Proton beam therapy – re-review

Clinical Expert

Smith Apisarnthanarax, MD

Associate Professor of Radiation Oncology

Director of Clinical Research

Associate Residency Program Director, Proton Therapy Fellowship Director,

Department of Radiation Oncology

University of Washington, Seattle Cancer Care Alliance
### Applicant Information

- **Name:** Smith Apisarnthanarax
- **Address:** 1959 NE Pacific St., Box 356043
- **City:** Seattle
- **State:** WA
- **ZIP Code:** 98195

### Business Activities

(a) If you or a member of your household was *an officer or director of a business* during the immediately preceding calendar year and the current year to date, provide the following:

<table>
<thead>
<tr>
<th>Title</th>
<th>Business name and address</th>
<th>Business type</th>
</tr>
</thead>
</table>

(b) If you or a member of your household did business under an assumed business name during the immediately preceding calendar year or the current year to date, provide the following information:

<table>
<thead>
<tr>
<th>Business name</th>
<th>Business address</th>
<th>Business type</th>
</tr>
</thead>
</table>

### Honorarium

If you *received an honorarium of more than $100* during the immediately preceding calendar year and the current year to date, list all such honoraria.

<table>
<thead>
<tr>
<th>Received from</th>
<th>Organization address</th>
<th>Service performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medtronic</td>
<td>3555 Koger Blvd. Ste 200, Duluth, GA, 3</td>
<td>Consultant for fiducial markers</td>
</tr>
</tbody>
</table>

### Sources of Income

(a) Identify *income source(s) that contributed 10 percent or more of the combined total gross household income* received by you or a member of your household during the immediately preceding calendar year and the current year to date.

<table>
<thead>
<tr>
<th>Source name and address</th>
<th>Received by</th>
<th>Source type</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Washington</td>
<td>Myself</td>
<td>Salary</td>
</tr>
</tbody>
</table>
(b) Does any income source listed on the previous page relate to, or could it reasonably be expected to relate to, business that has, or may, come before the Committee?

☐ Yes  If “yes,” describe:
☐ No

(c) Does an income source listed on the previous page have a legislative or administrative interest in the business of the Committee?

☐ Yes  If “yes,” describe:
☐ No

4. Business shared with a lobbyist

If you or a member of your household shared a partnership, joint venture, or similar substantial economic relationship with a paid lobbyist, were employed by, or employed, a paid lobbyist during [----missing text----], please list the following:

(Owning stock in a publicly traded company in which the lobbyist also owns stock is not a relationship that requires disclosure.)

<table>
<thead>
<tr>
<th>Lobbyist name</th>
<th>Business name</th>
<th>Type business shared</th>
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</thead>
<tbody>
<tr>
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</tr>
</tbody>
</table>

Provide the information requested in items 5, 6, and 7 below only if:

(a) Your response involves an individual or business that you or a member of your household did business with, or reasonably could be expected to relate to do business that has or may come before the Health Technology Clinical Committee.

(b) The information requested involves an individual or business with a legislative or administrative interest in the Committee.

5. Income of more than $1,000

If you or a member of your household shared a partnership, joint venture, or similar substantial economic relationship with a paid lobbyist, were employed by, or employed, a paid lobbyist during [----missing text----], please list the following:

(Owning stock in a publicly traded company in which the lobbyist also owns stock is not a relationship that requires disclosure.)

<table>
<thead>
<tr>
<th>Income source</th>
<th>Address</th>
<th>Description of income source</th>
</tr>
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<tbody>
<tr>
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</tbody>
</table>
6. Business investments of more than $1,000
(Do not list the amount of the investment or include individual items held in a mutual fund or blind trust, a time or demand deposit in a financial institution, shares in a credit union, or the cash surrender value of life insurance.)
If you or a member of your household had a personal, beneficial interest or investment in a business during the immediate preceding calendar year of more than $1,000, list the following:

<table>
<thead>
<tr>
<th>Business name</th>
<th>Business address</th>
<th>Description of business</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
</tr>
</tbody>
</table>

7. Service fee of more than $1,000
(Do not list fees if you are prohibited from doing so by law or professional ethics.)
List each person for whom you performed a service for a fee of more than $1,000 in the immediate preceding calendar year or the current year to date.

<table>
<thead>
<tr>
<th>Name</th>
<th>Description of service</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>

I certify that I have read and understand this Conflict of Interest form and the information I have provided is true and correct as of this date.

Print name: Smith Apisarnthanarax

Check one:  □ Committee member  □ Subgroup member  □ Contractor

Signature  Date
02/26/2019
SMITH APISARNTHANARAX, MD
1959 NE Pacific St, Seattle, WA 98195 | apisarn@uw.edu | 425-505-7722

EDUCATION AND TRAINING

University of North Carolina, Chapel Hill, NC
Chief Resident, Department of Radiation Oncology
07/2007-06/2008
Resident, Department of Radiation Oncology
07/2005 – 06/2009

University of Texas M.D. Anderson Cancer Center, Houston, TX
Postdoctoral Research Fellow, Department of Experimental Radiation Oncology
K.S. Clifford Chao, M.D. laboratory
07/2003 – 06/2005

Evanston Hospital (NorthShore University Health System), Evanston, IL
Intern, Department of Medicine
06/2002 – 06/2003

Warren Alpert Medical School of Brown University, Providence, RI
M.D., Program in Liberal Medical Education
08/1998 – 05/2002

Brown University, Providence, RI
B.A., Psychology, Program in Liberal Medical Education

CURRENT POSITION

Associate Professor of Radiation Oncology
Clinical Research Director
Associate Residency Program Director
Proton Therapy Fellowship Director
University of Washington School of Medicine, Seattle, WA

ACADEMIC APPOINTMENTS

Associate Professor of Radiation Oncology
University of Washington School of Medicine, Seattle, WA
05/2013 – Present
Assistant Professor of Radiation Oncology
University of Pennsylvania Perelman School of Medicine, Philadelphia, PA
09/2009 – 04/2013

CERTIFICATION AND LICENSURE

American Board of Radiology, Radiation Oncology
2010 – Present

Washington State Medical License, 2013 – Active
Pennsylvania State Medical License, 2009 – Inactive
New Jersey State Medical License, 2009 – Inactive
North Carolina State Medical License, 2006 – Inactive

HONORS AND AWARDS

2nd place, “Proton Therapy: Advanced Applications for the Most Challenging Cases” Cureus publishing competition, 2017

University of Washington Radiation Oncology Residency Teacher Award, 2016

Association of Residents in Radiation Oncology (ARRO) Educator of the Year, 2011

Travel Grant Award, American Society of Therapeutic Radiology and Oncology (ASTRO) Translational Symposium, 2008

Roentgen Resident/Fellow Research Award, Radiological Society of North America (RSNA), 2008

Scholars in Training (SIT) Travel Award, Radiation Research Society (RRS), 2008

1st Place Clinical/Translational Poster, University of North Carolina Lineberger Comprehensive Cancer Center Annual Scientific Retreat, 2008


Travel Award, Best of American Society of Clinical Oncology (ASCO), 2007

Travel Award, International Society of Gastrointestinal Oncology (ISGIO), 2005

PROFESSIONAL MEMBERSHIPS/ACTIVITIES

American Society of Therapeutic Radiology and Oncology (ASTRO)

Abstract Reviewer, Gastrointestinal Track
2018 – Present

Full Member
2009 – Present
Journal Peer Reviewer
Hepatology, 2018 – Present
Journal of the National Comprehensive Cancer Network, 2018 – Present
Journal of Clinical Oncology, 2018 – Present
Physica Medica: European Journal of Medical Physics, 2017 – Present
Liver Transplantation, 2017 – Present
BMC Cancer, 2015 – Present
International Journal of Particle Therapy, 2015 – Present
American Journal of Clinical Oncology, 2015 – Present
Cancer, 2013 – Present
International Journal Radiation Oncology Biology Physics, 2009 – Present
Practical Radiation Oncology, 2009 – Present

EDITORIAL BOARDS
International Journal Radiation Oncology Biology Physics
Associate Editor, Gastrointestinal Section
2015 – Present

COMMITTEES
NATIONAL
ABR Radiation Oncology Online Assessment GI committee
2018 – Present

RSS Liver SRS/SBRT Accreditation Committee
2018 – Present

ACR/ASTRO Practice Parameter for the Performance of Proton Beam Radiation Therapy Committee
2017 – Present

College of American Pathologists (CAP) Committee
2013 – Present

INSTITUTIONAL
Clinical Research Oversight Committee
Fred Hutchinson/University of Washington Cancer Consortium
2014 – Present

Scientific Review Committee
Fred Hutchinson/University of Washington Cancer Consortium
2014 – 2017

Member, Data Safety Monitoring Committee
University of Pennsylvania/Abramson Cancer Center
2010 – 2013

**Patient Education Committee, Chairperson**
*University of Pennsylvania Radiation Oncology*
2011 – 2012

**Residency Education Committee**
*University of North Carolina Radiation Oncology*
2007 – 2008

**DEPARTMENTAL**
**Residency Clinical Competency Committee**
*University of Washington Radiation Oncology*
2014-Present

**Residency Education Committee**
*University of Pennsylvania Radiation Oncology*
2011 – 2013

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**CLINICAL TRIALS / ACTIVITIES**

- Functional Liver Imaging with Sulfur Colloid SPECT/CT in Primary and Metastatic Liver Cancer Patients Receiving Liver-Directed Treatment: A Pilot Study, PI
- RTOG 1112: Randomized Phase III Study of Sorafenib Versus Stereotactic Body Radiation Therapy Followed by Sorafenib in Hepatocellular Carcinoma, Institutional Site PI

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**EDUCATIONAL ACTIVITIES**

- **Preceptor, Cultural Competency and Awareness in the Doctor-Patient Relationship: Communication and Culture Course**
  *University of Pennsylvania Perelman School of Medicine*
  2010

- **Preceptor, Doctoring Course**
  *University of Pennsylvania Perelman School of Medicine*
  2011 – 2013

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**LECTURES**

“Notes, Notes, Notes: Tips of Making a Great Radiation Oncology Note,” University of Washington, Radiation Oncology, resident didactic lecture, 07/2017.
**GRANTS**

McCabe Pilot Award: Pilot Study of Imaging Proliferation with $^{18}$F-FLT to Assess Early Treatment Response to Chemoradiotherapy in Locally Advanced Rectal Cancer, McCabe Advisory Committee, (Smith Apisarnthanarax, PI: Daniel Pryma, Co-Investigator), $34,548/annual direct costs, 1% effort (Role in grant: PI)


**PUBLICATIONS**

**PEER REVIEWED**


19. Gandhi SJ, Liang X, Ding X, Zhu TC, Ben-Josef E, Plastaras JP, Metz JM, Both S, Apisarnthanarax S. Clinical decision tool for optimal delivery of liver stereotactic


NON-PEER REVIEWED


BOOKS

**BOOK CHAPTERS**


**ABSTRACTS/ POSTER PRESENTATIONS**


patients receiving definitive radiation therapy. 2011 ASCO Annual Meeting and ASTRO 53rd Annual Meeting 2011, poster presentation.


**INTERNATIONAL MEETINGS**


**NATIONAL MEETINGS**


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INVITED PRESENTATIONS

INTERNATIONAL

1. "PET/CT Imaging in Radiation Oncology: Improving Oncologic Care," Ramathibodhi Hospital, Bangkok, Thailand, 03/2012.

2. "Advanced Radiation Therapy in GI Cancers: From Photons to Protons," Thai Society of Therapeutic Radiology and Oncology (THASTRO), Pattaya, Thailand, 03/2012.


NATIONAL


2. "Emergencies in Radiation Oncology," Thai Physicians Association of America (TPAA), Dallas/Fort Worth, TX, 09/2012.


6. “Clinical Decision: Photons or Protons?” Clinical Liver Focus Group, Miami Cancer Institute, Miami, FL, 01/2018.


REGIONAL


LOCAL


OTHER SCHOLARLY ACTIVITIES


PROFESSIONAL COMMUNITY ACTIVITIES

Proton Beam Therapy

Adoption: July 11, 2014

Number and Coverage Topic:
20140516A – Proton Beam Therapy

HTCC Coverage Determination:
Proton Beam Therapy is a covered benefit with conditions consistent with the criteria identified in the reimbursement determination.

HTCC Reimbursement Determination:
- Limitations of Coverage
  - Proton Beam Therapy is a covered benefit with conditions for:
    - Ocular cancers
    - Pediatric cancers (e.g., medulloblastoma, retinoblastoma, Ewing’s sarcoma)
    - Central nervous system tumors
    - Other non-metastatic cancers with the following conditions:
      - Patient has had prior radiation in the expected treatment field with contraindication to all other forms of therapy, and
      - At agency discretion.
- Non-Covered Indicators
  - Proton Beam Therapy is not covered for all other conditions.
Re-review

Proton Beam Therapy

Original Proton Beam Therapy (PBT) determination: July 2014

Basis for re-review: Newly available published evidence.

- Adults and pediatrics
- 189 new studies (137 adult/53 pediatric) met inclusion criteria
- Quality of comparable studies marginally better
- Table A provides the best summary

Ionizing Radiation Treatment

- 3D-conformal RT (3DRT)
  Delivers radiation to a 3d volume using imaging studies and software to precisely target RT delivery

- Intensity Modulated RT (IMRT)
  Delivers a non-uniform beam to the target by changing the intensity of the beam

- Proton beam therapy (PBT)
  Uses a beam of protons to irradiate diseased tissue
Key Questions #1 and #2

1. What is the comparative impact of PBT with curative intent on:
   a) Survival;
   b) Disease progression;
   c) Health-related quality of life; and
   d) Other patient outcomes?

2. What is the comparative impact of salvage treatment on:
   a) Survival;
   b) Disease progression;
   c) Health-related quality of life; and
   d) Other patient outcomes?
Key Questions #3

3. What are the comparative harms associated with the use of PBT:
   a) Relative to its major alternatives, including acute (i.e., within the first 90 days after treatment) and late (>90 days) toxicities;
   b) Systemic effects such as fatigue and erythema;
   c) Toxicities specific to each cancer type; and
   d) Risks of secondary malignancy, and radiation dose?

Key Questions #4 and #5

4. What is the differential effectiveness and safety of PBT according to factors such as:
   - Age
   - Disability
   - Treatment protocols
   - Race/ethnicity
   - Sex
   - Comorbidities
   - Tumor characteristics

5. What is the comparative cost-effectiveness of PBT in the short- and long-term?
Proton Beam Therapy Concerns

Agency Medical Directors

**SAFETY** = Medium

**Efficacy** = High

**Cost** = High

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Proton Beam Therapy Diagnosis Codes

Range of diagnosis codes utilized for claims analysis*

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>ICD-10 Description/ICD-9 Description</th>
<th>ICD-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>C00-C14</td>
<td>Malignant Neoplasm of Lip, Oral cavity, and Pharynx</td>
<td>140-149</td>
</tr>
<tr>
<td>C15-C26</td>
<td>Malignant Neoplasm of Digestive Organs</td>
<td>150-159</td>
</tr>
<tr>
<td>C30-C39</td>
<td>Malignant Neoplasm of Respiratory and Intrathoracic</td>
<td>160-165</td>
</tr>
<tr>
<td>C40-C41</td>
<td>Malignant Neoplasm of Bone and Articular Cartilage</td>
<td>170-176</td>
</tr>
<tr>
<td>C43-C44</td>
<td>Malignant Neoplasm of Skin</td>
<td>170-176</td>
</tr>
<tr>
<td>C45-C49</td>
<td>Malignant Neoplasm of Mesothelial and Soft Tissue</td>
<td>170-176</td>
</tr>
<tr>
<td>C50</td>
<td>Malignant Neoplasm of Breast</td>
<td>170-176</td>
</tr>
<tr>
<td>C51-C63</td>
<td>Malignant Neoplasm of Genital organs</td>
<td>179-189</td>
</tr>
<tr>
<td>C64-C68</td>
<td>Malignant Neoplasm of Urinary Tract</td>
<td>190</td>
</tr>
<tr>
<td>C69-C72</td>
<td>Malignant Neoplasm of Eye, Brain, CNS</td>
<td>191-192</td>
</tr>
<tr>
<td>C73-C75</td>
<td>Malignant Neoplasm of Endocrine</td>
<td>194</td>
</tr>
<tr>
<td>C76-C80</td>
<td>Malignant Neoplasm Ill Defined, Secondary (and Other)</td>
<td>195</td>
</tr>
<tr>
<td>C81-C96</td>
<td>Malignant Neoplasm of Lymphoid</td>
<td>196, 200-208</td>
</tr>
<tr>
<td>D37-D48, D49</td>
<td>Neoplasm uncertain or unspecified behavior</td>
<td>235-239</td>
</tr>
<tr>
<td>D10-D36, D3A</td>
<td>Benign tumors</td>
<td>210-229</td>
</tr>
</tbody>
</table>

*1) Not all diagnosis codes were represented in the data.
2) Utilization and cost analyses contain V and/or Z codes when substituted for a primary diagnosis.
### Proton Beam Therapy

#### Procedure Codes

<table>
<thead>
<tr>
<th>CPT</th>
<th>Procedure Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>77520</td>
<td>Proton treatment delivery; simple, without compensation</td>
</tr>
<tr>
<td>77522</td>
<td>Proton treatment delivery; simple, with compensation</td>
</tr>
<tr>
<td>77523</td>
<td>Proton treatment delivery; intermediate</td>
</tr>
<tr>
<td>77525</td>
<td>Proton treatment delivery; complex</td>
</tr>
</tbody>
</table>

#### 2013 – 2017

**Proton Beam Therapy**

**Sessions and Total Treatment Paid Dollars (Pd$)**

N = 63; 70% Medicare/UMP

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Avg Number of Sessions</td>
<td>31</td>
<td>23</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Avg Pd$/Session</td>
<td>$4,648</td>
<td>$4,683</td>
<td>$2,365</td>
<td>$2,474</td>
</tr>
<tr>
<td>Avg Pd$ Total Treatment</td>
<td>$144,095</td>
<td>$107,717</td>
<td>$44,997</td>
<td>$53,520</td>
</tr>
</tbody>
</table>

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<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>Avg Number of Sessions</td>
<td>30</td>
<td>30</td>
<td>27</td>
<td>39</td>
</tr>
<tr>
<td>Avg Pd$/Session as Secondary Payer</td>
<td>$235</td>
<td>$227</td>
<td>$225</td>
<td>$220</td>
</tr>
<tr>
<td>Avg Pd$ Total Treatment as Secondary Payer</td>
<td>$9,112</td>
<td>$6,131</td>
<td>$6,553</td>
<td>$6,409</td>
</tr>
</tbody>
</table>
2013 – 2017
Proton Beam Therapy
Sessions and Total Treatment Paid Dollars (Pd$)¹
Total Treatment includes all services incurred on day of Proton Beam Treatment Session
N = 183

<table>
<thead>
<tr>
<th>MEDICAID MCO/FFS</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avg Number of Sessions</td>
<td>27</td>
<td>23</td>
<td>23</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Avg Pd$²/Session</td>
<td>$1,698</td>
<td>$598</td>
<td>$655</td>
<td>$667</td>
<td>$654</td>
</tr>
<tr>
<td>Avg Pd$² Total Treatment</td>
<td>$56,087</td>
<td>$18,697</td>
<td>$18,281</td>
<td>$18,543</td>
<td>$21,019</td>
</tr>
</tbody>
</table>

¹ Average Pd$ calculated using Line_Paid_Amt field. If Line_Paid_Amt was $0, and Allow_Amt was >$0, MCO_Reported_Paid_Amount was used.
Proton Beam Therapy

Current State Agency Policies

Covered with Conditions
per HTCC Determination

- PEBB/UMP
- Medicaid Managed Care and Fee-for-Service
- Labor and Industries

Proton Beam Therapy Other Payers

Aetna: (last reviewed 05.09.2018)
1. Chordomas or chondrosarcomas
2. Malignancies in children (21 years of age and younger)
3. Uveal melanomas confined to the globe

United Healthcare: (last reviewed 01.01.2019)
1. Intracranial arteriovenous malformations (AVMs)
2. Ocular tumors, including intraocular/uveal melanoma
3. Skull-based tumors
4. Localized, unresectable hepatocellular carcinoma with conditions
5. PBT may be covered for a diagnosis that is not listed above as proven, including recurrences or metastases in selected cases with conditions
**Proton Beam Therapy Other Payers**

**Cigna:** (last reviewed 01-17-2019)
1. Chordomas and chondrosarcomas of the base of the skull, localized and in the postoperative setting
2. Uveal melanoma, when PBT is considered preferential compared to brachytherapy
3. Select cases of localized unresectable hepatocellular carcinoma
4. Stage IIA seminoma
5. Malignancies in children (age less than 18 years)

**Medicare:** (last reviewed 9-2017)
1. Had NCD in 2015, later retired
   - Target volume close to critical structure, avoid a "hotspot", previous irradiation to avoid exceeding cumulative dose
2. Included ocular tumor, skull base, CNS, primary HCC, pediatric CNS and head and neck
3. Coverage considered investigational in other areas

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**Guidelines**

**National Comprehensive Cancer Network**
- May be appropriate for bone, CNS, head and neck, liver, lung, lymphoma, ocular, sarcoma, thymoma
- Not Recommended for prostate

**AIM Specialty Network**
- Recommend for CNS, ocular, pediatric
- Not Recommended for breast, esophageal, GI, pancreatic, gyn, head and neck, liver, lung, lymphoma, prostate

**American College of Radiology**
- Recommend for head and neck, may be appropriate for lymphoma and prostate
- Not Recommended for bone, gyn, lung

**National Institute for Health and Care Excellence (NICE)**
- Recommend brain, spinal, paraspinal and pediatric
Proton Beam Therapy

**Adult Summary**

Similar conclusions or no new data:

- Bladder
- Bone
- Breast
- GI
- GYN
- Head and neck
- Lung
- Lymphoma
- Mixed/various/other
- Prostate
- Sarcoma
- Seminoma
- Thymoma
- Arteriovenous malformations
- Hemangiomas
- Pituitary adenomas
- Prostate

**Brain/spinal**

- Larger studies, benefits and harms are similar

**Esophageal**

- Increased OS after one year and PFS better
- More GI events but rest of adverse effects lower esp. pulmonary

**Liver**

- OS, PFS and local control similar compared to TACE
- Fewer hospitalizations for complications
- *ongoing RCT this is early data

**Ocular**

- 5 year OS lower with PBT but fewer local recurrence over 10 years
- One study visual acuity worse and one better with PBT
Proton Beam Therapy

**Adult Recommendation**

Cover with conditions if:
- Esophageal
- Liver
- Brain
- Ocular

• Non-coverage all other

---

Proton Beam Therapy

**Pediatric Summary**

Similar conclusions with very few new studies:
- Bone
- Head/neck
- Ocular
- Lymphoma
- Rhabdomyosarcoma
- Mixed/various
Proton Beam Therapy

Pediatric Summary

Brain
- Incremental benefit in terms of decreased harms (hypothyroidism)
- Overall survival and tumor recurrence similar maybe slight trend towards favoring PBT

Salvage in ocular tumors and salivary tumors
- Small comparative study of each, insufficient
- Less grade 2 or 3 mucositis trend

Pediatric Recommendation

- Cover with conditions if:
  - Central nervous system
  - Non-coverage all other

OR

- Cover all pediatric cancers
Questions?

More Information:
www.hca.wa.gov/about-hca/health-technology-assessment/proton-beam-therapy
### Scheduled presentations:

**Proton Beam Therapy – re-review**

<table>
<thead>
<tr>
<th></th>
<th>Name</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Andrew L. Chang, MD</td>
<td>National Association for Proton Therapy</td>
</tr>
<tr>
<td>2</td>
<td>William F. Hartsell, MD</td>
<td>National Association for Proton Therapy</td>
</tr>
<tr>
<td>3</td>
<td>Sameer Keole, MD</td>
<td>National Association for Proton Therapy</td>
</tr>
<tr>
<td>4</td>
<td>Steven Frank, MD</td>
<td>National Association for Proton Therapy</td>
</tr>
<tr>
<td>5</td>
<td>Ramesh Renan, MD</td>
<td>Seattle Cancer Care Alliance</td>
</tr>
<tr>
<td>6</td>
<td>Ralph Emoian, MD</td>
<td>Seattle Cancer Care Alliance</td>
</tr>
<tr>
<td>7</td>
<td>Charles Bloch, MD</td>
<td>Seattle Cancer Care Alliance</td>
</tr>
<tr>
<td>8</td>
<td>Jing Zeng, MD</td>
<td>Seattle Cancer Care Alliance</td>
</tr>
<tr>
<td>9</td>
<td>Annika Andrews</td>
<td>Seattle Cancer Care Alliance</td>
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(Order subject to change.)
Disclosure

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If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:
I am the owner and President of Proton Doctors Professional Corporation, which employs physicians who treat patients with Proton Therapy.

Travel is being paid for by the Seattle Cancer Care Alliance, who are the operators of the proton center in Seattle.

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If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may attach additional sheets explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

2019 Apr 26 Andrew Chang

So we may contact you regarding your presentation, please provide the following:
Disclosure

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If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

Varian, Elekta, Eli Lilly, Cy Immunix, Hitachi, Grants - Honors, Board Membership, Advisory, Consultant, Ownership. No relationship with NCCN.

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If yes to #7, provide name and funding Sources:

Travel funding Seattle Cancer Care Alliance (SCCA).

If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may attach additional sheets explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

Date: 4/26/19
Print Name: [Redacted]

So we may contact you regarding your presentation, please provide the following:

Email Address: [Redacted]
Phone Number: [Redacted]
Disclosure

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Board Member - American Society for Radiation Oncology; Board Member and Chair
Proton Collaborative Group (co-operative research group); Travel Funding - SCCA

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__________________________________________________________________________

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I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

William F. Hartsell, MD

Signature: William F. Hartsell, MD

Date: 4/25/19

Print Name: William F. Hartsell, MD

So we may contact you regarding your presentation, please provide the following:

Email Address: _______________________

Phone Number: _______________________

conflict_of_interest_121814-FINAL.docx
## Disclosure

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If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

**SCCA is paying travel expenses for this meeting**

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I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

**Sameer Keole**

_Contact Information:_

Email Address: keole.sameer@mayo.edu

Phone Number: [redacted]
### Disclosure

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If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

I serve as Medical Director of the SCCA proton Center. I do not derive any salary directly from the center, but receive an administrative stipend from the University of Washington.

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If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may attach additional sheets explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

Signature: ____________________________ Date: 4/25/19

Print Name: Ralph Erminger

So we may contact you regarding your presentation, please provide the following:

Email Address: ralph@uw.edu

Phone Number: ____________________________
Explanation of relationship with SCCA Proton Therapy:

There could be a perception that because part of my practice is at SCCA Proton Therapy I would have a conflict of interest. I do not believe this is the case for the following reasons:

1. I am employed by the University of Washington which is a separate entity from SCCA Proton Therapy.
2. My employer is contracted to provide physician services to SCCA Proton Therapy, but SCCA Proton Therapy does not underwrite my salary.
3. The vast majority of my renumeration is from salary.
4. The small portion of my renumeration related to the patients I treat is largely independent of whether I treat them at SCCA Proton Therapy or other sites of practice. (If there are subtle differences, I am not aware of them.)
5. My employer (University of Washington) does not set goals for how many patients I treat at SCCA Proton Therapy.
6. I do not receive grants or other financial assistance from SCCA Proton Therapy.

Ralph Ermoian, MD
Associate Professor of Radiation Oncology
University of Washington
Disclosure

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If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

I am an employee of the University of Washington School of Medicine and providing clinical services at the SCCA Proton Therapy Facility

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If yes to #7, provide name and funding Sources:

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I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

Charles Bloch
4/23/19

Email Address: cdbloch@uw.edu

Phone Number: 206-306-2834
Disclosure
Any unmarked topic will be considered a “Yes”

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I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

Jing Zeng
Date: 4/21/2019
Print Name

So we may contact you regarding your presentation, please provide the following:

Email Address: jzeng13@uw.edu
Phone Number: 206-598-4110
Disclosure
Any unmarked topic will be considered a "Yes"

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If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

I am the President & CEO of the SCSA Proton Therapy Center. I am a board member of the same. The company reimburses work related travel expenses.

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If yes to #7, provide name and funding Sources:

see above - paid executive of SCSA Proton Therapy Center.

If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may attach additional sheets explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X [Signature] 4-26-19 [Print Name]

So we may contact you regarding your presentation, please provide the following:

Email Address: annika.andrews@seattleprotons.org
Phone Number: [Redacted]
Disclosure
Any unmarked topic will be considered a "Yes"

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Signature: ___________________________ Date: 4/25/2019
Print Name: BAO-NGOC NGUYEN

So we may contact you regarding your presentation, please provide the following:

Email Address: bao-ngoc.nguyen@seattleprotons.org
Phone Number: ___________________________
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If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

Employed at Seattle Cancer Care Alliance Proton Therapy Center

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I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

[Signatures]

25 April 2019

Print Name

So we may contact you regarding your presentation, please provide the following:

Email Address: Jason.Dixon@seattleprotons.org

Phone Number: [Redacted]
Disclosure

Any unmarked topic will be considered a "Yes"

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N/A

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If yes to #7, provide name and funding Sources:

employee of Seattle Proton Center LLC (dba SSA Proton Therapy Center)

If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may attach additional sheets explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

[Signature] 4/28/2014 [Print Name]  [Date]

So we may contact you regarding your presentation, please provide the following:

Email Address: Kimberly.m.dansie@seattleprotons.org

Phone Number: [Redacted]

conflict_of_interest_121814-FINAL.docx
## Disclosure

Any unmarked topic will be considered a "Yes"

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- Seattle Cancer Care Alliance Proton Therapy Center

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[Signature] 4/25/2019 [Print Name]

So we may contact you regarding your presentation, please provide the following:

Email Address: [redacted]

Phone Number: [redacted]
**Disclosure**

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Seattle Cancer Care Alliance, Proton Therapy Center

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Signature: [Redacted]  Date: 4/28/19  Print Name: [Redacted]

So we may contact you regarding your presentation, please provide the following:

Email Address: Meredith.carrels@seattleprotons.org

Phone Number: [Redacted]
### Disclosure

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X  

Lindsay Knapp  

Date: 4/26/19  

So we may contact you regarding your presentation, please provide the following:

Email Address: Lindsay.Knapp@seattleprotons.org

Phone Number: [Redacted]
Disclosure

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X

Signature

4/25/19

Date

Amy Walgamott

Print Name

So we may contact you regarding your presentation, please provide the following:

Email Address: amy.walgamott@seattleprotons.org

Phone Number: [Redacted]
History of Proton Radiation Therapy

Andrew L. Chang, MD
President, PDPC
AndrewLChangMD@gmail.com

History of Radiation

- First x-ray image by Wilhelm Roentgen
  - Submitted for publication Dec 28, 1895
  - Published Jan 5, 1896 “On A New Kind Of Rays”
    - *Nature* 53 pg 274-276
  - Winning first Nobel Prize for Physics 1901

“I have seen my death” – Bertha Roentgen
History of Radiation Oncology

- 1896: Radioactivity discovered by Becquerel in uranium compounds;
- 1898: Discovery of radioactivity in radium and polonium by Marie and Pierre Curie.
  - Becquerel, Curie, and Curie win 1903 Nobel Prize in physics
- 1952: Discovery of DNA structure

History of Proton Therapy

- 1904: William Bragg describes the Bragg peak (wins Nobel Prize in Physics 1915)
- 1930: Ernest Lawrence’s “proton merry-go-round” – the first cyclotron (800 KeV) (for which he wins the Nobel Prize in 1939)
- 1954: First medical use – UC Berkeley
- 1961: Routine practice at Harvard, LBL
- 1989: FDA approved device for proton therapy
Proton Therapy is NOT Experimental

- Over 150,000 patients worldwide have been treated with proton therapy
- First patient treatments with proton therapy occurred in 1954
- Neither of the two largest medical regulatory bodies in the United States consider proton therapy experimental for the treatment of cancer
  - FDA approved first device in 1989
  - Medicare pays for proton therapy in the treatment of cancer
- No oncologists consider proton therapy experimental for the treatment of cancer

Pediatric Proton Therapy: Patterns of Care across the United States

Andrew L. Chang, MD; Toruun I. Yock, MD; Anita Mahajan, MD; Christine Hill-Kaiser, MD; Sameer Keole, MD; Lilia Loredo, MD; Oren Cahlon, MD; Kevin P. McMullen, MD; William Hartsell, MD; and Daniel J. Indelicato, MD

- All operating US proton facilities in 2010, 2011, 2012, & 2013 were sequentially surveyed.
- In 2013, 722 children and adolescents (14 – 157) treated with proton therapy in 11 US centers
  - In 2012, 694 pediatric patients (6 – 140)
  - In 2011, 613 pediatric patients (4 – 124)
  - In 2010, 465 pediatric patients (1 – 111)
- In PTCOG Survey of 2014, 989 pediatric patients treated
- In 2013, 22% of pediatric patients treated at US proton therapy centers were from outside the United States (range 4.0% – 51.1%), and in 2012: 19% (0% - 60.8%)
10 y/o F w/ M0 medulloblastoma

Conventional Craniospinal

CSI to TD 23.4 Gy

Proton Craniospinal

IMRT and proton therapy in a patient with Ewing’s sarcoma

Two 16 year old patients with paraspinal Ewing tumor

Source: Sameer Keole, MD “Protons (P+): Why They Make Sense”
Ewing’s sarcoma follow-up

IMRT

Nearly Identical Location and Tumor Size

Protons

At Diagnosis

18 Months, 12 month follow-up

Kidney

Source: Sameer Keole, MD “Protons (P+) Why They Make Sense”

Proton therapy is a preferred treatment in many adult and pediatric cancers, and is a highly effective treatment for tumors in the head, brain, neck, lung and prostate.”

“Proton therapy is a preferred treatment in many adult and pediatric cancers, and is a highly effective treatment for tumors in the head, brain, neck, lung and prostate.”
‘The Cause of My Life’
Inside the fight for universal health care.
Published July 18, 2009 by Edward M. Kennedy

In 1964, I was flying with several companions to the Massachusetts Democratic Convention when our small plane crashed and burned short of the runway. My friend and colleague in the Senate, Birch Bayh, risked his life to pull me from the wreckage. Our pilot, Edwin Zimny, and my administrative assistant, Ed Moss, didn’t survive. With crushed vertebrae, broken ribs, and a collapsed lung, I spent months in New England Baptist Hospital in Boston. To prevent paralysis, I was strapped into a special bed that immobilizes a patient between two canvas slings. Nurses would regularly turn me over so my lungs didn’t fill with fluid. I knew the care was expensive, but I didn’t have to worry about that. I needed the care and I got it.

Now I face another medical challenge. Last year, I was diagnosed with a malignant brain tumor. Surgeons at Duke University Medical Center removed part of the tumor, and I had proton-beam radiation at Massachusetts General Hospital. I’ve undergone many rounds of chemotherapy and continue to receive treatment. Again, I have enjoyed the best medical care money (and a good insurance policy) can buy.

But quality care shouldn’t depend on your financial resources, or the type of job you have, or the medical condition you face. Every American should be able to get the same treatment that U.S. senators are entitled to.

This is the cause of my life.

“...I had proton beam radiation at Massachusetts General Hospital...I have enjoyed the best medical care money (and a good insurance policy) can buy...Every American should be able to get the same treatment that U.S. Senators are entitled to”

United States District Court
Southern District of Florida

“It is undisputed among legitimate medical experts that proton radiation therapy is not experimental... To deny a patient this treatment, if it is available, is immoral and barbaric.”
Thank you
Proton Beam Radiation for Oropharyngeal Cancer

Steven J. Frank, MD
Professor and Deputy Head, Radiation Oncology
Executive Director, UT Particle Therapy Institute

DISCLOSURES

- NCI U19 IMPT vs IMRT Oropharynx
- Honoria or Grants from ELEKTA, NIH/NCI, Varian, Hitachi, Eli Lilly
- Varian Advisory Board/Consultant
- Founder and Director C4 Imaging
Define the Value of Proton Therapy

\[ \text{Value} = \frac{\Sigma \text{(Outcomes)}}{\Sigma \text{(Costs)}} \]
Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer


- 72 Gy in 42 fx in 6 wks
- 70 Gy in 35 fx in 7 wks
- CDDP 100 mg/m2 q3w

Conclusion: HPV status is an independent prognostic factor for Overall survival and Progression-free Survival for patients with OPSCC

Ang KK et al. NEJM 2010
Conclusion: Classification of patients into risk of death categories; low risk, intermediate risk, high risk

Ang KK et al. NEJM 2010

The Peak of Intensification for Oropharyngeal Tumors

Randomized Phase III Trial of Concurrent Accelerated Radiation Plus Cisplatin With or Without Cetuximab for Stage III to IV Head and Neck Carcinoma: RTOG 0522


- OPC (70%), Larynx (22.6%), Hypopharynx (7.4%)
- Radiation Therapy: 72/42 fx (3DRT or 70/35 in 6 wks (IMRT)
- CDDP: 100 mg/m2 q3w
- Cetuximab: 400mg/m2 and 250 mg/m2 weekly
Conclusion: Adding Cetuximab to Radiation-Cisplatin did not improve outcomes

MD Anderson | RTOG 0522

Conclusion: p16+ patients had better OS, PFS and less LF and DM (treatment interruption in 26.9% of patients)
**RTOG-0522 (n=425)**  
Phase III IMRT/CDDP +/- Cetuximab

- PEG use at 6 months 34.6%  
  - Patients with recurrence at 1 year excluded  
  - PEG use at 6 months 41% (not excluded)

- Overall Survival by PEG use at 6 months  
  - HR (Y/N) 2.62 [1.33- 5.16] (p < 0.004)

- FACT-HN Functional Well Being  
  - Mean 1.5 vs. -0.5 (p < 0.012)

---

**RTOG 0522 – Toxicity Arm A:**  
IMRT + Cisplatin

**Feeding tube dependency:**  
1 yr: 21.2%  
2 yr: 13.5%  
3 yr: 12.1%

Ang et al. *JCO* 2014; 32(27)
RTOG 0522 – p16+ OPC

Disease outcomes at 3 yrs:

Progression-free survival (PFS): 72.8%
Overall survival (OS): 85.6%

Local regional failure (LRF): 17.3%
Distant Metastasis (DM): 6.5%

Ang et al. JCO 2014; 32(27)

Feeding tube, PRO and survival in RTOG studies

Feeding tube rates in RT-cisplatin treated patients

RTOG 0522 (n=568):

6 months following RT start (4 months post RT): 40.7%

RTOG 1016 (n=384):

End of treatment: 51.6%; 4 months post RT: 27.7%

Feeding tube, survival and quality of life in RTOG 0522

unpublished NRG analysis in patients without a recurrence/progressive disease in their first year on study.

patients with a feeding tube at 6 months vs. those without are associated with an increased hazard of death (univariate analysis; multivariate pending)

patients without feeding tubes experienced an improvement in functional well-being while those with a feeding tube did not (p=0.012).

Formal NRG request for full ancillary study ongoing
SEER/MEDICARE
PEG Tubes and Survival

SEER/Medicare analysis on the relationship between feeding tube and survival

N=3183 pts aged 65-80, any HN site with complete information, excluding stage I-II larynx

Multivariate analysis (cox model, or competing risk) adjusted on age, race, comorbidity, tumor stage, tumor site, type of RT, performance of surgery, use of chemotherapy and placement of feeding tube during treatment

Feeding tube 6 months post RT predicts dependency in the long term

Source: Blanchard and Frank Unpublished

PEG Tube Dependency Correlates with Worse Survival

SEER/MEDICARE Database – PEG Dependency 6m
- 47% increase risk of death
- 56% increase risk of death related to cancer
  (note: statistical association is unchanged when patients die within 12 and within 24 months post-treatment)

<table>
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<th>Competing risks survival</th>
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<tr>
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<td>Overall</td>
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<td></td>
<td>HR</td>
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<tr>
<td>On tube 8 months since RT start</td>
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<tr>
<td>Yes vs. No</td>
<td>1.47</td>
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Source: Blanchard and Frank Unpublished
De-Intensification Strategies with Radiation Therapy

Primary Intention:
- Reduce radiation dose to normal tissues

Secondary Intention:
- Reduce radiation dose to tumor thereby reducing dose to normal tissues

Optimizing Cure + Quality of Life
Reduce Radiation Dose to Normal Tissue Structures

NRG
Photons
NRG - HN002 (Phase II)
Mayo
UNC
Reduce Dose to Tumor
Reduce Dose to Normal Tissues

MDA
Protons/Photons
IMPT CRT (Phase III)
IMPT unilateral (Fit Bit)
SOAR (Recurrent)
MR-Linac (Phase II)
Reduce Dose to Normal Tissues

MDA RO PI’s: Frank, Gunn, Phan, Fuller
Optimizing Cure + Quality of Life

Future trials

MDA
Protons

Dose Optimization to Tumor

Reduce Dose to Normal Tissues

• TORS
• IO

The Value of Proton Therapy
‘Tumor - Better Radiation Drug’

Relative Biological Effectiveness (RBEs) variations of protons in HN cancer cell lines [HPV +/-]

Effect of HPV status on the response of HNSCC cell lines by photons or protons

More unrepaired DNA double strand breaks caused by proton beams versus X-ray (4Gy, at 24 hours after irradiation)

More cell senescence and mitotic catastrophe caused by proton beams versus X-ray (4 Gy irradiation)
Different protein expression profile caused by proton beams versus X-ray
(after 4 Gy, accessed by reverse-phase protein array assays)

UMSCC-47 cells in panel A, B, C and HNS cells in panel D, E, F
SCC-152 cells in panel A, B, C and SqCC/Y1 cells in panel D, E, F

Difference of DNA damage repair related proteins caused by proton beams versus X-ray
(at 4 hours after 4 Gy irradiation)

Wang L & Frank SJ (AACR-AHNS 2017)
The Value of Proton Therapy

‘Normal Tissue: Eliminates unnecessary radiation’


Would we agree to receive 25 Gy to a large fraction of our brain or abdomen in exchange for some thousand of dollars, with no known credibly hypothesized medical benefit?

Once protons is clinically available, is the burden of proof on conventional x-ray therapy?
How many extra intra-oral x-ray equivalents is IMRT over IMPT?

Anterior Oral Mucositis

Side effect of 25 Gy

<table>
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<td>50% reduction in feeding tubes</td>
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Frank SJ et al. *IJROBP* 2014
How many intra-oral x-rays is 25 Gy?

5
50
500
5000
5,000,000

1 Gy – 1 Sv
Each Intra oral x-ray is 0.002 mSv
200,000 intra-oral x-ray per 1 Gy

http://www.radiologyinfo.org/en/safety/?pg=sfty_xray
Why Proton Therapy?

*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)
- +83% Additional Cancer Risk* (2,500 CTs, 65 yo)


IMRT for Oropharyngeal Carcinoma-Beam Path Toxicities

Beam path toxicities seen with IMRT including AOC mucositis.

Less out-of-field mucositis seen with IMPT.


April 10, 2013
Patient with HPV+ BOT SCC after 66 of 66 Gy(RBE) IMPT
Proton Therapy for Oropharyngeal Tumors
50% reduction in feeding tubes

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

IMPT - Oropharyngeal Tumors

3/2011 – 7/2014, MD Anderson Cancer Center
50 consecutive oropharynx patients
IMPT (46 – MFO, 4 – SFO)
84% male, 16% female
50% never smokers
98% Stage III-IV
64% concurrent CRT
98% evaluable p16+

**IMPT**

**Oropharyngeal Tumors**

Median follow-up – 29 months

No CTC-AE Grade 4/5 toxicities

11 pts had gastrostomy tube during treatment

0 patient had gastrostomy tube at last follow-up

5 pts had disease recurrence

  - 1 local, 1 LR, 2 regional, 1 distant

2-yr actuarial OS (94.5%) and PFS (88.6%)


**Potential Benefit for OPC**

**Dosimetric Advantages**

1st 25 patients treated w/ IMPT for OPC

Matched with 25 patients treated w/ IMRT

<table>
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<tr>
<th>Structures</th>
<th>IMPT Mean± SD(cGy)</th>
<th>IMRT Mean± SD(cGy)</th>
<th>P value</th>
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<td>AOC-mean</td>
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<td>3047±789</td>
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<tr>
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<td>4054±1530</td>
<td>5060±804</td>
<td>0.0001</td>
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<tr>
<td>BOT-mean</td>
<td>3896±1692</td>
<td>5145±1012</td>
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<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>

Source: Holliday and Frank et al., Medical Dosimetry 2016
### Potential Benefit for OPC- Dosimetric Advantages

<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>RV-mean</td>
<td>738±407</td>
<td>1179±682</td>
<td>0.0134</td>
</tr>
</tbody>
</table>

Source: Medical Dosimetry 2016

---

### Potential Benefit for OPC- Dosimetric Advantages

<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>
</table>

Source: Medical Dosimetry 2016
IMPT Benefit for OPC-Toxicity Reduction

The 25 pts treated with IMPT for OPC matched with 25 pts treated with IMRT

<table>
<thead>
<tr>
<th></th>
<th>IMPT (N = 25) No. (%)</th>
<th>Matched IMRT (N = 25) No. (%)</th>
<th>Entire IMRT Cohort (N = 998) No. (%)</th>
<th>p-value (IMPT v. Matched IMRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeding Tube Incidence</td>
<td>5 (20%)</td>
<td>12 (48%)</td>
<td>475 (48%)</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Feeding tube duration was similar: 4.2 (2.6-11.6) mo IMPT and 4.7 (1.4-20) mo IMRT

Source: Frank et al ASTRO 2013

IMPT Benefit for OPC-Toxicity Reduction

25 IMPT patients evaluated by a speech pathologist prior to (77%) and after (100%) treatment

Table: Acute toxicities

- Dysphagia per SLP: 2 (8%)
- Abnormal MBS: 1 (4%)
- Aspiration (per MBS): 0 (0%)
- Stricture (per MBS/EGD): 0 (0%)

Figure 1. Distribution of acute toxicities (n=25)

Figure 2. Dietary outcomes (n=25)

Source: Hutcheson and Frank (ASTRO 2013)
OPC recurrence analysis


IMPT vs IMRT for OPC
First comparative results of PROs

OPC 2006-2015 at MDACC
Prospective registries
IMPT or IMRT with chemotherapy
35 CRT with IMPT
46 CRT with IMRT
PRO- MDASI-HN

Source: Sio and Frank et al. Int J Radiat Oncol Biol Phys
Baseline similar between groups

Top 5 symptoms
- Taste problems
- Dry mouth
- Swallowing-chewing difficulties
- Lack of appetite
- Fatigue

Source: Sio and Frank et al. Int J Radiat Oncol Biol Phys
Oropharyngeal Cancer SCC
IMPT vs IMRT – PFS

Blanchard P et al. Radiotherapy and Oncology 2017

MDACC case-Matched analysis IMPT vs IMRT

Deleterious effect of feeding tube placement on survival:

• HR: 3.09 (1.19-8.00), p=0.02
• Adjusted on age, T and N stage and comorbidity index

Source: Blanchard and Frank et al. Radiotherapy and Oncology 2017
Which Head and Neck Disease Sites are Randomized Trials Permissible?

- Salivary Gland Tumors
  - Unresectable Adenoid Cystic Carcinoma
- Periorbital Tumors
- Nasopharyngeal Cancer
- Oropharyngeal Cancer
- Paranasal Sinus Tumors
  - Postoperative Radiation in Areas of Tissue Heterogeneity
- Reirradiation

H-N Phase III Randomized Trial
Oropharyngeal Cancer - IMPT vs IMRT

**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)
  - Treatment 33 days
  - Recovery 10 wks
  - PROs
- IMRT (70 Gy)
  - Chemotherapy (locally advanced disease)
  - Treatment 33 days
  - Recovery 10 wks
  - PROs

**Follow-up**
- No Surgery
  - PROs Q3 mo
  - Follow-up
- Surgery
  - PROs Q3 mo
  - Follow-up

Frank – PI, Busse, Foote Co-PIs
Study CONSORT Diagram

(current as of January 2019)

Consented
N= 205

Randomized
N= 203

Group 4 IMRT to IMPT
N= 1

IMRT W/D Consent
N= 8

IMRT On Study
N= 152

Treatment w/ IMRT
N= 5

IMRT Censored
N= 6

IMRT On Study
N= 82

IMPT
N= 150

IMPT W/D Consent
N= 4

IMPT On Study
N= 92

Treatment w/ IMPT
N= 25

IMPT Censored
N= 5

IMPT On Study
N= 62

The value proposition for HN proton therapy

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

Phase II-III Randomized Trial of Advanced Stage Oropharynx Tumors
Value Proposition - H&N

Cumulative Cost of Care During Radiation Therapy

Value = \frac{\Sigma \text{(Outcomes)}}{\Sigma \text{(Costs)}}

Thaker N et al. Oncology Payers 2014
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Head and Neck Cancers

Version 1.2017 — February 6, 2017

NCCN.org

Effects of Unnecessary Radiation
Adolescent and Young Adult Guidelines (19-39 yrs)
Conclusion

Head and Neck proton therapy is safe and effective
IMPT is the future of head and neck radiation therapy
Randomized trials are needed to define the value
- N. America – Oropharynx HPV+
The biology will inform for dose de-escalation (?MATH?)
Disclosures

- NCI U19 IMPT vs IMRT Oropharynx
- Honoria and/or Grants from ELEKTA, Eli Lilly, NIH/NCI, Varian, Hitachi, Augmenix and IBA
- Varian Advisory Board/Consultant
- Founder and Director, C4 Imaging

Value-based Pilot with Texas System

Third party administrators (TPA) often cite overutilization and cost as justifications for restrictive proton beam therapy (PBT) coverage policies.

We collaborated with a state-wide self-funded employer, The University of Texas System (UTS), to implement a PBT coverage pilot ensuring appropriate access to care without increasing cost.

This pilot conducts a value-based assessment of PBT through evaluation of utilization trends and comprehensive charge analysis of medical claims.
Background Summary - 2015

Topic: UT SELECT Coverage for Proton Therapy
Date: May 19, 2015 (Austin, TX)
Attendees: UT System, BCBS-TX, and MDACC

2015 Discussion Points:
- Proton Beam Therapy (PBT) has high measurable value
- PBT is safe, effective, and medically necessary when prescribed
- UT System employees and dependents have limited access for PBT
- BCBS-TX policy does not incorporate current peer reviewed literature
- BCBS-TX definition of medical necessity is not consistent with Medicare (TX)
- Proposed PBT coverage for UT SELECT agrees with MD Anderson Proton Therapy Policy (MDAPTP), AMA, Medicare, and Retired Novitas LCD.
- MD Anderson self-funded cancer management program uses MDAPTP
- UT System wanted to minimize impact on policy holders
- Estimated additional cost to UT System < 0.5% of total medical claims
**Background Summary – 2015**

*Action Item:*
Determine pilot structure and complete cost analysis with UT System & BCBS-TX

---

**Pilot Structure & Endpoint**

The pilot obtained Institutional IRB approval.

All patients enrolled on a IRB approved prospective clinical trial.

Coverage for head and neck, esophageal, breast, lung, prostate, and randomized clinical trials.

Value based analysis

- Patient satisfaction (PROs)
- Clinical outcomes and toxicities
- Total net charges (cost of care)

A primary endpoint was cost of care

- Claims = 1 month pre-treatment, treatment, and ≥ 6 months post-treatment.

UT System provides administrative override to BCBS-TX and payment at contracted in-network rate.
Proton Therapy Coverage Pilot Status

Enrollment

1st patient – April, 2016
Permitted enrollment – 40/year
Actual treated in 3 yrs – 22 pts (only 7/year)

Pilot Data and Analysis

Average prior authorization time was reduced to <1 business day (BD) vs. 17 BDs (prior to pilot)

9 HN, 8 GU, 3 BRST, & 2 THOR (22 PBT total)

22 additional patients who met pilot eligibility were treated w/ X-Rays during same timeframe

Out of these, 17 were case-matched to 17 photon patients with ≥6 month follow-up

PBT claims were compared with case-matched photon patients (enrollment period, employer, site, indication, & stage)
### Case-Match: Patient Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Protons (n=17)</th>
<th>Photons (n=17)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Patients (%)</td>
<td>No. Patients (%)</td>
<td></td>
</tr>
<tr>
<td>Service</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HN</td>
<td>7 (41)</td>
<td>7 (41)</td>
<td>0.99</td>
</tr>
<tr>
<td>GU</td>
<td>6 (35)</td>
<td>6 (41)</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>3 (18)</td>
<td>3 (18)</td>
<td></td>
</tr>
<tr>
<td>Thoracic</td>
<td>1 (6)</td>
<td>1 (6)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11 (65)</td>
<td>11 (65)</td>
<td>0.99</td>
</tr>
<tr>
<td>Female</td>
<td>6 (35)</td>
<td>6 (35)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean, (range)</td>
<td>64 (39-85)</td>
<td>59 (47-77)</td>
<td>0.12</td>
</tr>
<tr>
<td>ECOG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>3 (18)</td>
<td>4 (24)</td>
<td>0.99</td>
</tr>
<tr>
<td>0</td>
<td>14 (72)</td>
<td>13 (76)</td>
<td></td>
</tr>
<tr>
<td>Follow-Up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean, (range)</td>
<td>16.2 (6.5-33.2)</td>
<td>21.0 (7.7-32.5)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

### Case-Match: Treatment Factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Protons (n=17)</th>
<th>Photons (n=17)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Patients (%)</td>
<td>No. Patients (%)</td>
<td></td>
</tr>
<tr>
<td>Stage (AJCC VII)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-4</td>
<td>5 (29)</td>
<td>7 (41)</td>
<td>0.85</td>
</tr>
<tr>
<td>0-2</td>
<td>11 (65)</td>
<td>9 (53)</td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>1 (6)</td>
<td>1 (6)</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>4 (24)</td>
<td>5 (29)</td>
<td>0.99</td>
</tr>
<tr>
<td>Non-Squamous</td>
<td>13 (76)</td>
<td>12 (71)</td>
<td></td>
</tr>
<tr>
<td>Indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definitive</td>
<td>10 (59)</td>
<td>8 (47)</td>
<td>0.49</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>7 (41)</td>
<td>9 (53)</td>
<td></td>
</tr>
<tr>
<td>No. of Fractions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean, (range)</td>
<td>28 (10-39)</td>
<td>28 (5-39)</td>
<td>0.84</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6 (35)</td>
<td>4 (24)</td>
<td>0.45</td>
</tr>
<tr>
<td>No</td>
<td>11 (65)</td>
<td>13 (76)</td>
<td></td>
</tr>
</tbody>
</table>
Proton Therapy Coverage Pilot Status

**QoL Data Reliability**

Highly Reliable QoL (Quality of Life) data

- 81.4% (PBT Pilot) vs. 69% (Related Protocols)

<table>
<thead>
<tr>
<th></th>
<th># expected by protocol</th>
<th># of Collected</th>
<th>*Complete Rate (%)</th>
<th>*Average Compliance Rate of all Related Protocols</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>18</td>
<td>17</td>
<td>94.4%</td>
<td>94.4%</td>
</tr>
<tr>
<td>During Treatment</td>
<td>37</td>
<td>32</td>
<td>86.5%</td>
<td>69.0%</td>
</tr>
<tr>
<td>Follow-up</td>
<td>42</td>
<td>30</td>
<td>71.4%</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>97</strong></td>
<td><strong>79</strong></td>
<td><strong>81.4%</strong></td>
<td><strong>69.0%</strong></td>
</tr>
</tbody>
</table>

*Statistical comparison was not made at this point, due to the limited sample size

---

Outcomes - Clinical

**Quality of Life (QOL)**

Patients Quality of Life returning to baseline faster

**Figure 4. MDADI and FACT Score Change over Time**

(The lower scores indicate the more severe symptom burden)

- NO Grade 4 or 5 Toxicities (Hospitalization, ICU, Death)
Outcomes – Cost Comparison
(Normalized Relative Average Cost Ratios)

Scale:
Higher Cost

MD Anderson PBT Pilot Total Cost of Care Analysis Summary

<table>
<thead>
<tr>
<th>Cost</th>
<th>Cost per Covered Life</th>
<th>% of Claims</th>
</tr>
</thead>
<tbody>
<tr>
<td>$748,819</td>
<td>$2.38</td>
<td>0.10%</td>
</tr>
<tr>
<td>-$426,522</td>
<td>-$2.29</td>
<td>-0.06%</td>
</tr>
<tr>
<td>-$1,175,341</td>
<td>-$4.68</td>
<td>-0.16%</td>
</tr>
</tbody>
</table>

Projected
Actual
Total Difference

WA - Health Technology Clinical Committee
PBT Pilot Cost Analysis Summary

NET employer cost savings with PBT
The average net billed charges were -21.0% lower for PBT
Percentage of RT-to-Total charges was 77% vs. 65% for PBT & Photons (p=.09)
Photon (X-Ray) patients had more ancillary costs [IM, Pharm, Lab, ER, DI]
Hypofractionated PBT regimens add value [5/17 patients]

Proton Therapy Coverage Pilot Summary
Outcomes have been excellent
The cost to the UT System is less than expected
Patient selection is rigorous and accrual was less than predicted
Patient, Physician, and Administrative satisfaction is very high
Administrative burden has been significantly reduced
Protocol data is very reliable
Patient Reported Outcomes are favorable
Proton Therapy is safe and effective
Conclusions
The UT System and MD Anderson have demonstrated that a successful proton therapy coverage pilot is feasible
Collaboration with employers can improve access & reduce cost
The UT System has committed to the expansion of proton therapy
Comprehensive PBT coverage for all UT System policy holders

Conclusion
Objective evidence-based treatment guidelines and policies can ensure appropriate patient selection while reducing administrative burden.
Patient, physician, & administrative satisfaction is very high.
Protocol data is very reliable, patient reported outcomes are favorable, PBT is safe and effective.
This state-wide insurance coverage pilot demonstrates that appropriate access to PBT does not result in overutilization or increased employer cost.
MD Anderson

Proton Therapy’s Next Generation

The MD Anderson Proton Therapy Center [2]

Acknowledgements
Matthew Ning, MD
Aashish Shah, MD,JD
Laura Chambers (UT System Executive Director of Office Employee Benefits)
Laura Garlock (UT System, Sr Benefits Analyst)
Ben Melson (MDACC Sr VP & CFO)
Jim Incalcaterra (Exec. Director, Financial Planning & Analysis)
Michelle Ruben (Director, Clinical Rev./ Reimbursement)
Robin Simmons (Assoc. Dir, Rev Cycle Analytics)
Annette Johnson (Revenue Cycle Analytics)
Kathleen Garrett (Revenue Cycle Analytics)
Rong Ye (Statistical Analyst)
Menna Teferra (Research Admin)
Kristen Cover (VP Marketing and Communications)
Maru Navarro (Graphic Designer)
Thank you! Questions?

Acknowledgments

Proton Physics Team
- Michael Gillin
- Ron Zhu
- Rhade Mohan
- Narayan Sahoo
- Richard Wu
- Falk Poenisch
- Xiaodong Zhang

Proton Dosimetry Team

Proton Therapy Team

Head and Neck Team
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- David Rosenthal
- William Morrison
- Adam Garden
- Brandon Gunn
- Beth Beadle
- Jack Phan
- Dave Fuller

Matthew Palmer

Hitachi
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**Phone:** 1-866-632-4782

**Email:** proton@mdanderson.org

**Referring Physicians:** https://my.mdanderson.org/public/physicians

A Pioneer in Proton Therapy

MD Anderson Proton Therapy Center
HTCC Public Comments
Re-Review of Proton Therapy
May 17, 2019

Speakers
• Ramesh Rengan, MD, PhD
  o Ceding their time to Dr. Rengan: Lindsay Knapp, Meredith Fane, Meredith Cassels
• Ralph Ermoian, MD
  o Ceding their time to Dr. Ermoian: Amy Walgamott
• Charles Bloch, PhD, DABMP, DABR, FAAPM
• Jing Zeng, MD
Ramesh Rengan, MD, PhD

Professor and Interim Chair, Department of Radiation Oncology, University of Washington School of Medicine
Medical Director, SCCA Proton Therapy Center
Associate Member, Clinical Research Division, Fred Hutchinson Cancer Research Center

Conflict of Interest Disclosure

- Medical Director of the SCCA Proton Center
  - No direct salary

General Radiation Principles

1. There is no benefit to radiation to normal tissues
2. Proton therapy reduces radiation to normal tissues compared to x-ray radiation by 10-90% in most situations
3. Reduction of harm from this reduction in radiation exposure is not something that can be captured in prospective randomized trials
General Radiation Principles

- **Reduction of radiation exposure (ALARA) has been accepted as basic standard clinical practice without prospective clinical trial evidence to support it**
  - Worldwide acceptance of proton therapy for children
  - Low-dose CT scanners: no randomized trials required for deployment

- **HOWEVER, healthcare resources are finite**
  - We must be good stewards of expensive and labor-intensive technology
  - Our center has a rigorous process for patient selection for suitability for proton therapy

Selection Process & Peer Review

Prior to patient treatment, each case is reviewed at least 5 times to ensure protons are the superior treatment option
Who Benefits from Proton Therapy?

- Pediatric Patients
- Re-irradiation
- Ocular
- Tumors near Organs at Risk (OARs)

Ocular Tumors
- Protons
- Photons

Decrease in radiation exposure to underlying brain tissue, when using protons

Head & Neck Cancers
- Protons
- Photons

Images represent a reduction in radiation to the head and brain, when using protons

Medulloblastoma: Craniospinal Irradiation
- Protons
- Photons

Images represent a reduction in radiation to the entire chest and abdomen cavities, when using protons

Pediatric Neuroblastoma
- Protons
- Photons
- Photons

Images represent a reduction in radiation to the abdomen, when using protons
Commitment to Evidence Generation

• 2 registries & more than 25 open clinical trials
  o Disease sites include breast, brain, prostate, thoracic, pediatric, and other cancers

• 70% of the Center’s patients have enrolled in the Proton Collaborative Group registry

• Over 100 patients have enrolled in proton clinical trials since the Center’s opening in 2013

The evidence report would suggest a proton beam therapy coverage policy in Washington State that would be among the most restrictive in the country.

Overly restrictive coverage policies can come with severe consequences to patients’ health and to the financial well-being of insurers.

Aetna Settlement=$25 Million
Ralph Ermoian, MD
Pediatric Radiation Oncologist, UW Medical Center, Seattle Children’s, SCCA Proton Therapy Center
Associate Professor, Department of Radiation Oncology, University of Washington School of Medicine
Adjunct Associate Professor, Pediatrics, University of Washington School of Medicine

Conflict of Interest Disclosure
• None

Pediatric Patients
• We consider photons or protons for each patient, about 2/3 receive protons and 1/3 receive photons
  o Common to decline referrals when we feel photons at least as good
• Distribution of proton patients
  o 2/3 have brain/central nervous system tumors;
  o 1/3 have rhabdomyosarcoma, neuroblastoma, bone tumors, and lymphoma, and other non-brain tumor
• Matches the increasing use of protons in treating children in the world’s 54 proton centers (Radiother Oncol. 2019 Mar;132:155-161)
  o We are only proton center in the Northwest
Craniospinal Irradiation: If a patient lives another 60 years, which plans serves her/him best?

![Diagram showing different irradiation plans for craniospinal treatment](image)

**Acta Oncologica**, 57:9, 1240-1249

**Our basis for treating many patients with protons**

- Many studies at least equivalent disease control
- Side effects impact patients for decades to come
- Studies show proton therapy associated with:
Challenges of Data Generation

• RCT would require parents consenting to their children being randomized to receive photons with much higher doses to developing normal tissue with known increased risks and side effects.
• Benefits of treating with protons in pediatric tumors, including neurocognitive and secondary malignancies, will take decades to manifest.
• Children’s Oncology Group (COG)—the largest pediatric oncology cooperative research organization– allows for physician discretion rather than randomization of radiation modality on most protocols.
  o Likely will have later subset analysis.
• We participate in most COG trials and offer our patients enrollment on two registry studies (including a national proton registry trial).

Proton Coverage for Pediatric Patients is the Standard in the Northwest

• Most insurers—private and public--cover protons.
  o Only a handful of insurance denials among hundreds of referred pediatric patients; all but one overturned.
  o Oregon public insurance provides coverage for pediatric patients.
  o Kaiser California and British Columbia Cancer Agency.
  o Other states referring to our center include Alaska, Hawaii, Idaho, Montana, and Utah.
  o Evicore has recently updated is coverage to include all patients receiving craniospinal irradiation and all pediatric malignancies.
  o It would be remarkable if Washington were the exception.
Charles Bloch, PhD, DABMP, DABR, FAAPM

Associate Professor, Department of Radiation Oncology, University of Washington School of Medicine

Associate Director of Medical Physics, Seattle Proton Therapy Center

Conflict of Interest Disclosure

• University of Washington Employee
• Physicist at the SCCA Proton Therapy Center

About Me

• Medical Physicist with 25+ years of experience with proton therapy
• UW Employee providing clinical support at the SCCA Proton Therapy Center
• Head & Neck Cancer Patient
  o Proton radiation therapy January – March 2017
  o Cancer free for 2+ years
Why Proton Therapy was the Superior Modality for Me

- Unilateral disease – left tonsil primary, positive lymph nodes in left neck
- Salivary Gland preservation – important for dental health (poor dental health associated with heart disease), speech, eating.

Coverage Denied

- HCA decided not to cover protons for my type of cancer
  - UW to everyone: We provide the best treatment options anywhere
  - UW to employees: Except for you
- Recommendations in the final report continue to discount the benefits of proton therapy, including improved quality of life, and reductions in costs from potential side effects.
My Outcome after Proton Therapy

• Reduced risk of secondary cancers
• Reduced risk of side effects and associated health costs
  o No PEG feeding tube required
  o Preservation of salivary function
  o Reduced risk of swallowing dysfunction
  o Reduced risk of aspiration pneumonia
• Continued working during first 3 weeks of RT
• Returned to work full time 2 weeks after completion of RT
Jing Zeng, MD

Associate Professor, Department of Radiation Oncology, University of Washington School of Medicine

Associate Medical Director, Seattle Proton Therapy Center

Conflict of Interest Disclosure

• Associate Medical Director of the SCCA Proton Center
  o No direct salary

The evidence report would suggest a proton beam therapy coverage policy in Washington State that would be among the most restrictive in the country.

Everywhere else in the country has been increasing coverage for proton therapy, Washington State is taking steps backwards from 2014 to now.

Coverage Variance Across the U.S.

<table>
<thead>
<tr>
<th></th>
<th>Medco</th>
<th>Cigna</th>
<th>Aetna</th>
<th>United Healthcare</th>
<th>Medicare</th>
<th>Florida Blue</th>
<th>CareFirst BCBS of Maryland, D.C., &amp; Virginia</th>
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</table>

- The evidence report would suggest a proton beam therapy coverage policy in Washington State that would be among the most restrictive in the country.
- Everywhere else in the country has been increasing coverage for proton therapy, Washington State is taking steps backwards from 2014 to now.
Our Recommendations

- Proton therapy coverage should include:
  - All patients enrolled in a trial or registry
    - Consistent with HCA policy for IMRT Coverage
  - Ocular melanoma
  - Brain/spinal
  - All pediatric patients
  - Reirradiation
  - Tumors in close proximity to organs at risk such as head and neck cancers, left sided breast cancer and some lymphomas
Proton Beam Therapy: Re-Review
Presentation to
Washington State Health Care Authority
Health Technology Clinical Committee
Andrea C. Skelly, PhD, MPH
May 17, 2019

Report prepared by:
Andrea C. Skelly, PhD, MPH
Erika D. Brodt, BS
Shelby Kantner, BA
Naomi Schwartz, BA, MPH
Aaron Ferguson, BA

Update of 2014 Report

• 2014 Report: Systematic review and budget impact analysis
• Rationale: Newly available published evidence
• Objective: Update the 2014 HTA on proton beam therapy (PBT) by systematically reviewing, critically appraising and analyzing new research evidence on the safety and efficacy of PBT, both as a primary or as a salvage therapy (i.e., for recurrent disease or failure of initial therapy), for the treatment of multiple types of cancer as well as selected noncancerous conditions in adults and children.
• Consistent with the 2014 report, comparative studies are the focus of the update.
Background: Cancer

• It’s estimated that 1.7 million new cases of cancer are diagnosed yearly and cancerous conditions are responsible for over half a million deaths per year. There are > 100 cancer types.

• The National Cancer Institute projects the total cost of cancer care in the United States in 2020 to be $174 billion.

• Tumors that respond well to radiation therapy are referred to radiosensitive tumors; radiation therapy may be curative for the following (but not limited to these):
  – prostate cancers
  – head and neck cancers
  – non-small cell lung cancer

Background: Radiation Therapy (RT)

~50% of all cancer patients benefit from RT in the management of their disease; it may be the sole therapy used

RT may be used for a variety of reasons
  – cure a radiosensitive tumor
  – shrink a tumor pre-operatively
  – prevent recurrence or spread postoperatively (adjuvant treatment)
  – treat a recurrent tumor or as a palliative treatment

Most common forms of RT are external beam radiation therapy (EBRT) and brachytherapy (internal radiation therapy)
  – **EBRT:** Radiation is delivered externally using a machine to aim high-energy beams directly at the tumor from outside the body
  – **Brachytherapy:** Radiation is delivered internally; small seeds of radioactive material are directly placed into or very close to the tumor
Background: Radiation Therapy (RT) Planning

- **Goal:** damage cancer cells while minimizing damage to surrounding healthy cells including sensitive structures and organs at risk (OARs)
- **Two-dimensional Radiation Therapy (2DRT)/Conventional Radiation Therapy (CRT)**
  - Utilizes X-ray technology used to take two-dimensional scans of the tumor location
- **Three-dimensional Conformal Radiation Therapy (3DCRT)**
  - Utilizes computer-based three-dimensional imaging (CT, MRI) to more accurately map the location and size of the tumor in three dimensions, as well as identify any critical organs at risk (OAR; RT beams are matched very precisely to the shape of the tumor and delivered from all directions).

Background: Radiation Therapy (RT) Delivery

- **Classification** of EBRT may be by the type of beam or particle used (i.e. electron, photon or proton) with photon RT being the most widely available and commonly used.
- **Intensity Modulated Radiation Therapy (IMRT):** beam intensity can be altered to lessen intensity near OARS, deliver high dose to tumor volume; may be done with photons or protons
- **Stereotactic Radiosurgery (SRS)/Stereotactic Body Radiation Therapy (SBRT):** may deliver photons, protons, gamma rays in fewer fractions at a much higher dose vs. IMRT; brain/spine most common use; rigid immobilization required due to smaller planning target volumes
- **Delivery techniques specific to PBT**
  - passive scattering
  - uniform scanning
  - pencil beam scanning (PBS)
Background: Physical Properties of Radiation Particles

- **Photons:** neutrally charged, light; characterized by a high deposit of energy near to the body surface with an exponential decrease of energy release as a function of depth ("exit dose"). Healthy tissue downstream from the tumor could be at an increased risk of exposure to unnecessary radiation.

- **Protons:** heavy positively charged particles; PBT deposits peak radiation energy more precisely at or around the target followed by sharp decline in energy output to deeper tissues via a phenomenon known as the Bragg peak. A greater dose of radiation may be delivered to the target neoplasm(s) while mitigating unwanted radiation delivered to surrounding tissue.

Figure adapted from Levin, et al. Br J Cancer. 2005;93(8):849-854 and 2014 report

Background: Radiation Therapy (RT) Delivery

Comparison of dose distributions of three-dimensional conformal photon radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), and passive scattered conformal proton therapy (PSPT) treatment plans

Background: Radiation Therapy (RT) Delivery

- **Proton Beam Therapy** treatment room (gantry) at the Seattle Cancer Care Alliance Proton Therapy Center
- Protons are delivered using a cyclotron

- **Photon RT treatment** room (gantry) at Beacon Hospital for delivering CRT, IMRT, and 3DCRT (photons)
- Photons are delivered using a Linear Accelerator (LINAC)

Background: Harms of Radiation Therapy (RT)

- Side effects of RT occur when healthy tissues in the path of the radiation beam are damaged
- Effects vary from person to person depending on a variety of factors:
  - location of the tumor/field of radiation
  - type of RT/method of delivery
  - timing of treatment
  - dose per fraction and total dose
  - a person’s overall health
  - patient age, developmental stage
Background: Additional Considerations

• Assumption that the biological effects of protons are equivalent to that of photons, challenged by recent studies that suggest there is less certainty

• There is more uncertainty around the end of the dose range when deep-seated tumors are considered

• The effects of neutrons, which are produced by passively-scattered proton beams, result in additional radiation dose to the patient and their effects on the patient are less known

Key Questions

1. What is the **comparative impact of PBT treatment with curative intent** on survival, disease progression, health-related quality of life, and other patient outcomes versus radiation therapy alternatives and other cancer-specific treatment options?

2. What is the **comparative impact of salvage treatment** (including treatment for recurrent disease) with PBT versus major alternatives on survival, disease progression, health-related quality of life, and other patient outcomes versus radiation therapy alternatives and other cancer-specific treatment options?

3. What are the **comparative harms associated with the use of PBT relative to its major alternatives**, including acute (i.e., within the first 90 days after treatment) and late (>90 days) toxicities, systemic effects such as fatigue and erythema, toxicities specific to each cancer type (e.g., bladder/bowel incontinence in prostate cancer, pneumonitis in lung or breast cancer), risks of secondary malignancy, and radiation dose?

4. What is the **differential effectiveness** and safety of PBT according to factors such as age, sex, race/ethnicity, disability, presence of comorbidities, tumor characteristics (e.g., tumor volume and location, proliferative status, genetic variation) and treatment protocol (e.g., dose, duration, timing of intervention, use of concomitant therapy)?

5. What is the **comparative cost-effectiveness of PBT** in the short- and long-term relative to other types of radiation therapy, radiation therapy alternatives or other cancer-specific treatment options (e.g., surgery, chemotherapy)?
PICO Scope: Inclusion Criteria

- **Population**: Persons undergoing cancer treatment for primary or recurrent disease, to include:
  - bone cancer, brain, spinal, and paraspinal tumors, breast cancer, esophageal cancer, gastrointestinal cancer, gynecologic cancer, head and neck cancer, liver cancer, lung cancer, lymphomas, ocular tumors, pediatric cancers, prostate cancer, sarcomas, seminoma, thymoma, other cancers, and noncancerous conditions (arteriovenous malformations, hemangiomas, other benign tumors)

- **Interventions**: Proton Beam Therapy

- **Comparators**: Other radiation alternatives (e.g., intensity-modulated radiation therapy (IMRT), stereotactic radiation techniques and other external beam therapies, and brachytherapy). Other treatment alternatives specific to each condition type treated, and may include chemotherapy, immunotherapy, surgical procedures, and other devices (e.g., laser therapy for ocular tumors)

- **Primary Outcomes (SOE)**: Improvement in OS, PFS, or LC; adverse events directly attributable to PBT; cost-effectiveness outcomes (QALY, ICER)

---

PICO Scope: Inclusion Criteria

**Study Design**:

- KQ1-4: focus on high quality (low risk of bias) comparative studies (e.g., RCT, comparative observational studies); case series were considered but were not the primary focus of evaluation
- KQ3: studies reporting direct PBT harms
- KQ5: full formal economic analyses

**Publication**: Full-length studies published in English in peer-reviewed journals; studies published subsequent to the 2014 report. (EXCLUDED – meeting abstracts, white papers, editorials, letters; model policies were not within report scope)
**Threats to internal validity: Bias and Confounding**

**Selection bias**
- Control selection
- Loss to follow-up
- Confounding by indication (treatment allocation)
- Self-selection, differential referral

**Attrition bias**
- Loss to f/u, differential f/u, exclusions
- Handling of missing data

**Performance bias**
- Concurrent interventions equal
- Measurement of potential confounders
- Protocol adherence

**Detection bias**
- Comparable length of f/u in each group
- Blinded assessment
- Validated, reliable measurement
- Consistent measurement of groups

**Reporting bias**
- Reporting of specified outcomes

**Confounding**
- Baseline characteristics (measured and unmeasured)

> All may impact observation of an effect or lack of effect. Many are difficult to control in retrospective comparative cohort studies.

---

**Individual Studies: Risk of Bias**

<table>
<thead>
<tr>
<th>Criteria</th>
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</thead>
<tbody>
<tr>
<td>• Random sequence generation (RCT)</td>
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<tr>
<td>• Statement of allocation concealment (RCT)</td>
</tr>
<tr>
<td>• Intent-to-treat analysis (RCT)</td>
</tr>
<tr>
<td><strong>RCTs and observational studies</strong> *</td>
</tr>
<tr>
<td>• Blind, independent assessment of outcomes/analysis</td>
</tr>
<tr>
<td>• Complete follow-up of &gt;80%</td>
</tr>
<tr>
<td>• &lt;10% difference in follow-up between groups</td>
</tr>
<tr>
<td>• Controlling for possible confounding</td>
</tr>
<tr>
<td>• Multivariate analysis, matching (including propensity)</td>
</tr>
</tbody>
</table>

*case series are considered at high risk of bias
Strength of Evidence (SOE) Criteria – Appendices D, E

Overall body of evidence for primary outcomes:

- **Risk of bias (one criterion):** the extent to which majority of included studies protect against bias
- **Consistency:** degree to which estimates are similar in terms of range and variability.
- **Directness:** evidence directly related to patient health outcomes.
- **Precision:** level of certainty surrounding the effect estimates.
- **Publication/reporting bias:** selective reporting or publishing.

SOE – Application of criteria (see report methods)

- RCT evidence initially considered “High”; Observational evidence is initially considered “Low”.
- Where RCTs are unavailable, unethical or not feasible, **high quality** nonrandomized observational studies (NROS) may provide “best evidence”;
  - **The quality of nonrandomized studies is not elevated** (bias may still be present). Decision makers need to accept and consider the greater uncertainty of such evidence; one should not have greater confidence in the effect estimates from such studies;
  - NROS with **few** methods limitations, **which control for bias** may be initially considered “Moderate” vs. “Low” when such studies may be at lower risk of bias due to confounding;
  - Ideally, studies which controlled for confounding with ≥ 80% follow-up and ≤10% difference in follow-up between treatments.
Systematic Review Process

Studies meeting eligibility criteria
Efficacy: RCTs; Effectiveness: Observational studies
Harms: RCTs, Observational studies
Full Economic studies

Risk of Bias Appraisal (Study)
Low, Moderately Low, Moderately High, High

Synthesis/Analysis

Overall Strength of Evidence Determination (GRADE/AHRQ)
Across comparative studies reporting primary outcomes

Strength of Evidence Ratings

<table>
<thead>
<tr>
<th>High</th>
<th>Very confident that effect is true.</th>
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<tbody>
<tr>
<td>Moderate</td>
<td>Moderately confident.</td>
</tr>
<tr>
<td>Low</td>
<td>Limited confidence.</td>
</tr>
<tr>
<td>Insufficient</td>
<td>No evidence or no confidence in effect.</td>
</tr>
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</table>

Reconciliation with 2014 report, net health benefit

General considerations: Evidence quality, comparators, whether new evidence was a major change in the evidence base or substantial changes in effect size or statistical significance beyond “borderline”, evidence of substantial harm

Net health benefit: considers clinical benefit and potential harms vs. comparators (based on ICER 2014 report methods);

• Superior: moderate-to-large net health benefit vs. comparator(s)
  E.g. ↑ effectiveness (mod to large), ↓ in harms

• Incremental: a small net health benefit vs. comparators(s)
  E.g. small ↑ effectiveness, no difference in harms; or no difference in effectiveness, small ↓ in harms

• Comparable: while there may be tradeoffs in effectiveness or harms, overall net health benefit is comparable vs. comparator(s)

• Inferior: a negative net health benefit vs. comparator(s)

• Insufficient: Evidence is insufficient to determine the presence and magnitude of a potential net health benefit vs. comparators(s)
Literature Search Results

1. Total Citations (n=2328)
   Search, n=1920
   Public Comment, n=408

2. Title/Abstract exclusion (n=2063)

3. Retrieved for full-text evaluation (n=283)

4. Excluded at full-text review (n=68)
   (see appendix C for list of excluded articles and reasons for exclusion)

5. Publications included (n=215)*
   Adult (n=155 publications)
   2 RCTs, 1 quasi-RCT, 33 Comparative, 115* Case Series, 4 Economic
   Pediatric (n=56 publications)
   13 Comparative, 41* Case Series, 2 Economic
   Contextual Studies (n=4)
   2 RCTs, 2 Comparative

*One study (Hoppe 2017) contributes data for both adults and pediatric populations

Overview of Evidence Base

2014 Report: 2 RCTs; 38 comparative (most retrospective; indirect non-contemporaneous case series); 245 case series; 13 economic; 4 contextual

2019 Report: 2 RCTs, 1-quasi RCT; 49 comparative (47 retrospective); 156 case series; 6 cost-effectiveness; 4 contextual

Retrospective comparative study limitations which may impact results:

- treatment groups based on historical changes in RT methods; differential length of follow-up
- Potential for treatment selection bias/confounding by indication
- Completeness of F/U and loss to F/U poorly reported or could not be determined
- Differences in baseline characteristics in most studies; potential for residual confounding
Organization of Results

Results for comparative studies reported by tumor category/location

- KQ 1. Comparative impact, PBT with curative intent
- KQ 2. Comparative impact, PBT for salvage, recurrent disease
- KQ 3. Comparative harms and safety
- KQ 4. Differential effectiveness or safety (no studies identified)
- KQ 5. Comparative cost-effectiveness (where available)

**Pediatric Tumors**

- Comparative studies KQ1-5*
- Overview comparing 2014 and 2018 report

**Adult Tumors**

- Comparative studies KQ1-5*
- Overview comparing 2014 and 2019 report

*Summaries of cases series data are found Appendix F, page 26

Evidence Base: Pediatric Tumors

**2014 report:** Did not report by tumor location; included 1 poor quality comparative cohort and 41 case series

**2019 update:** New studies (since 2014 report) by tumor type

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<th>Tumor</th>
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<th>Case series* # publications</th>
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<td>Bone</td>
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<tr>
<td>Brain</td>
<td>8 studies (6 retrospective, 2 prospective); (11 publications)</td>
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<tr>
<td>Head and neck</td>
<td>1 retrospective (Safety)</td>
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<td>Lymphoma</td>
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<td>Ocular</td>
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**Studies:** Bulk of the new evidence is in pediatric brain tumors; all comparative studies at moderately high ROB, 2 were prospective; case series considered to be high ROB
OS: Compared with IMRT or 3DRT, no statistical differences at any time across 3 retrospective and 1 prospective study; some differences may be clinically important. (SOE Low)

Additional retrospective study: HR 0.99 (95% CI 0.41 to 2.4) for PBT vs. CRT (SOE Low)

Case series: Appendix F

PFS: Versus IMRT or 3DRT, PBT tended to have better PFS; NS for ependymoma at 3 years, NR at 6 year; NS for medulloblastoma. (SOE Low)

Sato: Lower recurrence with PBT; Disease-related mortality PBT (4.9%) versus IMRT (31.6%) (SOE Low)

Case series: Summaries in Appendix F Tables
Endocrine-related toxicities: Tended to be less common with PBT vs. 3DRT or IMRT; statistical significance not uniformly reached; all patients in Eaton and Bielamowicz had chemotherapy; (SOE Low)

Roles of sample size, selection bias and potential for residual confounding are not clear. Eaton prospectively enrolled PBT group; others are retrospective studies.

KQ 3: Pediatric Brain Tumors; Safety – Endocrine-related

CASE SERIES

<table>
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<th>Author/Year</th>
<th>Toxicity</th>
<th>% (n/N) or % (95% CI)</th>
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<td>Indelicato 2018</td>
<td>Late Grade ≥2 Hormone Deficiency</td>
<td>7.3% (13/179)*</td>
</tr>
<tr>
<td>MacDonald 2013</td>
<td>Hypothyroidism (Grade NR) Growth Hormone Deficiency</td>
<td>3.2% (1/32) 8% (2/25)</td>
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<tr>
<td>Yock 2016</td>
<td>Cumulative Incidence, Any Hormone Deficiency†</td>
<td>27% (16% to 39%) 55% (41% to 67%) 63% (48% to 75%)</td>
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<tr>
<td>Greenberger 2014</td>
<td>K-M 10 year Rate, Any Endocrine Deficiency</td>
<td>50% (95% CI NR) ‡</td>
</tr>
</tbody>
</table>

*33% of patients had pre-radiation chemotherapy. Growth Hormone Deficiency most common 11/13.
†52/59 patients had concurrent chemotherapy; 6 patients had photon RT for part of treatment. growth hormone deficiency was most common followed by thyroid deficiency.
‡Assessed in all patients with intracranial tumors (n=29). Data estimated from figure; driven by high % of growth hormone deficiency and hypothyroidism.
**KQ 3: Pediatric Brain Tumors; Safety – Other Toxicities**

*Other toxicities (acute and late):* Tended to be similar or less common with PBT vs. 3DRT or IMRT; statistical significance not uniformly reached; all studies were retrospective (SOE Low); Note: Song 2014 PBT n = 30, photon n = 13

**KQ 3: Pediatric Brain Tumors; Specific toxicities**

**CASE SERIES with >100 patients**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Studies</th>
<th>Studies</th>
<th>%n/N or Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>White matter lesion</td>
<td>Bojaxhiu 2018</td>
<td>Any grade: 11% (11/171)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 3: 0.6% (1/171)</td>
<td></td>
</tr>
<tr>
<td>Radiation Necrosis (early or late)</td>
<td>Bojaxhiu 2018</td>
<td>Any grade: 17% (29/171)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 4: 0.6% (1/171)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 5: 1.2% (2/171)</td>
<td></td>
</tr>
<tr>
<td>Radiation injury to CNS or brainstem</td>
<td>Gentile 2018, Indelicato 2014, 2018, Giantsoudi 2016</td>
<td>Grade 3: 0.6% (3/516) to 1.8% (2/111)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 4: 0.2% (1/516) to 0.9% (1/111)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 5 (Death): 0.3 (1/131) to 0.6% (1/313)</td>
<td></td>
</tr>
<tr>
<td>Vasculopathy</td>
<td>Indelicato 2017</td>
<td>Grade NR: 1.8% (3/166)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indelicato 2018</td>
<td>Grade 2: 3.4% (6/179)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hall 2018</td>
<td>3 yr cumulative, serious: 2.6% (CI NR)</td>
<td></td>
</tr>
<tr>
<td>Vascular Injury</td>
<td>Hall 2018</td>
<td>Stroke w/permanent deficit: 1.2% (7/644)</td>
<td></td>
</tr>
<tr>
<td>Hearing loss</td>
<td>Indelicato 2018</td>
<td>Grade ≥2 (hearing aid): 6.1% (11/179)*</td>
<td></td>
</tr>
</tbody>
</table>

Tables in Appendix F, Tables 60-68
### KQ 3: Pediatric Brain Tumors; Safety – Neurocognitive

<table>
<thead>
<tr>
<th>Change per year in IQ scores</th>
<th>Consistency</th>
<th>Focal PBT vs. surgery</th>
<th>NS difference PBT vs. Photon RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahalley 2016 (N=150)</td>
<td>Unknown</td>
<td>NS differences FSIQ, any subscale; scores remained stable for both groups over time.</td>
<td>⬤偏低</td>
</tr>
<tr>
<td>Various brain tumors; Retro cohort 32.4 vs. 64.8 months</td>
<td>Serious Imprecision Yes (-1)</td>
<td>CSI PBT vs. surgery (adjusted β coefficient, 95%CI) FSIQ: -2.1 (-3.8 to -0.3), p = 0.020 PSI: -2.6 (-4.7 to -0.3), p = 0.019. NS differences for all other subscales (all p-values &gt;0.05)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

| Kahalley 2019 (N=93)       | Unknown     | Focal PBT vs. surgery | NS for focal PBT vs. surgery; CSI PBT associated decline in FSIQ and PSI vs. surgery; clinical significance is not described. |
| Various brain tumors Prospective, ongoing cohort 33.6 to 37.2 months | Serious Imprecision Yes (-1) | | ⬤偏低 |

### KQ 5: Pediatric Brain Tumors; Cost-effectiveness

<table>
<thead>
<tr>
<th>Population; Interventions</th>
<th>Hirano 2014 (Japan); QHES: 50 (poor quality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBT (following chemotherapy) vs. CRT</td>
<td></td>
</tr>
<tr>
<td>ICER</td>
<td>Depends on utility: EQ-5D: $21,716/QALY, HU13: $11,773/QALY SF-6D: $20,150/QALY</td>
</tr>
<tr>
<td>Author's Conclusion</td>
<td>At threshold of $46,729/QALY (JPY 5 million/QALY), PBT is more cost-effective than conventional X-ray therapy</td>
</tr>
<tr>
<td>Limitations</td>
<td>• Inadequate description of PBT costs; incomplete delineation of operational costs • Clinical outcomes data are from case series • Radiation doses derived from small series (8 patients) • Limited outcomes considered: no long-term outcomes related to motor/physical or intellectual challenges or long-term health challenges or costs • Utilities based on hearing aid use, not specific to post-radiation population of children • Utilities derived from western countries and adult populations; may not be applicable to this study population; ICER varies by utility used • May not be applicable to US</td>
</tr>
</tbody>
</table>
### KQ 5: Pediatric Brain Tumors; Cost-effectiveness

<table>
<thead>
<tr>
<th>Mailhot Vega 2015 (USA), QHES: 48/100 (poor quality)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
</tr>
<tr>
<td><strong>ICER</strong></td>
</tr>
<tr>
<td><strong>Author’s Conclusion</strong></td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
</tr>
<tr>
<td>- Limited parameters in model; no long-term toxic effects (e.g. auditory, cognitive) other than GHD; parameters, assumptions not transparently described;</td>
</tr>
<tr>
<td>- Data from case-series; no long term comparative data to validate assumption of no difference in treatments or lifetime horizon</td>
</tr>
<tr>
<td>- Basis of PBT including operational costs not detailed; no detailed costing</td>
</tr>
<tr>
<td>- Sensitivity analyses were limited</td>
</tr>
<tr>
<td>- Utilities from adult study; assumes costs of therapy for adults and children are similar</td>
</tr>
</tbody>
</table>

---

### Pediatric Tumors: Head/neck

**KQ 3. Safety, toxicities**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies, Year, N, Tumor</th>
<th>Reason for Downgrade</th>
<th>PBT vs. other RT* Effect estimate (95% CI)</th>
<th>Conclusion Quality (SoE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Toxicity</td>
<td>Grant (N=24) 1 Retro cohort (N=24) salivary gland tumors (rare)</td>
<td>Serious ROB Yes1 (-1) Consistency Unknown Imprecision Yes3 (-1)</td>
<td><strong>adjuvant PBT vs. adjuvant photon RT</strong> Grade 2/3 toxicities: Dysphagia (0 vs. 3/11); Otitis externa (1/13 vs. 2/11); Mucositis (6/13 vs. 10/11, RR 0.51 (0.27, 0.94)</td>
<td>Mucositis less common following adjuvant PBT; other toxicities were similar between groups. ⬤批示 INSUFFICIENT</td>
</tr>
</tbody>
</table>

* PBT (passive scatter n=8, intensity modulated n=5) vs. other RT (electron beam n=8, IMRT n=3)
Pediatric Tumors: Ocular, KQ 2 (Salvage), 3 (Safety)

KQ 1, 4, 5: No comparative evidence identified

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies, Year, N, Tumor</th>
<th>Reason for Downgrade</th>
<th>PBT vs. other RT * Effect estimate (95% CI)</th>
<th>Conclusion</th>
<th>Quality (SoE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enucleation</td>
<td>Agarwal 2016 (N=39 patients, 47 eyes) Retinoblastoma Retrospective cohort</td>
<td>Serious ROB Yes (1) Consistency Unknown Imprecision Yes (2)</td>
<td>OS: 97.4% across groups Enucleation-free survival: 38.5% vs. 54.5% Enucleation performed: 37.5% (6/16 eyes) vs. 29.6% (8/27 eyes)</td>
<td>Enucleation-free survival was lower with PBT (small sample size)</td>
<td>☐☐☐☐ INSUFFICIENT</td>
</tr>
</tbody>
</table>

Toxicity

PBT vs. ERT
Acute Toxicity:
PBT 93.8% vs. ERT 74.1%; p =0.22 (mostly skin erythema)
Late/long-term (≥1 eyes):
≥1 event: 62.5% (10/16 eyes) vs. 55.6% (15/27 eyes); p=0.275
PBT vs. Other Tx*
Cataract: 5 vs. 10
Vitreous hemorrhage: 3 vs. 4
Radiation retinopathy: 2 vs. 3
Visual acuity Δ: 0 vs. 4
Strabismus: 1 vs. 2

Although acute toxicities were more common with PBT vs. ERT, differences were not statistically significant. Evidence is limited.

Pediatric Tumors- Summary

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence per 100,000</th>
<th>Numbers of Studies (2019 are NEW)</th>
<th>Net Health Benefit vs. Comparators Type of Net Benefit (B, H) SOE</th>
<th>Impact of new comparative studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cancer Types</td>
<td>18.3</td>
<td>CC=1; CS=41; Econ=3</td>
<td>CC=10; CS=41</td>
<td>Incremental B: = H: ↓ Low**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>3.1</td>
<td>---</td>
<td>CC=8; CS=25 Econ = 2</td>
<td>N/A</td>
</tr>
<tr>
<td>Bone</td>
<td>0.9</td>
<td>---</td>
<td>CS=1</td>
<td>N/A</td>
</tr>
<tr>
<td>Head/Neck</td>
<td>NR†</td>
<td>---</td>
<td>CC= 1; CS=3</td>
<td>N/A</td>
</tr>
<tr>
<td>Ocular (salvage)</td>
<td>0.4</td>
<td>---</td>
<td>CC=1; CS=2</td>
<td>N/A</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2.4</td>
<td>---</td>
<td>CS=2</td>
<td>N/A</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>NR</td>
<td>---</td>
<td>CS=6</td>
<td>N/A</td>
</tr>
<tr>
<td>Mixed/Various</td>
<td>NR</td>
<td>---</td>
<td>CS=1</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* PBT (passive scatter, n=16 eyes) vs. photon or electron RT (n=27 eyes) or brachytherapy (n=4 eyes).
SUMMARY of 2019 findings: Pediatric

Incremental Net Health Benefit of PBT vs. other tx (mostly photon): brain tumors based on 6 retrospective, 2 prospective cohorts

No comparative evidence identified: (Summary in Appendix F)
- Bone, Lymphoma, soft tissue (rhabdomyosarcoma)
- Various/mixed

No evidence met inclusion criteria for other pediatric conditions

Insufficient evidence to determine comparative net health benefit
- head/neck (salivary gland tumors),
- Salvage treatment for ocular tumors (retinoblastoma)

Economic: 2 poor quality CUA; Conclusions regarding CE are challenging given data sources used (case series, utilities from other populations), model limitations (parameters, time horizon) and limited sensitivity analyses

SUMMARY: Pediatric

- **2014 vs. 2019**: 10 new comparative studies, (8 retrospective); 8 in patients w/ brain tumors vs. 1 poor quality comparative study was included in 2014; 2014 report did not separate out pediatric tumor types

- **Pediatric brain tumors**:  
  - Low SOE suggests incremental comparative net health benefit of PBT (benefits comparable, harms lower)

- **Other pediatric tumors**: comparative evidence for head/neck and ocular tumors and case series for other tumor categories was considered insufficient

- **KQ4**: no evidence identified
Evidence Base Overview – New Studies, Adult Tumors

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Comparative*</th>
<th></th>
<th></th>
<th>Case series*</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Curative</td>
<td>Salvage</td>
<td>Total</td>
<td>Curative</td>
<td>Salvage</td>
</tr>
<tr>
<td>Bladder</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Bone</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Brain</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>6*</td>
<td>5*</td>
<td>1</td>
</tr>
<tr>
<td>Breast</td>
<td>2, 1 Econ</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Esophageal</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>GI (Pancreas)</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Head and neck</td>
<td>8, 1 Econ</td>
<td>8</td>
<td>0</td>
<td>23</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>Liver</td>
<td>2 (1 RCT), 1 Econ</td>
<td>2 (1 RCT)</td>
<td>0</td>
<td>12</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Lung</td>
<td>7 (1 RCT)*</td>
<td>6 (1 RCT)*</td>
<td>1</td>
<td>12</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Ocular</td>
<td>3, 1 Econ</td>
<td>3</td>
<td>0</td>
<td>22</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Prostate</td>
<td>4 (1 quasi-RCT)</td>
<td>4 (1 quasi-RCT)</td>
<td>0</td>
<td>11 (12 pub)</td>
<td>11 (12 pub)</td>
<td>0</td>
</tr>
<tr>
<td>Hemangiomas (benign)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Other benign tumors†</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4*</td>
<td>3*</td>
<td>1</td>
</tr>
<tr>
<td>Various/mixed</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>37†, 4 Econ</strong></td>
<td><strong>34†</strong></td>
<td><strong>3</strong></td>
<td><strong>114 (115 pub)</strong>*</td>
<td><strong>101 (102 pub)</strong>*</td>
<td><strong>13</strong></td>
</tr>
</tbody>
</table>
Adult tumors results

- Focus on new comparative studies reporting primary outcomes (OS, PFS)
  - 34 curative intent, 3 salvage
  - All but 3 studies (2 RCTs, 1 quasi-RCT) were retrospective cohorts which were at moderately high risk of bias
  - Not all studies reported on primary outcomes
- Results presented alphabetically by tumor type/location for comparative studies

KQ 1 (Curative Intent): Adult brain tumors
Overall (OS) and Progression-Free Survival (PFS)

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Probability of 5-year OS</th>
<th>Propensity score-matched (n=322)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma</td>
<td>Photon + PBT boost vs. any photon</td>
<td>adj. HR 0.66, 95% CI (0.53 to 0.83); favors PBT</td>
</tr>
<tr>
<td></td>
<td>Photon alone</td>
<td>46.1% vs. 35.5%, p=0.009</td>
</tr>
</tbody>
</table>

Adeberg (2017), N=136 High-grade Glioblastoma Retrospective comparative cohort

SOE Low for all
### KQ 2 (Salvage Therapy): Adult brain tumors

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies, Year, N, Tumor</th>
<th>Reason for Downgrade</th>
<th>PBT (passive scatter) vs. Photon Effect estimate (95% CI)</th>
<th>Conclusion Quality (SoE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability, overall survival</td>
<td>Gunther 2017 (N=37)</td>
<td>Serious ROB</td>
<td>OS 6 mos.: 78.6% vs. 69.6%, p=0.15 1 year: 70% vs. 38%, p=NR</td>
<td>No statistical difference between groups in OS at 6 months, statistical testing not reported at 1 year; no statistical difference in CNS relapse risk. Sample size may have played a role in these findings.</td>
</tr>
<tr>
<td>CNS relapse</td>
<td>Retro cohort, CNS involvement in lymphoma or leukemia (pre-SCT)</td>
<td>Consistency Unknown Serious Imprecision Yes³ (-1)</td>
<td>7% (1/14) vs. 0% (0/23); p=1.0</td>
<td>✽◯◯◯ INSUFFICIENT</td>
</tr>
</tbody>
</table>

### KQ 3 (Safety): Adult brain tumors

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies, Year, N, Tumor</th>
<th>Reason for Downgrading</th>
<th>PBT boost + photon vs. Photon alone Effect estimate (95% CI)</th>
<th>Conclusion Quality (SoE)</th>
</tr>
</thead>
</table>
| Acute Toxicity (≤3 mos.)                   | Adeberg 2017 (N=132)    | Curative Intent       | Grade 22: 9% (6/66) vs. 14% (9/66), p=NR  
Grade 3: 0% (0/66) vs. 7.5% (5/66), p<0.1  
Grade 4: 0% (0/66) vs 0% (0/66)  
|                                                           | Primary Glioblastoma (high-grade) | Consistency Unknown Serious Imprecision Yes³ (-1) | 0% (0/66) vs 0% (0/66)  
Neurocognitive deficits‡‡  
Worse: 3% (2/66) vs. 6% (4/66)  
New: 9% (6/66) vs. 2% (2/66)  
Sensorimotor deficits‡‡  
Worse: 3% (2/66) vs. 5% (3/66)  
New: 11% (7/66) vs. 14% (9/66)  
Seizures‡‡  
Worse: 0% (0/66) vs. 0% (0/66)  
New: 2% (1/66) vs. 6% (4/66) p=NS for all | NS differences between groups; unclear if some may be clinically important. Sample size may have played a role in these findings. |
| Radiation necrosis                        |                          |                       |                                                             | ✽✽✽✽ LOW |
| Change in symptomology, % (n/N)           |                          |                       |                                                             |             |
### KQ 3 (Safety): Adult brain tumors

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies, Year, N, Tumor</th>
<th>Reason for Downgrade</th>
<th>PBT vs. Photon Effect estimate (95% CI)</th>
<th>Conclusion Quality (SoE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Toxicity (during CSI)</strong></td>
<td>Gunther 2017 (N=37) Retro cohort CNS involvement in lymphoma or leukemia (pre-SCT) <em>Salvage Therapy</em></td>
<td>Serious ROB Yes¹ [-1] Consistency Unknown Serious Imprecision Yes² [-1]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
|  |  |  | • Mucositis, any Grade: 7% (1/14) vs. 44% (10/23); RR 0.16 (0.02 to 1.15)**  
  • Mucositis, Grade 3: 7% (1/14) vs. 9% (2/23), p=0.1  
  • Gastrointestinal (Grade NR): 29% (4/14) vs. 30% (7/23), p=1.0  
  • CNS (Grade NR): 21% (3/14) vs. 13% (3/23), p=0.65 | PBT resulted in a lower frequency of mucositis (any grade); no other differences were seen over acute or late term. Sample size may have played a role in these findings. |
| **“Late” Toxicity** |  |  |  |  |

### KQ 3: Adult Brain Tumors; Specific toxicities

**CASE SERIES**

<table>
<thead>
<tr>
<th>Outcome</th>
<th># Studies</th>
<th># With outcome</th>
<th>Total N (range of N’s)</th>
<th>Median F/U (months)</th>
<th>% or Range (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Grade ≥3</td>
<td>6</td>
<td>29</td>
<td>515 (23-280)</td>
<td>20.1 to 56.9</td>
<td>0% to 17.4%*</td>
</tr>
<tr>
<td>Late Grade ≥3</td>
<td>2</td>
<td>14</td>
<td>142 (46 to 96)</td>
<td>42.1 to 56.9</td>
<td>3.1% to 23.9%*</td>
</tr>
<tr>
<td>5-yr, Toxicity-free survival (Grade ≥3)</td>
<td>1</td>
<td>N/A</td>
<td>96</td>
<td>56.9</td>
<td>89.1% (82-96%)</td>
</tr>
<tr>
<td>% of weight lost</td>
<td>1</td>
<td>≤2%: 30 &gt;2-5%: 15 &gt;5-10%: 4 &gt;10%: 1</td>
<td>50</td>
<td>20.1</td>
<td>≤2%: 60% &gt;2-5%: 30% &gt;5%-10%: 8% &gt;10%: 2%</td>
</tr>
<tr>
<td>Radiation Necrosis (Late, grade NR)</td>
<td>1</td>
<td>11</td>
<td>46</td>
<td>42.1</td>
<td>23.9%</td>
</tr>
<tr>
<td>Brain Necrosis (Late Grade ≥3)</td>
<td>1</td>
<td>3</td>
<td>96</td>
<td>56.9</td>
<td>3.1%</td>
</tr>
<tr>
<td>PBT-related neurotoxicity, Grade ≤2§</td>
<td>1</td>
<td>7</td>
<td>16</td>
<td>56</td>
<td>44%</td>
</tr>
<tr>
<td>RT-related Mortality</td>
<td>1</td>
<td>1</td>
<td>96</td>
<td>56.9</td>
<td>1%</td>
</tr>
</tbody>
</table>

**Appendix Table F9**
Summary: Adult brain tumors

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence (per 100,000)</th>
<th>Numbers of Studies</th>
<th>Net Health Benefit vs. Comparators Type of Net Benefit (B, H)</th>
<th>Impact of new studies (retrospective comparative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain/Spinal</td>
<td>6.5</td>
<td>CC=2; CS=6</td>
<td>CC=5; CS=6</td>
<td>Incremental</td>
</tr>
</tbody>
</table>

2014 vs. 2019: Different tumors for curative intent (medulloblastoma, intramedullary glioma vs. high grade glioblastoma, high grade glioma) and different PBT protocols and comparators (PBT vs photon, IMRT in 2014, PBT boost vs. photon, PBT vs. photon in 2019) across reports contribute to different conclusions regarding NHB. Studies in the 2019 report were larger (including one large database study which did not report harms). Evidence for PBT vs. photon for CNS metastasis (salvage) was insufficient.

KQ 1 (Curative Intent): Adult breast cancer, OS

<table>
<thead>
<tr>
<th>Probabilibty overall survival (OS)</th>
<th>Studies, Year, N, Tumor</th>
<th>Reason for Downgrading</th>
<th>PBT vs. Photon/Electron Boost Effect estimate (95% CI)</th>
<th>Conclusion Quality (SoE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability overall survival (OS)</td>
<td>Chowdhary 2019 (N=724,492) Retro comparative database study (NCDB)</td>
<td>Consistency Unknown</td>
<td>91.9% vs. 88.9% (unadjusted probabilities)</td>
<td>No statistical difference between PBT versus photon/electron boost therapy for the probability of OS at 5 years.</td>
</tr>
</tbody>
</table>

- Study did not report on safety/harms;
- No comparative studies were identified for KQ2 (salvage), 3 (safety), or 4 (differential efficacy/safety)
KQ 3: Breast Cancer; Toxicities
CASE SERIES

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th># With outcome</th>
<th>Total N (range of N's)</th>
<th>Median F/U (months)</th>
<th>Range (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Grade ≥2</td>
<td>1</td>
<td>62</td>
<td>100</td>
<td>60</td>
<td>62%</td>
</tr>
<tr>
<td>Acute Grade ≥3</td>
<td>2</td>
<td>1</td>
<td>128</td>
<td>9.3 to 60</td>
<td>0 - 3.6%</td>
</tr>
<tr>
<td>Late Grade ≥2</td>
<td>1</td>
<td>NR</td>
<td>100</td>
<td>60</td>
<td>7 [events]</td>
</tr>
</tbody>
</table>

Limited information available from case series;

Appendix Table F12

KQ 5, Cost-effectiveness: Adult breast cancer

Mailhot Vega 2016 (USA), QHES 73/100;

| Population | Women with breast cancer aged 40, 50, or 60; with or without CRFs (Hypothetical cohorts) |
| Interventions | PBT (timing, intent unclear) vs. Photon |

ICER

- Varied by dose, ± cardiac risk factors, age; Range for 50 year old women, no CRF $890,000/QALY (lowest doses) to $90,000/QALY (highest doses); with ≥1 CRF, $90,000/QALY to $49,000/QALY
- Doses cost-effective at $50,000/QALY in women with
  - no CRFs: none; ≥1 CRF: beginning at mean heart dose (MHD) 9 Gy and 10 Gy for 50 and 60 years
- Doses cost-effective at $100,000/QALY in women with
  - no CRFs: MHD 10 Gy for 40 year-old women, 9 Gy for 50 year-old women
  - ≥1 CRF: MHD ≥6 Gy for 40, 60 year-old women; MHD ≥5 Gy for 50 year-olds

SA

- No CRFs: PBT not cost-effective at $50,000/QALY or less and $100,000/QALY in all ages (7 Gy for 50 year-old women, 9 Gy for 40 & 60 year-old)
- ≥1 CRF, ICER range: $49,757/QALY to $161,285/QALY based on age, dose

Author’s Conclusion

- For women w/o CRFs, PBT not cost-effective at a WTP of $50,000/QALY. PBT more likely to be cost-effective for women with ↑ risk of CHD and for younger patients.

Limitations

- Unclear Markov model methods; sensitivity analyses show substantial variation in CE
- Outcomes other than CHD, death not modeled; utilities not detailed;
- Lifetime horizon, but no comparative long-term data
- PBT: not clear that costs captured all aspects of operation
- Components of CHD treatment costs not reported; modeled PCI but not CABG
- Data from case series on PBT, case-control study of radiation-related risk for IHD in women receiving RT between 1958 and 2001 (impact of newer RT methods is unclear)
Summary: Adult breast cancer

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence (per 100,000)</th>
<th>Numbers of Studies</th>
<th>Net Health Benefit vs. Comparators</th>
<th>Impact of new retrospective comparative studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>124.7</td>
<td>CS=4; Econ=3</td>
<td>CC=1</td>
<td>CS=4; Econ=1</td>
</tr>
</tbody>
</table>

2019 Economic, 1 CUA: Hypothetical cohort models suggest PBT is not cost effective in women w/o CRFs vs. photon RT but may be for younger women and those with ↑ CAD risk, depending on dose. Modeling is based on case-series and case-control data (which may not reflect more recent RT methods), model parameters are not well documented; sensitivity analyses show substantial variation in CE.

2014 vs. 2019: In the absence of studies directly comparing the safety/adverse events PBT with other radiation therapy, the net health benefit is unclear.

KQ 1 (Curative Intent): Adult esophageal tumors

Overall Survival (retrospective cohort studies)

SOE Low for all

Definitive Chemoradiotherapy: PBT vs. IMRT

Xi 2017: adj. HR 1.5 (95% CI 1.1 to 1.9), p=0.01; log rank p=0.01

Fang 2018: adj. HR 1.5 (95% CI 0.9 to 2.4), p=0.10; log rank p=0.10* (propensity score matched)
### KQ 1 (Curative Intent): Adult esophageal tumors

#### Mortality (retrospective cohort studies)

<table>
<thead>
<tr>
<th>Author, Year, N, Tumor type</th>
<th>Timing</th>
<th>Photon (various)</th>
<th>Effect size (95% CI)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Makishima (2015), N=44 Definitive Chemoradiotherapy SOE Insufficient</td>
<td>SCC (100%) NR median f/u 22.3 mos.</td>
<td>XRT: 31.6% (6/19)</td>
<td>RR 0.63 (0.23 to 1.77)†</td>
<td>p=0.425</td>
</tr>
<tr>
<td>Lin (2017), N=580 Trimodal Therapy (Chemotherapy, Radiation and Surgery) SOE Low</td>
<td>AC (92%) or SCC (8%) 1 mo. post-op</td>
<td>Any photon: 1.5% (7/469)</td>
<td>P=0.590</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3DCRT: 1.9% (4/214)</td>
<td>IMRT: 1.2% (3/255)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0% (0/111)</td>
<td>Any photon: 2.6% (12/469)</td>
<td>2 mos. post-op 0.9% (1/111)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any photon: 4.3% (20/469) 3DCRT: 4.2% (9/214)</td>
<td>IMRT: 4.3% (11/255)</td>
<td>3 mos. post-op† 0.9% (1/111)</td>
</tr>
</tbody>
</table>

### KQ 1 (Curative Intent): Adult esophageal tumors

#### Progression- or Disease-Free Survival

<table>
<thead>
<tr>
<th>Author, Year, N</th>
<th>Probability (%)</th>
<th>Definitive Chemoradiotherapy: PBT IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xi 2017: (N=343, stage III)</td>
<td>55</td>
<td>62</td>
</tr>
<tr>
<td>Fang 2018: (N=133, stage III/IV only)</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

For 1-year: 62%; 2-years: 55%; 3-years: 50%; 4-years: 45%; 5-years: 41%
KQ 1 (Curative Intent): Adult esophageal tumors

**Distant Metastasis- and Locoregional Failure-Free Survival**

**Definitive Chemoradiotherapy:**

- DMFS: Xi 2017 (N=343)
  - AC (71%) or SCC (29%)
  - Stage III (66%)
  
  - Probability (%)
    - 1-year: 78
    - 2-years: 69
    - 3-years: 57
    - 4-years: 55
    - 5-years: 51

- LRFFS†
  - Adj. HR 1.46 (95% CI 1.02 to 2.10), p=0.041; Log-rank p=0.08

**SOE Low for all**

KQ 3 (Safety): Adult esophageal tumors

**SOE Low for all**

- Any toxicity, Grade ≥3
- Radiation pneumonitis, Grade ≥3
- Pulmonary fibrosis, Grade ≥3
- Pericardial effusion, Grade ≥3
- Esophageitis, Grade ≥3
- Esophageal fistula, Grade ≥3
- Esophageal stricture, Grade ≥3

**PD-RT (PBT vs. IMRT)**

- Any pulmonary event (Grade NR)
- Any GI event (Grade NR)
- Any wound event (Grade NR)

**Timing (0-200 days)**

- Radiation-induced Lymphopenia, Grade ≥3

**Proportion of patients (%)**
KQ 3 (Safety): Adult esophageal tumors

Fewer AEs/toxicities were seen with PBT across two retro cohort studies with different treatment protocols; Not all were statistically significant. (Makishima [N=44], chemoradiotherapy, Lin, trimodal therapy); toxicity grade NR for Lin; clinical significance is unclear.

SOE Low for all

Proportion of patients (%)

KQ 3: Esophageal tumors; Toxicities
CASE SERIES

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th># With outcome</th>
<th>Total N</th>
<th>F/U (mos)</th>
<th>Range (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Hematological Grade 3, 4 (NOS)</td>
<td>1</td>
<td>10</td>
<td>40</td>
<td>24</td>
<td>25%</td>
</tr>
<tr>
<td>Acute Grade 3 or 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1</td>
<td>26</td>
<td>47</td>
<td>29</td>
<td>55.3%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td>21</td>
<td></td>
<td></td>
<td>44.7%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
<td>13</td>
<td></td>
<td></td>
<td>27.7%</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td>2.1%</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
<td>10.6%</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Late Grade 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>1</td>
<td>2</td>
<td>40</td>
<td>24</td>
<td>5%</td>
</tr>
<tr>
<td>Pericarditis, pericardial effusion</td>
<td>1</td>
<td>0</td>
<td>47</td>
<td>29</td>
<td>0%</td>
</tr>
<tr>
<td>Lung (pneumonitis)</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td>2.1%</td>
</tr>
<tr>
<td>Esophageal</td>
<td>3</td>
<td>5</td>
<td></td>
<td></td>
<td>6.4% (4.3% stenosis, 2.1% fistula)</td>
</tr>
</tbody>
</table>

Small sample sizes noted; Appendix Table F15
Summary: Adult esophageal tumors

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence (per 100,000)</th>
<th>Numbers of Studies</th>
<th>Net Health Benefit vs. Comparators</th>
<th>Impact of new retrospective comparative studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal</td>
<td>4.6</td>
<td>CC=2; CS=7</td>
<td>Insufficient</td>
<td>New retrospective comparative evidence lead to different conclusions</td>
</tr>
</tbody>
</table>

2014 vs. 2019: The 2014 report included 2 (1 large) fair-quality comparative studies and concluded that the evidence was limited and inadequate to compare the potential benefits and harms of PBT relative to other radiation modalities.

Evidence from 5 new retrospective comparative observational studies suggest that PBT may of incremental benefit compared to IMRT and other forms of radiation (3DCRT, XRT) with better survival outcomes and similar, or slightly better safety profile (SOE Low). Results for safety were mixed; for some outcomes differences may be clinically important.
**KQ 1 (Curative Intent): Adult head and neck (non-skull base)**

**Overall, Progression-Free Survival, Mortality**

<table>
<thead>
<tr>
<th>Probability (%)</th>
<th>PBT</th>
<th>IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year</td>
<td>83.3</td>
<td>95.5</td>
</tr>
<tr>
<td>3-years</td>
<td>94.3</td>
<td>95.3</td>
</tr>
<tr>
<td>3-years</td>
<td>86.4</td>
<td>85.8</td>
</tr>
</tbody>
</table>

- **p=0.08** adj. HR 0.55 (95% CI 0.12 to 2.5)
- **adj. HR 1.0 (95% CI 0.39 to 2.6)**

**All-cause mortality:**
- 1 small matched-pairs cohort (N=30, primary nasopharyngeal cancer) [Holliday 2015]:
  - PBT 10% (1/10);
  - IMRT 5% (1/20);
  - p=NS

*SOE Low* for primary oropharyngeal and nasopharyngeal cancer;
*Insufficient* for salivary cancer (primary or metastatic)

**KQ 1 (Curative Intent): Adult head and neck (non-skull base)**

**Locoregional and Distant Control (No SOE)**

<table>
<thead>
<tr>
<th>Probability (%)</th>
<th>PBT</th>
<th>IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year</td>
<td>80.0</td>
<td>96.5</td>
</tr>
<tr>
<td>3-years</td>
<td>91.0</td>
<td>89.7</td>
</tr>
<tr>
<td>3-years</td>
<td>83.3</td>
<td>91.3</td>
</tr>
<tr>
<td>3-years</td>
<td>87.0</td>
<td>90.5</td>
</tr>
</tbody>
</table>

- **p=0.47** HR 1.03 (95% CI 0.35 to 3.0)
- **p=0.66** HR 0.33 (95% CI 0.04 to 2.7)

1 small matched-pairs retro cohort (N=30, primary nasopharyngeal cancer) [Holliday 2015]:

- **Local Failure**:
  - PBT 0%; IMRT 5% (1/20)
- **Distant Metastases**:
  - PBT 10% (1/10);
  - IMRT 5% (1/20)
  - p=NS for both
### KQ 3 (Safety): Adult head and neck (non-skull base)

**ACUTE toxicity, adverse events; NS differences in grade ≥ 3 for PBT vs. IMRT (3 studies)**

<table>
<thead>
<tr>
<th>Event</th>
<th>PBT</th>
<th>IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatitis, grade ≥ 2</td>
<td>26.0</td>
<td>56.5</td>
</tr>
<tr>
<td>Mucositis, grade ≥ 2</td>
<td>32.2</td>
<td>52.2</td>
</tr>
<tr>
<td>Fatigue, grade ≥ 2</td>
<td>8.7</td>
<td>8.7</td>
</tr>
<tr>
<td>Weight loss, grade ≥ 1</td>
<td>14.0</td>
<td>14.0</td>
</tr>
<tr>
<td>Nausea, grade ≥ 2</td>
<td>15.5</td>
<td>15.5</td>
</tr>
<tr>
<td>Dysguesia, grade ≥ 2</td>
<td>87.9</td>
<td>87.9</td>
</tr>
<tr>
<td>Dysphagia, grade ≥ 2</td>
<td>87.9</td>
<td>87.9</td>
</tr>
<tr>
<td>Dermatitis, grade ≥ 3</td>
<td>52.1</td>
<td>52.1</td>
</tr>
<tr>
<td>G-tube presence or weight loss, grade ≥ 3</td>
<td>14.6</td>
<td>14.6</td>
</tr>
<tr>
<td>Fatigue, grade ≥ 2</td>
<td>21.6</td>
<td>21.6</td>
</tr>
<tr>
<td>Nausea, grade ≥ 2</td>
<td>20.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Mucositis, grade ≥ 3</td>
<td>38.0</td>
<td>38.0</td>
</tr>
<tr>
<td>Dermatitis, grade ≥ 3</td>
<td>32.0</td>
<td>32.0</td>
</tr>
<tr>
<td>Nausea, grade ≥ 2</td>
<td>33.5</td>
<td>33.5</td>
</tr>
<tr>
<td>Fatigue, grade ≥ 2</td>
<td>36.2</td>
<td>36.2</td>
</tr>
<tr>
<td>Any event, grade 3</td>
<td>90.0</td>
<td>90.0</td>
</tr>
<tr>
<td>Hospitalization (unscheduled)</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>G-tube presence</td>
<td>21.0</td>
<td>21.0</td>
</tr>
<tr>
<td>ER visits</td>
<td>63.9</td>
<td>63.9</td>
</tr>
<tr>
<td>Dermatitis, grade ≥ 3</td>
<td>65.2</td>
<td>65.2</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>38.1</td>
<td>38.1</td>
</tr>
<tr>
<td>Accessory salivary gland cancer</td>
<td>51.5</td>
<td>51.5</td>
</tr>
<tr>
<td>Any event, grade 2</td>
<td>52.1</td>
<td>52.1</td>
</tr>
<tr>
<td>Fatigue, grade ≥ 2</td>
<td>56.5</td>
<td>56.5</td>
</tr>
<tr>
<td>Xerostomia, grade ≥ 2</td>
<td>56.5</td>
<td>56.5</td>
</tr>
<tr>
<td>Any event, grade 3</td>
<td>57.5</td>
<td>57.5</td>
</tr>
<tr>
<td>Swallowing dysfunction</td>
<td>58.0</td>
<td>58.0</td>
</tr>
<tr>
<td>Nausea, grade ≥ 3</td>
<td>78.0</td>
<td>78.0</td>
</tr>
<tr>
<td>Dermatitis, grade ≥ 3</td>
<td>80.9</td>
<td>80.9</td>
</tr>
<tr>
<td>Any event, grade 3</td>
<td>86.6</td>
<td>86.6</td>
</tr>
<tr>
<td>Fatigue, grade ≥ 2</td>
<td>90.0</td>
<td>90.0</td>
</tr>
<tr>
<td>Any event, grade 3</td>
<td>96.6</td>
<td>96.6</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>G-tube presence</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>ER visits</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Any event, grade 3</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Swallowing dysfunction</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>G-tube presence</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>ER visits</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Any event, grade 3</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**SOE Low**

### KQ 3 (Safety): Adult head and neck (non-skull base)

**LATE toxicity, adverse events**

<table>
<thead>
<tr>
<th>Event</th>
<th>PBT</th>
<th>IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss, grade ≥ 3</td>
<td>24.7</td>
<td>32.1</td>
</tr>
<tr>
<td>G-tube presence or weight loss, grade ≥ 3</td>
<td>14.6</td>
<td>14.6</td>
</tr>
<tr>
<td>Fatigue, grade ≥ 2</td>
<td>22.1</td>
<td>22.1</td>
</tr>
<tr>
<td>Xerostomia, grade ≥ 2</td>
<td>47.2</td>
<td>47.2</td>
</tr>
<tr>
<td>Any event, grade 3</td>
<td>30.0</td>
<td>15.0</td>
</tr>
</tbody>
</table>

**NS difference between PBT and IMRT with the exception of the composite outcome of g-tube + weight loss (neither outcome alone was significant) across two retrospective cohort studies; some differences may be of clinical importance. SOE Low**

---

**WA - Health Technology Clinical Committee**

32
Andrea C. Skelly, PhD, MPH
Aggregate Analytics, Inc.

KQ 3 (Safety): Adult head and neck (non-skull base)
Gastrostomy Tube Dependence

Retrospective studies, NS difference for PBT vs. IMRT in largest study, 2 smaller studies; two small studies (different tumors) report significantly lower g-tube dependence w/PBT; the large CIs suggest effect estimate instability, data are NR for the other; differences may be clinically important; SOE LOW

KQ 3 (Safety): Adult head and neck (non-skull base)
Osteoradionecrosis

SOE Insufficient
KQ 1 (Curative Intent): Adult head/neck (Skull base Chondrosarcoma) Disease-Specific and Progression-Free Survival

NS difference for PBT + surgery vs surgery in DSS at 5 or 10 years across patients in one small retro cohort; PFS was better with PBT; DSS and PFS were better with PBT in subanalysis of those with petroclival lesions

SOE Insufficient

KQ 3 (Safety): Adult head and neck (Skull base Chondrosarcoma) (small retrospective cohort)

<table>
<thead>
<tr>
<th></th>
<th>PBT (N=28)*</th>
<th>Surgery (N=47)†</th>
<th>RR (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any complication</td>
<td>68%</td>
<td>26%</td>
<td>2.7 (1.5 to 4.6)</td>
</tr>
<tr>
<td>Sensorineural hearing loss</td>
<td>39%</td>
<td>6%</td>
<td>6.2 (1.9 to 20.2)</td>
</tr>
<tr>
<td>Severe hearing loss</td>
<td>21%</td>
<td>4%</td>
<td>5.0 (1.1 to 23.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14%</td>
<td>0%</td>
<td>NC, p=0.008</td>
</tr>
<tr>
<td>Conductive hearing loss</td>
<td>11%</td>
<td>4%</td>
<td>p=0.28</td>
</tr>
<tr>
<td>Any grade ≥3 toxicity</td>
<td>25%</td>
<td>11%</td>
<td>p=0.10</td>
</tr>
<tr>
<td>Cranial nerve palsy</td>
<td>11%</td>
<td>19%</td>
<td>p=0.34</td>
</tr>
<tr>
<td>Treatment-related death</td>
<td>0%</td>
<td>2%</td>
<td>p=0.44</td>
</tr>
<tr>
<td>Vision loss</td>
<td>11%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>18%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Temporal lobe necrosis</td>
<td>18%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Cerebrospinal fluid leak</td>
<td></td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td></td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td></td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

SOE Insufficient: Most complications were more common with PBT (+ surgery) vs. surgery alone; “any” complication, hearing loss outcomes and dizziness were significantly higher with PBT; sample size is small, confidence intervals from crude RRs are large.
**KQ 3: Head and Neck Tumors; Selected acute toxicities reported across multiple CASE SERIES**

<table>
<thead>
<tr>
<th>Outcome</th>
<th># Studies</th>
<th># With outcome</th>
<th>Total N (range of N's)</th>
<th>Median F/U (months)</th>
<th>Range (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Grade ≥3 (any)</td>
<td>2</td>
<td>0</td>
<td>235 (76-159)</td>
<td>65.5 to 77</td>
<td>0%</td>
</tr>
<tr>
<td>Acute Grade ≥3 (specific)</td>
<td>1*</td>
<td>NR</td>
<td>33</td>
<td>43</td>
<td>(below)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
<td>79%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td>51%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td>18%</td>
</tr>
<tr>
<td>Acute Grade 3 only (no Grade 4)</td>
<td>1†</td>
<td>NR</td>
<td>50</td>
<td>29</td>
<td>(below)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
<td>46%</td>
</tr>
<tr>
<td>Mucositis</td>
<td>29</td>
<td></td>
<td></td>
<td></td>
<td>58%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td>24%</td>
</tr>
<tr>
<td>Any Acute Grade 3</td>
<td>2</td>
<td>23</td>
<td>102 (42-60)</td>
<td>13.6-69</td>
<td>12% - 30%</td>
</tr>
<tr>
<td>Acute treatment related- death</td>
<td>3</td>
<td>2</td>
<td>154 (33-61)</td>
<td>13.6 -43</td>
<td>0% -1.7%</td>
</tr>
</tbody>
</table>

* Tongue † oropharyngeal

Sample sizes for most are small precluding detection of rare events; Appendix Table F 25 has complete listing

---

**KQ 3: Head and Neck Tumors; Selected late toxicities reported across multiple CASE SERIES**

<table>
<thead>
<tr>
<th>Outcome</th>
<th># Studies</th>
<th># With outcome</th>
<th>Total N (range of N's)</th>
<th>Median F/U (months)</th>
<th>Range (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late Grade ≥3 (any) (&gt;3 months)</td>
<td>7</td>
<td>55</td>
<td>699 (34-222)</td>
<td>13.6 -77</td>
<td>1.3% to 20%</td>
</tr>
<tr>
<td>Late Grade ≥3 (any) (time NR)</td>
<td>4</td>
<td>77</td>
<td>512 (38-251)</td>
<td>15.2-87.3</td>
<td>9.4%-24%</td>
</tr>
<tr>
<td>2, 5 year rates, any late Grade 3 (skull-based chondrosarcoma)</td>
<td>1</td>
<td>N/A</td>
<td>159</td>
<td>77</td>
<td>42.9% (32.3, 50.4) 57.2% (42.8,68.4)</td>
</tr>
<tr>
<td>CNS necrosis (time NR)</td>
<td>2</td>
<td>2</td>
<td>306 (84-222)</td>
<td>28.8 -50</td>
<td>0.5% to 1.2%</td>
</tr>
<tr>
<td>Brain necrosis (Grade ≥3)</td>
<td>5</td>
<td>6</td>
<td>643 (38-251)</td>
<td>30 -87.3</td>
<td>0% to 7.9%</td>
</tr>
<tr>
<td>Temporal Lobe Rad Necrosis (Grade 3)</td>
<td>1</td>
<td>13</td>
<td>222</td>
<td>50</td>
<td>5.9%</td>
</tr>
<tr>
<td>Bone, soft tissue necrosis (Time NR)</td>
<td>5</td>
<td>19</td>
<td>349 (33-96)</td>
<td>24-57.5</td>
<td>0% to 15.2%</td>
</tr>
<tr>
<td>Late treatment related- death</td>
<td>6</td>
<td>9</td>
<td>332 (34-84)</td>
<td>13.3-30</td>
<td>0% to 3.7%</td>
</tr>
<tr>
<td>Toxicity-free survival (any grade)</td>
<td>1</td>
<td>N/A</td>
<td>251</td>
<td>88</td>
<td>84.2% (79.3- 89.5)</td>
</tr>
</tbody>
</table>

Appendix Table F 25 has complete listing
KQ 5, Cost-effectiveness: Oropharyngeal squamous cell carcinoma

<table>
<thead>
<tr>
<th>Population</th>
<th>65 year old patients with stage III-IVB oropharyngeal squamous cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions</td>
<td>PBT (timing unclear, accompanied by chemotherapy) vs. IMRT</td>
</tr>
</tbody>
</table>
| ICER | Societal perspective: HPV positive: $390,000/QALY; HPV negative: $695,000/QALY  
                  Payer perspective: HPV positive: $288,000/QALY; HPV negative: $516,000/QALY |
| One-way SA | Even under assumptions favoring PBT to reduce PEG dependence, improve long-term xerostemia, ICERS above $100,000/QALY (range $101,000/QALY to $1 million/QALY) |
| Other SA | Probability PBT cost-effective 0% (both perspectives) at WTP of $100,000/QALY and 0.4% (payer) and 0% (societal) at WTP $150,000/QALY  
                  PBT cost effective for 55 year-old patients at WTP $100,000/QALY in 0.4% for payer and 2% for societal; at WTP $150,000/QALY 25% (payer), 2% (societal) were cost-effective |
| Author’s Conclusion | PBT is not cost-effective using either societal or payer perspective; at extremes of PBT superiority it becomes cost-effective for younger HPV-positive patients |
| Limitations | • Oncologic outcomes assumed to be same for IMRT, PBT despite limited evidence  
                  • Lifetime time horizon, however no long-term comparative data available  
                  • Improved side effect profile of PBT assumed from minimal 1 case series  
                  • Societal costs assumed to be same for both treatment modalities  
                  • Disutilities for toxicities assumed to be additive, potentially under-estimating QALYs from IMRT |

Summary: Adult head and neck tumors

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence (per 100,000)</th>
<th>Numbers of Studies</th>
<th>Net Health Benefit vs. Comparators</th>
<th>Impact of new Retrospective comparative studies</th>
</tr>
</thead>
</table>
| Chondrosarcoma of the skull base | CC=1  
                  CS=15;  
                  Econ=2 | CC=7  
                  CS=14;  
                  Econ=1 | Insufficient low | Insufficient |

2014 vs. 2019: The 2014 report had 2 poor quality retrospective studies and concluded that the evidence was inadequate to compared potential benefit and harms of PBT vs. other radiation modalities.

7 new larger retrospective observational studies suggests net health benefits of PBT are comparable vs. IMRT for non-skull base tumors (SOE Low); statistical significance for harms was in consistent. Evidence is still insufficient for skull-base chondrosarcoma (1 small study).

PBT was not cost-effective in 1 CUA in patients w/oropharyngeal squamous cell carcinoma
### KQ 1 (Curative Intent): Adult liver (HCC)

**Overall and Progression-Free Survival**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies, Year, N, Tumor</th>
<th>Reason for Down-grade</th>
<th>Effect estimate (95% CI)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized Controlled Trial</td>
<td>PBT vs. TACE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability, overall survival (OS), Progression-free survival (PFS) 2 Years</td>
<td>Bush 2016 (N=69) RCT</td>
<td>Consistency Unknown Precision (-1)</td>
<td>OS: 59% (NR) (all patients)  • liver transplant post-treatment (n=22): 82% (NR) p=NS for both, data not provided by group PFs: 48% (NR) vs. 31% (NR); p=0.06</td>
<td>No significant difference in OS; PBT tended to result in improved PFS compared with TACE patients (not statistically significant). Results are from interim analysis of an ongoing trial.</td>
</tr>
<tr>
<td>Middle</td>
<td>Sanford 2019 (N=133) Retrospective cohort study</td>
<td>Consistency Unknown Precision (-1)</td>
<td>OS: 59.1% vs. 28.6%; adj. HR 0.47 (95% CI 0.27 to 0.82)</td>
<td>OS was significantly higher following PBT vs. IMRT</td>
</tr>
</tbody>
</table>

### KQ 3 (Safety): Adult liver (HCC)

**Randomized Controlled Trial**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies, Year, N, Tumor</th>
<th>Reason for Down-grading</th>
<th>Effect estimate (95% CI)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Toxicity (≤3 mos.)</td>
<td>Bush 2016 (N=69) RCT</td>
<td>Consistency Unknown Precision (-1)</td>
<td>Acute toxicity, generally limited to the following, which were experience by most patients (no data provided)*:  • PBT: fatigue and radiation skin reaction  • TACE: abdominal pain and nausea</td>
<td>Limited information provided on acute toxicity. Significantly fewer patients who received PBT required hospitalization in the month following treatment compared with TACE patients; total days hospitalized were significantly fewer in the PBT vs. the TACE group. Results are from interim analysis of an ongoing trial.</td>
</tr>
<tr>
<td>Hospitalization % (n/N) ≤1 month</td>
<td></td>
<td></td>
<td>For an acute event: 6.1% (2/33) vs. 41.7% (15/36); p&lt;0.001 Total days hospitalized: Overall: 24 (0.73 days per patient) vs. 166 (4.6 days per patient); p&lt;0.001; for  • routine observation: 0 vs. 53  • complications: 24 vs. 113</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>
### KQ 3 (Safety): Adult liver (HCC)

**Observational Comparative Study**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies, Year, N, Tumor</th>
<th>Reason for Down-grading</th>
<th>Effect estimate (95% CI)</th>
<th>Conclusion Quality (SoE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of nonclassic radiation-induced liver disease (RILD)* 3 months</td>
<td>Sandford 2019 (N=100)† Retrospective cohort study</td>
<td>Consistency Unknown Precision (-1)</td>
<td>adj. OR 0.26 (95% CI 0.08 to 0.86) (PBT, n=4 patients; IMRT, n=17 patients) Authors also report that the development of RILD at 3 months was associated with significantly worse OS (HR 3.83; 95% CI 2.12 to 6.92).</td>
<td>Lower risk of RILD in the acute period with PBT versus IMRT ◁◯◯◯ LOW</td>
</tr>
<tr>
<td>Death due to liver failure Median 14 months</td>
<td>Sandford 2019 (N=36)‡ Retrospective cohort study</td>
<td>Consistency Unknown Precision (-1)</td>
<td>53% (8/15) vs. 91% (19/21); RR 0.59 (95% CI 0.36 to 0.97)§</td>
<td>Lower risk of death due to liver failure with PBT versus IMRT; however data was from a small subset of patients. ◁◯◯◯ INSUFFICIENT</td>
</tr>
</tbody>
</table>

### KQ 3: Liver cancer, PBT toxicities

**CASE SERIES**

<table>
<thead>
<tr>
<th>Outcome</th>
<th># Studies</th>
<th># with outcome</th>
<th>Total N [range of N’s]</th>
<th>Range of Median F/U (mos)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curative Intent (HCC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Toxicity ≥ Grade 3</td>
<td>2</td>
<td>2</td>
<td>123 (40 to 83)</td>
<td>19.9 to 45</td>
<td>0% to 5%</td>
</tr>
<tr>
<td>Late Toxicity ≥ Grade 3</td>
<td>1</td>
<td>0</td>
<td>40</td>
<td>19.9</td>
<td>0%</td>
</tr>
<tr>
<td>Toxicity NOS (HCC or ICC) ≥ Grade 3</td>
<td>3</td>
<td>8†</td>
<td>249 (37 to 129)</td>
<td>11 to 55</td>
<td>5% to 11%</td>
</tr>
<tr>
<td>Treatment-related liver failure, death</td>
<td>2</td>
<td>4</td>
<td>250 (within 4-6 mos.)</td>
<td></td>
<td>0% to 2%</td>
</tr>
<tr>
<td>Mixed Curative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Toxicity ≥ Grade 3</td>
<td>3</td>
<td>1</td>
<td>213 (41 to 101)</td>
<td>4.9 to 31.3</td>
<td>0% to 1%</td>
</tr>
<tr>
<td>Late Toxicity ≥ Grade 3</td>
<td>2</td>
<td>0</td>
<td>112 (41 to 71)</td>
<td>15.2 to 31.9</td>
<td>0% to 0%</td>
</tr>
<tr>
<td>Radiation-Liver Disease</td>
<td>1</td>
<td>4</td>
<td>101</td>
<td>4.9</td>
<td>4%</td>
</tr>
<tr>
<td>Gastroduodenal Toxicity</td>
<td>5</td>
<td></td>
<td></td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Salvage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Toxicity ≥ Grade 3</td>
<td>1</td>
<td>0</td>
<td>89</td>
<td>30.1</td>
<td>0%</td>
</tr>
<tr>
<td>Metastatic Liver Tumors (Mixed curative)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late Toxicity ≥ Grade 3</td>
<td>1</td>
<td>2</td>
<td>133</td>
<td>NR</td>
<td>1.6%</td>
</tr>
<tr>
<td>↑ of ≥2 Child-Pugh Score</td>
<td>1</td>
<td>8</td>
<td></td>
<td></td>
<td>6%</td>
</tr>
</tbody>
</table>

Appendix Table F31-34
**KQ 5, Cost-effectiveness: Inoperable HCC**

**Leung 2017 (Taiwan), QHES S1/100**

<table>
<thead>
<tr>
<th>Population</th>
<th>Inoperable advanced, large hepatocellular carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBT study</td>
<td>Age 70, 67% male; Child-Pugh Class A 67%; tumor size 45mm; Hepatitis C 87%</td>
</tr>
<tr>
<td>SBRT study</td>
<td>Age 69.4, 78.4% male; Child-Pugh Class A 100%; tumor size 72mm; Hepatitis C 28%</td>
</tr>
</tbody>
</table>

**Intervention(s)**
- PBT (timing unclear, possibly primary treatment) vs. Stereotactic body radiation therapy (SBRT)

**ICER**
- NTS557,907/2.61 QALY = NTS213,354/QALY (New Taiwan Dollars)

**One-way SA**
- Very sensitive to utilities and direct costs in stable and progressive disease states (range NR)

**Other SA**
- Monte Carlo simulations: At NTS2,157,024/QALY, PBT has 97% chance of being cost-effective and SBRT has 4% chance

**Author's Conclusion**
- PBT is cost-effective for inoperable advanced HCC at a WTP threshold for Taiwan

**Limitations**
- Data from separate case series of PBT and SBRT; study selection not transparent; basis of utilities not described
- Intervention and comparator populations not comparable: differences in patient populations including tumor size, Child-Pugh class, other factors; impact on analysis unclear
- Components and basis for some medical costs not detailed
- Did not include non-cancer deaths
- One-way sensitivity analysis not clearly presented; limited evaluation of assumptions, robustness of model is not clear
- May not be applicable to US

---

**Summary: Adult liver (HCC)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence (per 100,000)</th>
<th>Numbers of Studies</th>
<th>Net Health Benefit vs. Comparators Type of Net Benefit (B, H) SOE</th>
<th>Impact of new comparative studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>8.1</td>
<td>CC=3; CS=26</td>
<td>RCT=1; CC=1 CS=12; Econ=1</td>
<td>Comparable B = H: = Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PBT vs. IMRT Incremental B = H: ↓ Low</td>
</tr>
</tbody>
</table>

**2014 vs. 2019:** The 2014 report included 3 comparative cohort studies (2 prospective, 1 retrospective) and concluded that PBT net health benefits were comparable vs. other treatments (photon, chemotherapy only, carbon ion; SOE low). 1 new RCT and 1 new larger comparative study suggest that PBT has incremental benefit vs. TACE and IMRT with similar efficacy/effectiveness but with a reduction in harms (SOE Moderate for TACE, Low for IMRT).

**2019 Economic:** 1 poor quality CUA (Taiwan) likely not applicable to US; Conclusions regarding CE are challenging given methodological concerns
KQ 1 (Curative): non-small cell lung cancer (NSCLC), OS

Overall Survival: NS differences between groups at 1-5 years in 1 RCT (SOE Moderate) or across 4 retrospective cohort studies (SOE Low); some differences may be clinically important
### KQ 3 (Safety): non-small cell lung cancer (NSCLC)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time</th>
<th>Studies, Year, N, Reason for Downgrade</th>
<th>PBT vs. Photon (various)* Effect estimate (95% CI)</th>
<th>Conclusion Quality (SoE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of radiation pneumonitis, Grade ≥31</td>
<td>1-5 years</td>
<td>Liao 2018 N=173 (ITT) RCT</td>
<td>Consistency Unclear Serious Imprecision (-1)</td>
<td>NS differences ☢☢☢☢ MODERATE</td>
</tr>
</tbody>
</table>

**Randomized controlled trials**

<table>
<thead>
<tr>
<th>Radiation esophagitis</th>
<th>Rate of radiation pneumonitis, Grade ≥31</th>
<th>Radiation pneumonitis</th>
<th>Radiation dermatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR (median 26 mos)</td>
<td>Remick 2017 N=61 Retro cohort</td>
<td>Remick 2017 N=61 Retro cohort</td>
<td>NR (median 26 months)</td>
</tr>
<tr>
<td>Serious ROB (-1)</td>
<td>Serious ROB (-1)</td>
<td>Serious ROB (-1)</td>
<td>Grade 3: 0% (0/27) vs. 0% (0/34), p=NR</td>
</tr>
<tr>
<td>Serious Imprecision (-1)</td>
<td>Grade 3: 3.7% (1/27) vs. 11.8% (4/34), p=0.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3: 22.4% (11/49) vs. 17.6% (15/85), OR 1.4 (0.7 to 2.9), p=0.37</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3: 0% (0/27) vs. 0% (0/34), p=NR</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Retrospective cohort studies**

<table>
<thead>
<tr>
<th>Radiation esophagitis</th>
<th>Radiation pneumonitis</th>
<th>Radiation dermatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR</td>
<td>Remick 2017 N=61 Retro cohort</td>
<td>NR (median 26 months)</td>
</tr>
<tr>
<td>Serious ROB (-1)</td>
<td>Serious ROB (-1)</td>
<td>Grade 3: 0% (0/27) vs. 0% (0/34), p=NR</td>
</tr>
<tr>
<td>Serious Imprecision (-1)</td>
<td>Grade 3: 3.7% (1/27) vs. 2.9% (1/34), p=NR</td>
<td></td>
</tr>
<tr>
<td>Grade 3: 0% (0/27) vs. 0% (0/34), p=NR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NS differences PBT vs. IMRT for other acute toxicities reported in Remick; (Table 32) 81

### KQ 3: NSC Lung cancer; Acute PBT toxicities

**CASE SERIES**

<table>
<thead>
<tr>
<th>Outcome</th>
<th># Studies</th>
<th># With outcome</th>
<th>Total N (range of N’s)</th>
<th>Median F/U (months)</th>
<th>Range (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Grade ≥3 (any) NSCLC</td>
<td>4</td>
<td>24</td>
<td>237 (50-74)</td>
<td>7.8-33.7</td>
<td>0%-39%</td>
</tr>
<tr>
<td>Acute Grade ≥3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1</td>
<td>14</td>
<td>64</td>
<td>27.3</td>
<td>9.4%</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td>0</td>
<td></td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>GI</td>
<td></td>
<td>7</td>
<td></td>
<td></td>
<td>10.9%</td>
</tr>
<tr>
<td>Hematologic</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<td>2%-22%</td>
</tr>
<tr>
<td>General</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<td>3%-9%</td>
</tr>
<tr>
<td>Acute treatment related- death</td>
<td>1</td>
<td>0</td>
<td>64</td>
<td>27.3</td>
<td>0%</td>
</tr>
</tbody>
</table>

Small sample sizes preclude identification of rare events

Appendix Table F35 82
KQ 3: NSC Lung cancer; Late PBT toxicities CASE SERIES

<table>
<thead>
<tr>
<th>Outcome</th>
<th># Studies</th>
<th># With outcome</th>
<th>Total N (range of N's)</th>
<th>Median F/U (months)</th>
<th>Range (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late Grade ≥3 (any) NSCLC</td>
<td>4</td>
<td>14†</td>
<td>237 (50-74)</td>
<td>7.8 -33.7</td>
<td>0%-17.6%*</td>
</tr>
<tr>
<td>Grade ≥3 Pulmonary</td>
<td>1</td>
<td>14</td>
<td>64</td>
<td>27.3</td>
<td>21.9%</td>
</tr>
<tr>
<td>Grade ≥3 Cardiac</td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td>4.7%</td>
</tr>
<tr>
<td>Grade ≥3 GI</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td>3.1%</td>
</tr>
<tr>
<td>Grade ≥3 Hematologic</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td>3.1%</td>
</tr>
<tr>
<td>Late tx related- death (≥3 mos)</td>
<td>3</td>
<td>7†</td>
<td>162 (50-57)</td>
<td>7.8-29</td>
<td>0%-10.5%</td>
</tr>
<tr>
<td>Late tx related- death (time NR)</td>
<td>2</td>
<td>0</td>
<td>70 (35 + 35)</td>
<td>80-83.1</td>
<td>0%</td>
</tr>
<tr>
<td>Grade 2 rib fracture (3-year)</td>
<td>1</td>
<td>N/A</td>
<td>52</td>
<td>33</td>
<td>30% (14.9 -52.1%)</td>
</tr>
<tr>
<td>Radiation necrosis</td>
<td>1</td>
<td>0</td>
<td>56</td>
<td>33.7</td>
<td>0%</td>
</tr>
<tr>
<td>Grade ≥3 Toxicities (any, Time NR) NSCLC</td>
<td>4</td>
<td>21</td>
<td>125 (35-55)</td>
<td>29-83.1</td>
<td>1.8% to 12.7%</td>
</tr>
<tr>
<td>Hematologic Grade 3</td>
<td>1</td>
<td>NR</td>
<td>30</td>
<td>14</td>
<td>10%-23%</td>
</tr>
<tr>
<td>Hematologic Grade 4</td>
<td></td>
<td>NR</td>
<td></td>
<td></td>
<td>3%-33%</td>
</tr>
<tr>
<td>Non-hematologic</td>
<td></td>
<td>5</td>
<td></td>
<td></td>
<td>16.7%</td>
</tr>
<tr>
<td>Treatment-related death</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td>0%</td>
</tr>
</tbody>
</table>

Small sample sizes preclude identification of rare events; Appendix Table F35

Summary: Adult Lung Cancer

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence (per 100,000)</th>
<th>Numbers of Studies</th>
<th>Net Health Benefit vs. Comparators</th>
<th>Impact of new comparative studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2014</td>
<td>2019</td>
<td>Type of Net Benefit (B, H) SOE</td>
<td>2014 vs. 2019</td>
</tr>
<tr>
<td>Lung</td>
<td>60.5</td>
<td>CC=4; CS=19; Econ=2</td>
<td>RCT=1; CC=69; CS=11</td>
<td>Comparable B: = H: = Low**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Comparable B: = H: = Low</td>
</tr>
</tbody>
</table>

**2014-discrepancies in SOE between Table E52 and Table 3; Low was listed in the ES table and text

- Data on primary outcomes were available for KQ 1 and 3 in studies of PBT for curative intent for treatment of NSCLC with PBT vs. IMRT, 3DXRT or various RT types
- KQ2: The comparative study identified did not report on survival or safety (see report)
- KQ 4 and 5: no comparative studies identified
- 2014 vs. 2019: The 2014 report included 3 large comparative studies and concluded that net health benefits for PBT were comparable to other RT (IMRT, 3DCRT, carbon ion, SOE low). Evidence from 1 RCT and 5 comparative observational studies published subsequent to the prior report also suggest that PBT is comparable to IMRT and other forms of radiation for benefits and harms. (SOE Low)
OS, Mortality: NS difference in OS at 2 years (PBT vs. BT) or mortality (PBT vs. SRS) in 2 retrospective cohort studies; however a significantly higher risk of mortality at 5 years was reported for PBT vs. BT in choroid melanoma patients (SOE Low).

Recurrence: Significantly less common for PBT vs BT (+ TSR for all) at 3 years (SOE Low); NS difference in local recurrence for PBT vs. SRS (SOE Insufficient).

Metastasis: NS difference at anytime point in one study.
KQ 3 (adverse events): Adult ocular tumors

Adverse events: Optic neuropathy was significantly less common with PBT vs. SRS; no other significant differences noted for either retrospective study (SOE Low).

KQ 3: Ocular tumors; Adverse events, CASE SERIES

<table>
<thead>
<tr>
<th>Outcome (all cancers)</th>
<th># Studies</th>
<th># With outcome</th>
<th>Total N (range of N’s)</th>
<th>Median F/U (months)</th>
<th>Range (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enucleation</td>
<td>14</td>
<td>428</td>
<td>7298 (36-2499)</td>
<td>30-77</td>
<td>0% - 15.6%</td>
</tr>
<tr>
<td>Neovascular Glaucoma</td>
<td>8</td>
<td>513</td>
<td>4611 (36-2499)</td>
<td>30-84</td>
<td>0% - 25%</td>
</tr>
<tr>
<td>Secondary Glaucoma</td>
<td>3</td>
<td>22</td>
<td>203 (36-107)</td>
<td>49.5-70.3</td>
<td>6% - 20%</td>
</tr>
<tr>
<td>Cataracts</td>
<td>8</td>
<td>444</td>
<td>2907 (36-1696)</td>
<td>30-70.3</td>
<td>6.1% - 62%†</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>7</td>
<td>2521</td>
<td>5596 (36-2499)</td>
<td>46.2-54.8</td>
<td>0% - 68.1%</td>
</tr>
<tr>
<td>Maculopathy</td>
<td>4</td>
<td>600</td>
<td>2975 (63-1696)</td>
<td>30-69</td>
<td>7.2% - 49%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>6</td>
<td>2391</td>
<td>635 (63-2499)</td>
<td>30-69</td>
<td>4.7% - 54.8%</td>
</tr>
<tr>
<td>Rubeosis</td>
<td>4</td>
<td>77</td>
<td>518 (36-351)</td>
<td>47 - 68.7</td>
<td>0% - 45%</td>
</tr>
<tr>
<td>Scleral necrosis</td>
<td>4</td>
<td>5</td>
<td>5696 (36-2499)</td>
<td>49.5-54.8</td>
<td>0% - 0.9%</td>
</tr>
<tr>
<td>Papillopathy</td>
<td>3</td>
<td>25</td>
<td>441 (36 to 351)</td>
<td>50 to 68.7</td>
<td>0% to 7.1%</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>4</td>
<td>152</td>
<td>1341 (62 to 865)</td>
<td>30 to 70.3</td>
<td>3.1% to 15.2%</td>
</tr>
</tbody>
</table>
### KQ 3: Ocular tumors; Event probabilities, CASE SERIES

<table>
<thead>
<tr>
<th>Outcome (KM probabilities)</th>
<th># Studies</th>
<th>Total N (range)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year Enucleation-free survival</td>
<td>3</td>
<td>2889 (54-2499)</td>
<td>77.4% to 95.1%</td>
</tr>
<tr>
<td>5-year Neovascular Glaucoma</td>
<td>3</td>
<td>3464</td>
<td>10.5% to 34.9%</td>
</tr>
<tr>
<td>5-year Globe Preservation</td>
<td>1</td>
<td>2499</td>
<td>94.8%</td>
</tr>
<tr>
<td>1, 2, 3, 4, 5, 10 year Retinopathy-free Survival</td>
<td>1</td>
<td>1127</td>
<td>87%, 53%, 33%, 21%, 15%, 7%</td>
</tr>
<tr>
<td>1, 2, 3, 4, 5, 10 year Optic Neuropathy-free Survival</td>
<td>1</td>
<td>1127</td>
<td>92%, 73%, 61%, 52%, 48%, 26%</td>
</tr>
<tr>
<td>1, 3, 5 year Incidence of Cataracts</td>
<td>1</td>
<td>1696</td>
<td>4.9%, 12%, 18.7%</td>
</tr>
<tr>
<td>1, 3, 5 year Vision-Impairing Cataracts</td>
<td>1</td>
<td>1696</td>
<td>1.2%, 6.7%, 12.8%</td>
</tr>
<tr>
<td>1, 2, 5 year Incidence of Dry Eye</td>
<td>1</td>
<td>853</td>
<td>6%, 11.2%, 23%</td>
</tr>
<tr>
<td>1, 2, 5 year Incidence of Severe Dry Eye</td>
<td>1</td>
<td>853</td>
<td>2.1%, 4.8%, 10.9%</td>
</tr>
<tr>
<td>5 yr Absence, Radiation-induced Retinopathy</td>
<td>1</td>
<td>629</td>
<td>14.2%</td>
</tr>
<tr>
<td>5 year Absence of Optic Neuropathy</td>
<td>1</td>
<td>629</td>
<td>36.6%</td>
</tr>
</tbody>
</table>

**Appendix Table F52**

### KQ 5, Cost-effectiveness: Adults, intraocular melanoma

<table>
<thead>
<tr>
<th>Population</th>
<th>59 years of age with intraocular melanoma; 5 year time horizon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention(s)</td>
<td>PBT (timing unclear) vs. enucleation</td>
</tr>
<tr>
<td>ICER</td>
<td>$106,100/QALY</td>
</tr>
<tr>
<td>One-way SA</td>
<td>Model sensitive to 13 parameters for all therapies: probability of local recurrence, end-of-life costs for disease, treatment costs, post-treatment utility</td>
</tr>
<tr>
<td></td>
<td>ICER range for low parameter values: $9,543/QALY to $234,683/QALY</td>
</tr>
<tr>
<td></td>
<td>ICER range for high parameter values: $9,522/QALY to $441,750/QALY</td>
</tr>
<tr>
<td>Author's Conclusion</td>
<td>PBT was not cost-effective compared to enucleation at WTP of $50,000/QALY; Results were not robust to sensitivity analyses and showed that decreased payment rates for PBT could be result in PBT being dominant over enucleation</td>
</tr>
<tr>
<td>Limitations</td>
<td>RR for progression from local recurrence to distant metastasis derived from study using plaque brachytherapy; may not apply to other treatment strategies</td>
</tr>
<tr>
<td></td>
<td>No costs of treatment complications</td>
</tr>
<tr>
<td></td>
<td>QOL data from study of general melanoma (not specific to this population)</td>
</tr>
<tr>
<td></td>
<td>Strong assumptions about costs (costs for recurrence; cost of radiotherapy substituted with cost of enucleation; no cost specific to distant metastasis)</td>
</tr>
<tr>
<td></td>
<td>Frequency of enucleation as treatment option is unclear</td>
</tr>
</tbody>
</table>
Summary: Adult Ocular Tumors

<table>
<thead>
<tr>
<th>Incidence (per 100,000)</th>
<th>Numbers of Studies</th>
<th>Net Health Benefit vs. Comparators Type of Net Benefit (B, H) SOE</th>
<th>Impact of new comparative studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.9</td>
<td>2014: RCT=1; CC=3; CS=21; Econ=1</td>
<td>Superior (Incremental)* B: ↑ H: ↓ Moderate</td>
<td>3 additional comparative studies with very different comparators. Prior report included primarily enucleation (4/7 studies) as comparator, also TTT (1 study); remaining 2 studies were indirect comparisons of case series. The net health benefit across all comparators (across both reports) is unclear.</td>
</tr>
<tr>
<td></td>
<td>2019: RCT=1; CC=3; CS=45</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*There is a discrepancy in the 2014 report between the summary table and report text.

**2019 Economic:** 1 good quality CUA of PBT vs. enucleation for intraocular melanoma found PBT not cost effective at WTP of $50K/QALY; results were not robust to sensitivity analysis.

**KQ 2, 4:** No comparative studies identified

---

**Summary: Adult Ocular Tumors**

<table>
<thead>
<tr>
<th>Tumor</th>
<th>2014 Report</th>
<th>2019 Report</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># studies</td>
<td>Comparator* (vs. PBT)</td>
</tr>
<tr>
<td>Ocular</td>
<td>8 (2 NCCS)</td>
<td>Enucleation (4) PBT + TTT (2) (1 RCT) PBT + endoresection (1) PBT + chemotherapy (1) PBT + laser (1)</td>
</tr>
</tbody>
</table>

**2014 vs. 2019 report:** The net health benefit across reports (and comparators) is unclear

- **There are substantial differences in comparators (above); tumor types differed**
- **2014 report:** ES table listed superior net health benefit for PBT; improved benefits appears to be based on statistically significant increases in OS across two cohort studies at 2-5 years, 50% higher probability of metastasis-free survival and lower cancer and metastasis-related mortality with PBT compared with enucleation. Determination of less harm is less clear. In the report, authors state “Limited, low-quality evidence suggests comparable rates of harm for PBT relative to treatment alternatives in patients with ocular tumors” consistent with incremental net benefit
- **2019 report:** Comparisons generally less invasive for 3 new cohort studies; Net health benefit varied by comparator. Most studies were of uveal melanoma
KQ 1 (Curative Intent): Prostate
Overall and Biochemical Relapse-Free Survival, Quasi RCT

Probability of Overall Survival

Probability of Biochemical Relapse-Free Survival

Khmelniksky 2018
Quasi-RCT (N=289)
Prostate Cancer

SOE Low

KQ 3 (Safety): Prostate
Toxicity – quasi-RCT

Acute Toxicity (frequency ± SD)

Late Toxicity (frequency ± SD)

Khmelniksky 2018
Quasi-RCT (N=289)
Prostate Cancer

Actuarial frequency of GI and GU toxicities Grade ≥3: 1.7% vs. 8.7%, p=NR

SOE Low
KQ 3 (Safety): Prostate Toxicity – Retrospective cohort studies (database) (cont.)

SOE Low
KQ 3: Prostate Cancer; Toxicities
CASE SERIES

<table>
<thead>
<tr>
<th>Outcome</th>
<th># Studies</th>
<th># With outcome</th>
<th>Total N (range of N's)</th>
<th>Median F/U (months)</th>
<th>Range (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Grade ≥3 Toxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>4</td>
<td>0</td>
<td>761 (49 to 423)</td>
<td>18 to 62.4</td>
<td>0%</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>5</td>
<td>12</td>
<td>1423 (49 to 1289)</td>
<td>14.5 to 66</td>
<td>0% to 0.9%</td>
</tr>
<tr>
<td>Late Grade ≥3 Toxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>8</td>
<td>18</td>
<td>4809 (49 to 1375)</td>
<td>14.5 to 70</td>
<td>0% to 1.2%</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>8</td>
<td>67</td>
<td>4809 (49 to 1375)</td>
<td>14.5 to 70</td>
<td>0% to 4.7%</td>
</tr>
</tbody>
</table>

Outcome, timing, grade

<table>
<thead>
<tr>
<th>Studies</th>
<th>N</th>
<th>Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year Incidence of Late Grade 3 GI Toxicity</td>
<td>1</td>
<td>1327</td>
</tr>
<tr>
<td>5-year Rate, Late Gastrointestinal Toxicities; Grades 1, 2, 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-year Rate, Late Genitourinary Toxicities; Grades 1, 2, 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative Incidence, Argon plasma coagulation application for rectal bleeding</td>
<td>1</td>
<td>423</td>
</tr>
</tbody>
</table>

KQ 4 (Contextual Studies): Prostate
Comparison of PBT Dose, Fractionation, Delivery Method

Hypo- vs. standard fractionation (1 RCT, 1 retrospective cohort)
• NS differences between groups in QoL (various measures) and GI or GU toxicities grade ≥3; no treatment related deaths

“Moderate” (MHF) vs. “extreme” (EHF) hypofractionation (1 RCT)
• 7-year OS: 97.5% for the entire population (3 deaths total; 7-year BCFFS statistically lower in the EHF group (46.2% vs. 76.2%; adjusted HR 3.2, 95% CI 1.5 to 6.9, p=0.003)
• NS differences between groups in acute or late GI or GU toxicities grade ≥3

Passive scatter vs. spot scanning technique (1 retrospective cohort)
• NS differences between groups in QoL (EPIC questionnaire) or cumulative frequencies of grade ≥2 GU and GI toxicities or of argon plasma coagulation application for rectal bleeding

SOE not done for contextual studies
**Summary: Adult Prostate Cancer**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence (per 100,000)</th>
<th>Numbers of Studies</th>
<th>Net Health Benefit vs. Comparators</th>
<th>SOE</th>
<th>Impact of new comparative studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>109.2</td>
<td>RCT=1 CC=9; CS=19; Econ=3</td>
<td>Quasi-RCT=1; CC=3; CS=11</td>
<td>Comparable B: = H: = Low**</td>
<td>Comparable B: = H: = Low</td>
</tr>
</tbody>
</table>

**2014 vs. 2019:** The 2014 report included 1 RCT and 5 comparative studies (4 were NCCS) that reported clinical outcomes and concluded that net health benefits for PBT were comparable to other treatments (photons alone, IMRT, 3DCRT, brachytherapy, watchful waiting; SOE low). Evidence from 1 new quasi-RCT and 3 new retrospective cohort studies also suggest that PBT is comparable to photons alone and IMRT for benefits and harms. (SOE Low)

**SUMMARY: Adult conditions/tumors**

- 2014 vs. 2019: 37 new comparative studies were identified.
- New studies identified for some tumors/conditions for which only case series (insufficient evidence) were available in the 2014 report; 4 new CUA were identified
- SOE was Low for all conditions/outcomes with the exception of one study of HCC
- Comparative net health benefit based on new evidence changed for some conditions; differences in comparators, tumor types, PBT treatment approaches and study quality likely explain differences in NHB considerations between the 2014 and 2019 reports.
- No studies permitted evaluation of differential effectiveness or safety
SUMMARY - Adult tumors

- No comparative evidence for:
  - Bladder cancer
  - Bone cancer
  - Lymphoma
  - Benign tumors (hemangioma, meningioma, pituitary)
  - Various/mixed tumor types

- No evidence meeting inclusion criteria was identified for:
  - Sarcoma
  - Seminoma
  - Thymoma
  - AVMs

SUMMARY - Adult tumors (cont.)

The net health benefit of PBT was *incremental* to other treatments:

- Esophageal tumors
- Liver tumors
- Ocular tumors (PBT + TSR vs. brachytherapy + TSR)

The net health benefit of PBT was *comparable* to other treatments:

- Brain/spinal tumors (curative) (PBT boost vs. photons alone)
- Head and neck tumors (non-skull-base)
- Lung cancer
- Prostate cancer

The net health benefit of PBT was *inferior* to other treatments for:

- Ocular tumors (PBT vs. brachytherapy alone)
SUMMARY - Adult tumors (cont.)

There was insufficient or unclear evidence of a net health benefit from comparative studies for:

- Brain/spinal tumors (salvage)
- Breast cancer
- GI tumors (Pancreas)
- Head and neck skull-base tumors (Chondrosarcoma)
- Ocular tumors (PBT vs. stereotactic radiotherapy)

**Economic Studies:** Conclusions are limited from hypothetical models; clinical data were from case series, many models did not fully specify factors that may impact CE or describe model inputs; for some sensitivity analyses suggest substantial variation in cost-effectiveness.

General SUMMARY

- Focus of 2014 and 2019 reports was on comparative studies
- Comparative evidence base: Retrospective cohort studies at moderately high risk of bias;
  - Selection bias
  - Attrition bias
  - Confounding/residual confounding
- RCTs may not be ethical or feasible in some populations.
- SOE took into account lack of RCT evidence and challenges of doing RCTs; however,
  - the quality of NROS is not elevated;
  - the greater uncertainty regarding effects needs to be considered
General SUMMARY

• Comparators 2014 vs. 2019 reports differed; for some conditions, comparators may not reflect current practices; 2014 report included non-FDA approved treatments (e.g., carbon ion)
• Heterogeneity across studies and the reports with regard to conditions/tumor types, stages, use of chemotherapy and adjunctive treatments and PBT treatment approaches
• >150 case series on many different tumor types do not answer questions of comparative effectiveness or safety.

Questions?
Key Questions and Background

Proton beam therapy – re-review

Background:

Clinical need and target population

Overall, it’s estimated that 1.7 million new cases of cancer are diagnosed yearly and cancerous conditions are responsible for over half a million deaths per year. Treatment options for cancerous and noncancerous conditions vary depending on the type and stage of cancer and can include radiation therapy, chemotherapy, targeted therapy (e.g. inhibitor drugs), immunotherapy (including monoclonal antibodies) and surgery. In recent years the use of proton beam therapy (PBT) has expanded to include a variety of conditions including a number of cancer types, noncancerous brain tumors and cancerous conditions afflicting the central nervous system as well as eyes, lungs, liver, prostate, spine, and pelvis.

Technology of interest

The use of protons for radiotherapy has a history of over 60 years of clinical use. In conventional radiotherapy, photons deliver radiation across tissue depths on the way toward the target tumor and beyond. In contrast, PBT, which is a form of external beam radiotherapy, deposits peak radiation energy more precisely at or around the target followed by sharp decline in energy output to deeper tissues via a phenomenon known as the Bragg peak (Larsson, 1958). Because the proton beam is focused on a specific area, a greater dose of radiation may be delivered to the target neoplasm(s) while mitigating unwanted radiation delivered to surrounding tissue (Levin, 2005). PBT use was initially directed towards conditions where sparing sensitive adjacent normal tissues was considered to be of utmost importance (such as cancerous or noncancerous malformations of the brain stem, eye, or spinal cord) or for many pediatric tumors because of the particular risk of pronounced acute and long-term toxicity in pediatric patients (Thorp, 2010). PBT may be most promising for tumors in close proximity to organs at risk (OAR).

In the past two decades the number of centers offering PBT has increased to over 20, with more planned or under construction, even given the high cost of facility construction and operation. Despite increasing availability of PBT and its potential for precise delivery of radiation therapy, evidence of its effectiveness compared with other forms of therapy and with the emerging techniques, such as intensity modulated radiation therapy (IMRT) is evolving and currently not unclear for some conditions.

Policy context/reason for selection:

This topic was originally reviewed in 2014. It is being re-reviewed in 2018 due to newly available published evidence.
Objectives

The aim of this report is to update the 2014 HTA on proton beam therapy (PBT) by systematically reviewing, critically appraising and analyzing new research evidence on the safety and efficacy of PBT, as a primary or as a salvage therapy (i.e., for recurrent disease or failure of initial therapy), for the treatment of multiple cancer types as well as selected noncancerous conditions in adults and children.

Key questions (from previous report):

1. What is the comparative impact of proton beam therapy (PBT) treatment with curative intent on survival, disease progression, health-related quality of life, and other patient outcomes versus radiation therapy alternatives and other cancer-specific treatment options (e.g., surgery, chemotherapy) for the following conditions:
   a. Cancers
      i. Bone tumors
      ii. Brain, spinal, and paraspinal tumors
      iii. Breast cancer
      iv. Esophageal cancer
      v. Gastrointestinal cancers
      vi. Gynecologic cancers
      vii. Head and neck cancers (including skull base tumors)
      viii. Liver cancer
      ix. Lung cancer
      x. Lymphomas
      xi. Ocular tumors
      xii. Pediatric cancers (e.g., medulloblastoma, retinoblastoma, Ewing’s sarcoma)
      xiii. Prostate cancer
      xiv. Soft tissue sarcomas
      xv. Seminoma
      xvi. Thymoma
      xvii. Other cancers
   b. Noncancerous Conditions
      i. Arteriovenous malformations
      ii. Hemangiomas
      iii. Other benign tumors (e.g., acoustic neuromas, pituitary adenomas)

2. What is the comparative impact of salvage treatment (including treatment for recurrent disease) with proton beam therapy versus major alternatives on survival, disease progression, health-related quality of life, and other patient outcomes versus radiation therapy alternatives and other cancer-specific treatment options (e.g., surgery, chemotherapy) for the condition types listed in key question 1?

3. What are the comparative harms associated with the use of proton beam therapy relative to its major alternatives, including acute (i.e., within the first 90 days after treatment) and late (>90 days) toxicities, systemic effects such as fatigue and erythema, toxicities specific to each cancer type (e.g., bladder/bowel incontinence in prostate cancer, pneumonitis in lung or breast cancer), risks of secondary malignancy, and radiation dose?
4. What is the differential effectiveness and safety of proton beam therapy according to factors such as age, sex, race/ethnicity, disability, presence of comorbidities, tumor characteristics (e.g., tumor volume and location, proliferative status, genetic variation) and treatment protocol (e.g., dose, duration, timing of intervention, use of concomitant therapy)?

5. What is the comparative cost-effectiveness of proton beam therapy in the short- and long-term relative to other types of radiation therapy, radiation therapy alternatives or other cancer-specific treatment options (e.g., surgery, chemotherapy)?

**Final scope:** (based on previous report and consideration of public comment)

**Inclusion and exclusion**

<table>
<thead>
<tr>
<th>Study Component</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Adults and children undergoing treatment of primary or recurrent disease to include:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cancers (bone, brain/spinal/paraspinal, breast, esophageal, gastrointestinal, gynecologic, head and neck, liver, lung, ocular, pediatric, and prostate cancers; lymphomas, sarcomas, seminomas, thymomas, other cancers)</td>
<td></td>
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<tr>
<td></td>
<td>• Noncancerous conditions (arteriovenous malformations, hemangiomas, other benign tumors).</td>
<td>• Conditions not amenable to proton-beam therapy or for which proton beam therapy would be contra-indicated.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>• Proton beam therapy (PBT) use as a curative therapy</td>
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<tr>
<td></td>
<td>• Primary or monotherapy</td>
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<tr>
<td></td>
<td>• “Salvage” treatment (e.g. following failure of initial therapy or disease recurrence)</td>
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<td></td>
<td>• “Boost” mechanism to conventional radiation</td>
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<td></td>
<td>• Combination therapy with other treatments (e.g., chemotherapy, surgery).</td>
<td>• Devices or therapies that are not FDA approved or cleared</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>• Other radiation therapy alternatives (e.g., intensity-modulated radiation therapy (IMRT), stereotactic radiation techniques, other external beam therapies, and brachytherapy)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Other treatment alternatives specific to each condition type treated; may include chemotherapy, immunotherapy, surgical procedures, and other devices (e.g., laser therapy for ocular tumors).</td>
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</tr>
<tr>
<td></td>
<td>• Dose/fractionation comparison (will be included for completeness as was done in prior report) but not formally evaluated as evidence</td>
<td>• Technologies or treatments that are not widely available or are no longer routinely used</td>
</tr>
<tr>
<td></td>
<td>• Devices or therapies that are not FDA approved or cleared</td>
<td></td>
</tr>
</tbody>
</table>

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**Final**

Proton beam therapy – re-review: key questions
## Study Component

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Inclusion</th>
<th>Exclusion</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical outcomes:</strong></td>
<td></td>
<td>• Non-clinical outcomes</td>
</tr>
<tr>
<td>Primary</td>
<td></td>
<td></td>
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<tr>
<td>• Overall survival/disease-free survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• All-cause and/or disease-related mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Direct measures of tumor regression, control or recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Incidence of metastases</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Secondary or indirect (intermediate) measures**

- Patient reported outcomes, including health-related quality of life (HrQoL), based on validated instruments
- Requirements for subsequent therapy
- Other outcomes specific to particular conditions (e.g., visual acuity for ocular tumors, shunt requirements for arteriovenous malformations)
- Intermediate measures of tumor recurrence such as biochemical measures

### Safety outcomes:

- Treatment-related harms, with a focus on adverse effects requiring medical attention, to include:
  - Generalized effects (e.g., fatigue, erythema)
  - Localized toxicities specific to each condition (e.g., urinary incontinence in prostate cancer, pulmonary toxicity in lung or breast cancer) to include consideration of:
    - Early (≤90 days post-treatment)
    - Late (>90 days post-treatment)
- Secondary malignancy risk due to radiation exposure

### Economic outcomes:

- Long term and short term comparative cost-effectiveness measures (e.g. ICER)

## Study Design

- Focus will be on highest quality (lowest risk of bias) comparative studies (e.g., randomized controlled trials, comparative cohort studies with concurrent controls) for questions 1-4.
- Case series will be considered but will not be the primary focus of evaluation for each key question.
- Case series in children with <10 patients will be considered if no comparative studies are available.
- Case series designed specifically to evaluate safety may be included
- Dosimetry and planning studies may be included for context. To the extent that they specifically answer the key questions, information will be included as part of the evidence base.

- Simulation studies
- Studies of low quality (high risk of bias)
- Comparative studies with fewer than 10 per treatment arm
- Case reports
- Case series in adults with <30 patients; Case series of ≥ 10 patients may be considered for very rare conditions.
- Studies comparing modes of therapy; dose comparisons may be included for completeness/context per previous report
### Study Component

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Formal, full economic studies will be sought for question 5. Studies using modeling may be used to determine cost-effectiveness.</td>
<td>• Abstracts, editorials, letters</td>
</tr>
<tr>
<td>• Studies published in English in peer reviewed journals, technology assessments or publically available FDA reports</td>
<td>• Duplicate publications of the same study that do not report different outcomes or follow-up times</td>
</tr>
<tr>
<td>• Studies published subsequent to the 2014 report (previous report search date through February 2014)</td>
<td>• Single reports from multicenter trials</td>
</tr>
<tr>
<td>• For question 5, comparative, full formal economic analyses (e.g., cost-effectiveness, cost-utility studies) published in English in a peer reviewed journal</td>
<td>• White papers</td>
</tr>
<tr>
<td>• For question 5, comparative, full formal economic analyses (e.g., cost-effectiveness, cost-utility studies) published in English in a peer reviewed journal</td>
<td>• Narrative reviews</td>
</tr>
<tr>
<td>• For question 5, comparative, full formal economic analyses (e.g., cost-effectiveness, cost-utility studies) published in English in a peer reviewed journal</td>
<td>• Articles identified as preliminary reports when full results are published in later versions</td>
</tr>
<tr>
<td>• For question 5, comparative, full formal economic analyses (e.g., cost-effectiveness, cost-utility studies) published in English in a peer reviewed journal</td>
<td>• Incomplete economic evaluations such as costing studies</td>
</tr>
</tbody>
</table>

### Figure 1. Analytic framework

![Analytic framework diagram]

- **Intervention**: Proton beam therapy
- **KQ 1, 2**: Primary Clinical Outcomes
  - Overall and/or disease-free survival
  - All-cause and/or disease-related mortality
  - Direct measures of tumor regression, control or recurrence
  - Incidence of metasteses
- **Secondary Outcomes**
  - Patient-reported outcomes, including quality of life, using validated instruments
  - Requirements for subsequent therapy
  - Condition-specific outcomes
- **KQ 3, 4**: Harms or adverse events
- **KQ 5**: Comparative Cost-effectiveness

### Study Component

- **Publication**
  - Studies published in English in peer reviewed journals, technology assessments or publically available FDA reports
  - Studies published subsequent to the 2014 report (previous report search date through February 2014)
  - Single reports from multicenter trials
  - White papers
  - Narrative reviews
  - Articles identified as preliminary reports when full results are published in later versions
  - Incomplete economic evaluations such as costing studies
HTCC Coverage and Reimbursement Determination
Analytic Tool

HTA’s goal is to achieve better health care outcomes for enrollees and beneficiaries of state programs by paying for proven health technologies that work.

To find best outcomes and value for the state and the patient, the HTA program focuses on three questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

**Principle One: Determinations are evidence-based**

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective\(^1\) as expressed by the following standards\(^2\):

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

**Principle Two: Determinations result in health benefit**

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms\(^3\):

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.
- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.

---

\(^1\) Based on Legislative mandate: See RCW 70.14.100(2).

\(^2\) The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

\(^3\) The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm
• In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.

• The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

### Using evidence as the basis for a coverage decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. **Availability of evidence:**

   Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. **Sufficiency of the evidence:**

   Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence using characteristics such as:

   • Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
   • The amount of evidence (sparse to many number of evidence or events or individuals studied);
   • Consistency of evidence (results vary or largely similar);
   • Recency (timeliness of information);
   • Directness of evidence (link between technology and outcome);
   • Relevance of evidence (applicability to agency program and clients);
   • Bias (likelihood of conflict of interest or lack of safeguards).

   Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

<table>
<thead>
<tr>
<th>Not Confident</th>
<th>Confident</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.</td>
<td>Very certain of evidentiary support. Further information is unlikely to change confidence</td>
</tr>
</tbody>
</table>

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4 Based on GRADE recommendation: [http://www.gradeworkinggroup.org/FAQ/index.htm](http://www.gradeworkinggroup.org/FAQ/index.htm)
3. **Factors for Consideration - Importance**

At the end of discussion a vote is taken on whether sufficient evidence exists regarding the technology’s safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

- Risk of event occurring;
- The degree of harm associated with risk;
- The number of risks; the burden of the condition;
- Burden untreated or treated with alternatives;
- The importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- The degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- Value variation based on patient preference.

**Clinical committee findings and decisions**

**Efficacy considerations**

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
  - Direct outcome or surrogate measure
  - Short term or long term effect
  - Magnitude of effect
  - Impact on pain, functional restoration, quality of life
  - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value?
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests’ accuracy?
  - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices?
Safety

- What is the evidence of the effect of using the technology on significant morbidity?
  - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
  - Adverse effect on health that can result in lasting harm or can be life-threatening?

- Other morbidity concerns?

- Short term or direct complication versus long term complications?

- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

Cost impact

- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

Overall

- What is the evidence about alternatives and comparisons to the alternatives?

- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?

Next step: Cover or no cover

If not covered, or covered unconditionally, the chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next step: Cover with conditions

If covered with conditions, the committee will continue discussion.

1) Does the committee have enough information to identify conditions or criteria?
   - Refer to evidence identification document and discussion.
   - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
   - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.

2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
   - What are the known conditions/criteria and evidence state
   - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.
**Clinical committee evidence votes**

**First voting question**

The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

**Discussion document:** What are the key factors and health outcomes and what evidence is there? (Applies to the population in the PICO for this review)

<table>
<thead>
<tr>
<th>Safety outcomes</th>
<th>Importance of outcome</th>
<th>Safety evidence/ confidence in evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine-related toxicities (e.g. thyroid, hormone, etc.)</td>
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<tr>
<td>Other Toxicities (e.g. vascular, vision, hearing etc)</td>
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<tr>
<td>White Matter Lesion</td>
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<tr>
<td>Radiation Necrosis</td>
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<tr>
<td>Injury to CNS or Brainstem</td>
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<tr>
<td>Vascular</td>
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<tr>
<td>Hearing Loss</td>
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<tr>
<td>Neurocognitive</td>
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<tr>
<td>Enucleation</td>
<td></td>
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<tr>
<td>Osteoradionecrosis</td>
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<table>
<thead>
<tr>
<th>Efficacy – effectiveness outcomes</th>
<th>Importance of outcome</th>
<th>Efficacy / Effectiveness evidence</th>
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</thead>
<tbody>
<tr>
<td>Overall Survival (OS)</td>
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<tr>
<td>Progression Free Survival (PFS)</td>
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<tr>
<td>Mortality</td>
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<tr>
<td>Distant Metastasis</td>
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<tr>
<td>Locoregional Failure-Free Survival</td>
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### Cost outcomes

<table>
<thead>
<tr>
<th>Cost outcomes</th>
<th>Importance of outcome</th>
<th>Cost evidence</th>
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<tbody>
<tr>
<td>Cost</td>
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<tr>
<td>Cost effectiveness</td>
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</table>

### Special population / Considerations outcomes

<table>
<thead>
<tr>
<th>Special population / Considerations outcomes</th>
<th>Importance of outcome</th>
<th>Special populations/ Considerations evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
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<tr>
<td>Race</td>
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<td>Gender</td>
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<tr>
<td>Ethnicity</td>
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</table>

### For safety:
Is there sufficient evidence that the technology is safe for the indications considered?

<table>
<thead>
<tr>
<th>Unproven (no)</th>
<th>Less (yes)</th>
<th>Equivalent (yes)</th>
<th>More in some (yes)</th>
<th>More in all (yes)</th>
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### For efficacy/ effectiveness:
Is there sufficient evidence that the technology has a meaningful impact on patients and patient care?

<table>
<thead>
<tr>
<th>Unproven (no)</th>
<th>Less (yes)</th>
<th>Equivalent (yes)</th>
<th>More in some (yes)</th>
<th>More in all (yes)</th>
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</table>

### For cost outcomes/ cost-effectiveness:
Is there sufficient evidence that the technology is cost-effective for the indications considered?

<table>
<thead>
<tr>
<th>Unproven (no)</th>
<th>Less (yes)</th>
<th>Equivalent (yes)</th>
<th>More in some (yes)</th>
<th>More in all (yes)</th>
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Discussion
Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second Vote
Based on the evidence about the technologies’ safety, efficacy, and cost-effectiveness, it is

[ ] Not covered  [ ] Covered unconditionally  [ ] Covered under certain conditions

Discussion item
Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon.

Next step: proposed findings and decision and public comment
At the next public meeting the committee will review the proposed findings and decision and consider any public comments as appropriate prior to a vote for final adoption of the determination.

1) Based on public comment was evidence overlooked in the process that should be considered?
2) Does the proposed findings and decision document clearly convey the intended coverage determination based on review and consideration of the evidence?

Next step: final determination
Following review of the proposed findings and decision document and public comments:

Final vote
Does the committee approve the Findings and Decisions document with any changes noted in discussion?

If yes, the process is concluded.

If no, or an unclear (i.e., tie) outcome chair will lead discussion to determine next steps.
### Medicare Coverage and Guidelines
**[From page 51 of Final Evidence Report]**

**Table 1. Overview of Medicare and Payer Policies**

<table>
<thead>
<tr>
<th>Payer (year)</th>
<th>Evidence Base Available</th>
<th>Policy</th>
<th>Rationale/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centers for Medicare and Medicaid Services 7,9,10</td>
<td>71 references, evidence not characterized</td>
<td>At present, there is no NCD for proton beam therapy; additionally, the only published LCD (L34634) on PBT that covered all states (including Washington) and was used in the prior report was retired as of Sept. 1st 2017 (<a href="https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34634&amp;ver=15&amp;Date=&amp;DocID=L34634">https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34634&amp;ver=15&amp;Date=&amp;DocID=L34634</a>), however, two LCDs (L35075 and L36658) applying to twelve states (not including Washington) are active with similar coverage conditions as the retired LCD. Conditions of the active and retired LCDs are provided below with additions from the active LCDs highlighted in bold:</td>
<td></td>
</tr>
</tbody>
</table>

#### Conditions for Medical Necessity
CMS considers PBT reasonable when sparing the surrounding normal tissue cannot be adequately achieved with photon-based radiotherapy and is of added clinical benefit to the patient.

Examples of treatment advantage may include:

1. The target VOLUME is in close proximity to one or more critical structures and a steep dose gradient outside the target must be achieved to avoid exceeding the tolerance dose to the critical structure(s)
2. A decrease in the amount of dose inhomogeneity in a large treatment VOLUME is required to avoid an excessive dose "hotspot" within the treated VOLUME to lessen the risk of excessive early or late normal tissue toxicity.
3. A photon-based technique would increase the probability of clinically meaningful normal tissue toxicity by exceeding an integral dose-based metric associated with toxicity.
4. The same or an immediately adjacent area has been previously irradiated, and the dose distribution within the patient must be sculpted to avoid exceeding the cumulative tolerance dose of nearby normal tissue.

Conditions considered frequently supported by the above requirements (Group 1) include:

- Ocular Tumors, including intraocular melanomas
- Skull-base tumors including but not limited to:
  - Chordomas
  - Chondrosarcomas
  - Primary or metastatic tumors of the spine where spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated
- Unresectable benign or malignant tumors of the CNS, including but not limited to:
  - Astrocytoma, glioblastoma, medulloblastoma, acoustic neuroma, craniopharyngioma, benign and atypical meningioma, pineal gland tumors, and arteriovenous malformations
- Primary hepatocellular cancer treated in a hypofractionated regimen
- Pediatric Primary or benign solid tumors in children treated with curative intent and occasional palliative

<p>| Rationale: NR |</p>
<table>
<thead>
<tr>
<th>Payer (year)</th>
<th>Evidence Base Available</th>
<th>Policy</th>
<th>Rationale/Comments</th>
</tr>
</thead>
</table>
|             |                         | treatment of childhood tumors when at least one of the four criteria noted above apply  
|             |                         | • Pituitary neoplasm  
|             |                         | • Advanced staged and/or unresectable malignant lesions of the head and neck  
|             |                         | • Malignant tumors of the paranasal and other accessory sinuses  
|             |                         | • Unresectable retroperitoneal sarcoma  
|             |                         | • **Patients with genetic syndromes making total volume of radiation minimization crucial such as but not limited to NF-1 patients and retinoblastoma patients**  |

Coverage is considered investigational and limited to providers who have demonstrated experience in data collection and analysis with a history of publication in the peer-reviewed medical literature for the following conditions (group 2):  
• Unresectable lung cancers, upper abdominal cancers, and left breast tumors  
• Advanced, unresectable pelvic tumors, pancreatic and adrenal tumors  
• Skin cancer with nerve innervation of the skull base  
• Unresectable lesions of the liver, biliary tract, anal canal and rectum  
• Non-metastatic prostate cancer, with documented clinical staging and demonstration of clinical necessity of PBT  
• **Hodgkin or Non-Hodgkin Lymphoma involving the mediastinum or in non-mediastinal sites where PBT has the potential to reduce the risk of pneumonitis or late effects of radiation therapy**

### Bellwether Policies

**Aetna (2018)**  
Literature Review (166 references) including:  
1 CER (VHA 2015), 2 CADTH assessments, 1 assessment of economic evaluation (VATAP, Flynn 2010), 1 AHRQ assessment (Trikalinos 2009), 4 HTAs (Wild 2013, RIHTA 2011, ICER 2008, Washington HTA 2014), guidelines from ASTRO NCCN, ACR, and Alberta Health Services; 7 SRs  
Aetna considers proton beam radiotherapy (PBRT) medically necessary in any of the following radiosensitive tumors:  
a. Chordomas or chondrosarcomas arising at the base of the skull or cervical spine without distant metastases; or  
b. Malignancies in children (21 years of age and younger); or  
c. Uveal melanomas confined to the globe (i.e., not distant metastases) (the uvea is comprised of the iris, ciliary body, and choroid [the vascular middle coat of the eye]).  

Aetna considers proton beam radiotherapy for treatment of prostate cancer not medically necessary for individuals with localized prostate cancer because it has not been proven to be more effective than other radiotherapy modalities for this indication. Proton beam therapy for metastatic prostate cancer is considered experimental and investigational.  
Aetna considers proton beam radiotherapy experimental and investigational for all other indications, including the following indications in adults (over age 21) (not an all-inclusive list) because its effectiveness for these indications has not been established:  
• Adenoid cystic carcinoma  
• Age-related macular degeneration (AMD)  
• Angiosarcoma  

**Rationale: NR**
<table>
<thead>
<tr>
<th>Payer (year)</th>
<th>Evidence Base Available</th>
<th>Policy</th>
<th>Rationale/Comments</th>
</tr>
</thead>
</table>
| (Lodge 2007; Lance, 2010; Brada et al, 2009; Efstathiou et al, 2009; ICER, 2008; Wilt et al, 2008; Brada et al, 2007; Olsen et al, 2007), various studies | - Atypical meningioma  
- Bladder cancer  
- Brain tumors  
- Breast cancer  
- Cardiac intimal sarcoma  
- Carotid body tumor  
- Cavernous hemangioma  
- Cervical cancer  
- Cholangiocarcinoma  
- Choroidal hemangioma  
- Dermatofibrosarcoma protuberans  
- Desmoid fibromatosis  
- Desmoid tumor (aggressive fibromatosis)  
- Ependymoma  
- Esophageal cancer  
- Ewing's sarcoma  
- Fibrosarcoma of the extremities  
- Gangliomas  
- Glioma  
- Head and neck cancer (including nasopharyngeal carcinoma)  
- Hemangioblastoma  
- Hemangioendothelioma  
- Hepatocellular carcinoma  
- Lymphomas (Large cell lymphoma, Hodgkin's lymphoma, Non-Hodgkin lymphoma)  
- Intracranial arterio-venous malformations  
- Leiomyosarcoma of the extremities  
- Liposarcoma  
- Liver metastases  
- Lung cancer (including non-small-cell lung carcinoma)  
- Maxillary sinus tumor  
- Mesothelioma  
- Multiple myeloma  
- Nasopharyngeal tumor  
- Non-uveal melanoma  
- Oligodendroglioma  
- Optic nerve schwannoma  
- Optic nerve sheath meningioma  
- Pancreatic cancer  
- Parotid gland tumor  
- Pineal tumor  
- Pituitary neoplasms  
- Rectal cancer  
- Retroperitoneal/pelvic sarcoma  
- Rhabdomyoma  
- Sacral chordoma  
- Salivary gland tumors (e.g., sublingual gland tumor, submandibular gland tumor)  
- Seminoma  
- Sino-nasal carcinoma  
- Small bowel adenocarcinoma  
- Soft tissue sarcoma  
- Squamous cell carcinoma of the eyelid, tongue/glottis  
<p>| - Thymic tumor |</p>
<table>
<thead>
<tr>
<th>Payer (year)</th>
<th>Evidence Base Available</th>
<th>Policy</th>
<th>Rationale/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Literature review (149 references) including: Guidelines from ASTRO, ACR, AAO, NCCN; 1 BCBS technology assessment, 2 ongoing trials; 4 AHRQ reviews</td>
<td>Updated 02/2018&lt;br&gt;Anthem considers proton beam radiation therapy, with or without stereotactic techniques, as <strong>medically necessary</strong> for any of the following conditions: &lt;br&gt;a. As primary therapy for melanoma of the uveal tract (iris, choroid, or ciliary body) involving tumors of up to 24 mm in largest diameter and 14 mm in height, and with no evidence of metastasis or extrascleral extension; or&lt;br&gt;b. As postoperative therapy for individuals who have undergone biopsy or partial resection of a chordoma or low-grade (I or II) chondrosarcoma of the basisphenoid region (for example, skull-base chordoma or chondrosarcoma) or cervical spine and have residual, localized tumor without evidence of metastasis; or&lt;br&gt;c. Pituitary adenoma when conventional stereotactic radiation is not an available option; or &lt;br&gt;d. Intracranial arteriovenous malformation (AVM) not amenable to surgical excision or other conventional forms of treatment; or&lt;br&gt;e. Central nervous system (CNS) lesions including but not limited to, primary or metastatic CNS malignancies or AVM, adjacent to critical structures such as the optic nerve, brain stem or spinal cord; or&lt;br&gt;f. Primary or benign solid tumors in children treated with curative intent.&lt;br&gt;Proton beam radiation therapy is considered <strong>not medically necessary</strong> for the following condition: &lt;br&gt;Choroidal neovascularization secondary to age-related macular degeneration (AMD).&lt;br&gt;Proton beam radiation therapy is considered <strong>investigational and not medically necessary</strong> when criteria are not met and for all other indications, including, but not limited to, the treatment of: &lt;br&gt;Localized prostate cancer.</td>
<td>Rationale: NR</td>
</tr>
</tbody>
</table>
### Table 2. Summary of proton beam therapy recommendations by cancer type across guidelines, appropriateness criteria, CMS coverage, and payer policies

<table>
<thead>
<tr>
<th>Condition</th>
<th>Guideline &amp; Appropriateness Criteria</th>
<th>Strength of Recommendation</th>
<th>Evidence Quality</th>
<th>CMS and Payer Policies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Cancer 202,229</td>
<td>NCCN: M ACR*: N</td>
<td>NCCN: Moderate</td>
<td>NCCN: 2A ACR*: NR</td>
<td>Investigational or NR</td>
</tr>
<tr>
<td>Breast Cancer 105</td>
<td>AIM: N</td>
<td>AIM: NR</td>
<td>AIM: NR</td>
<td>Investigational or NR</td>
</tr>
<tr>
<td>Esophageal Cancer 105</td>
<td>AIM: N</td>
<td>AIM: NR</td>
<td>AIM: NR</td>
<td>Investigational or NR</td>
</tr>
<tr>
<td>Gastrointestinal Cancer 105</td>
<td>AIM: N AIM: N (pancreatic)</td>
<td>AIM: NR</td>
<td>AIM: NR</td>
<td>Investigational or NR</td>
</tr>
<tr>
<td>Gynecologic Cancer 105,202,229</td>
<td>AIM: N ACR*: Y</td>
<td>AIM: NR ACR*: NR</td>
<td>AIM: NR ACR*: NR</td>
<td>Investigational or NR</td>
</tr>
<tr>
<td>Liver Cancer 105,202</td>
<td>NCCN: M AIM: N</td>
<td>NCCN: Moderate AIM: NR</td>
<td>NCCN: 2A AIM: NR</td>
<td>Investigational or NR</td>
</tr>
<tr>
<td>Lymphomas 105,202,229</td>
<td>NCCN: M AIM: N ACR: M</td>
<td>NCCN: Moderate AIM: NR</td>
<td>NCCN: 2A AIM: NR</td>
<td>Investigational or NR</td>
</tr>
<tr>
<td>Condition</td>
<td>Recommendation</td>
<td>Strength of Recommendation</td>
<td>Evidence Quality</td>
<td>Coverage</td>
</tr>
<tr>
<td>-----------</td>
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</tr>
<tr>
<td>Pediatric Cancers 74,229</td>
<td>NICE: Y AIM: Y</td>
<td>NICE: NR AIM: NR</td>
<td>NICE: Not sufficient</td>
<td>LCDs† CMS7,9,10: Y Payer Policies Aetna: Y Anthem: Y</td>
</tr>
<tr>
<td>Sarcomas 202</td>
<td>NCCN: M</td>
<td>NCCN: Moderate</td>
<td>NCCN: 2A</td>
<td>LCDs† CMS: Y (unresectable retroperitoneal sarcoma)</td>
</tr>
<tr>
<td>Seminomas</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Investigational or NR</td>
</tr>
<tr>
<td>Thymomas 202</td>
<td>NCCN: M</td>
<td>NCCN: Moderate</td>
<td>NCCN: 2A</td>
<td>Investigational or NR</td>
</tr>
</tbody>
</table>

ACR = American College of Radiology; AIM = American Imaging Management; ASTRO = American Society for Radiation Oncology; CMS = Centers for Medicare and Medicaid Services; CNS = central nervous system; LCD = local coverage determination; NCCN = National Cancer Care Network; NICE = The National Institute for Health and Care Excellence; NR = not reported; Y = Yes.

*ACR ratings are associated with N, M, and Y ratings based on their 1-9 rating system; in this table N = 1, 2, 3 (usually not appropriate); M = 4, 5, 6 (may be appropriate); and Y = 7, 8, 9 (usually appropriate). For more information on their rating system see Appendix Table L2.

†At the time of this report the only CMS policy related to proton beam therapy and applied to Washington State had been retired as of Sept. 2017; two LCDs active in twelve states (not including Washington State) are active however, with only minor differences in coverage determinations. Information on the coverage decisions are reported here for reference, more detail is available in section 2.7, Table 1.