radiotherapy

• Radiotherapy goal is to reduce unnecessary radiation

• Proton Therapy was developed due to its superior dosimetry.

• The upside of Proton Therapy is promising but still have roadblocks for widespread adoption.

We must Define the Value and Role of Proton Therapy in Radiotherapy and use it as a tool when indicated.

US NEED:
1.6 million people will be diagnosed with cancer in 2012.

960,000 will receive radiation
60%

320,000 are candidates for proton therapy
20%

1,000 more treatment rooms are needed.

14 existing centers have limited capacity & long waits.

Image Courtesy of ProNova
Questions & Answers

A Pioneer in Proton Therapy

MD Anderson Proton Therapy Center