Washington State Health Care Authority
Health Technology Assessment

# Proton Beam Therapy

**Clinical Expert**

**Lia Moriguchi Halasz, M.D.**

## Disclosure

Any unmarked topic will be considered a "Yes"

| | Potential Conflict Type | Yes | No |
|---|---|---|---|
| 1. | Salary or payments such as consulting fees or honoraria in excess of $10,000. | | ✓ |
| 2. | Equity interests such as stocks, stock options or other ownership interests. | | ✓ |
| 3. | Status or position as an officer, board member, trustee, owner. | | ✓ |
| 4. | Loan or intellectual property rights. | | ✓ |
| 5. | Research funding. | | ✓ |
| 6. | Any other relationship, including travel arrangements. | ✓ | |

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

I am an attending Radiation Oncologist with the Department of Radiation Oncology at University of Washington and treat patients at Seattle Cancer Care Alliance Proton Therapy, A ProCure Center.

| | Potential Conflict Type | Yes | No |
|---|---|---|---|
| 7. | Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government). | | ✓ |

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

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 [redacted] 4/17/14 Lia M. Halasz M.D.

*Signature* *Date* *Print Name*

**For questions contact:** Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126

**Lia Moriguchi Halasz, M.D.**

**Curriculum Vitae**

**Prepared:** March 21, 2014

**Place of birth:** Seattle, WA

**Citizenship:** United States

**Education:**

8/96-6/00 A.B. *magna cum laude*, Biochemical Sciences, Harvard College, Cambridge, MA

8/01-6/06 M.D., Harvard Medical School, Boston, MA

**Postgraduate Training:**

6/06-6/07 Internship, Internal Medicine, Brigham and Women's Hospital, Boston, MA

7/07-6/11 Residency, Radiation Oncology, Harvard Radiation Oncology Residency Program, Boston, MA

**Faculty Positions Held:**

10/11 to present Assistant Professor, Department of Radiation Oncology, University of Washington

10/11 to present Joint Assistant Professor, Department of Neurological Surgery, University of Washington

**Hospital Positions Held:**

10/11 to present Attending Physician, Department of Radiation Oncology, UW Medical Center

10/11 to present Attending Physician, Department of Radiation Oncology and Neurological Surgery, Harborview Medical Center

**Honors:**

1997 Detur Book Prize, Harvard College

2000 Joseph L. Barrett Teaching Award, Harvard College

2000 John Harvard and Elizabeth Cary Agassiz Scholarships for Academic Excellence

2000 Public Service Fellowship, Carl and Lily Pforzheimer Foundation

2000 Traveling Fellowship, Radcliffe College

2005 Research Training Fellowship, Howard Hughes Medical Institute

**Board Certification:**

2012-present Radiation Oncology, American Board of Radiology

**Current License to Practice:**

Full License, State of Washington

**Professional Organizations:**

2006-present Member, American Medical Association

2007-present Member, American Society for Radiation Oncology

2007-present Member, American Society for Clinical Oncology

2012-present Member, Society for Neuro-Oncology

2013-present Member, American Association for Women Radiologists

**Teaching Responsibilities:**

2011-present University of Washington Radiation Oncology Residency, attending and lecturer

2014 University of Washington Medical Student Preceptorship, preceptor

2008-2010 Suffolk University Oncology Pathology course, lecturer, 8% of responsibility for course

**Editorial Responsibilities:** none

**Special National Responsibilities:**

2014 American Society for Radiation Oncology, Central nervous system abstract selection committee

**Special Local Responsibilities:**

10/13-present Seattle Children's Cancer and Blood Disorders Center Data Safety Monitoring Board, Seattle, WA

10/13-present Expert consultant for Institute for Clinical and Economic Review Proton report, Boston, MA

12/12-present Clinical Research Committee for Procure Proton Centers, Seattle, WA

8/12 Peer reviewer for Oregon Health Sciences University SBRT Report, Portland, OR

10/11-present Radiation Safety Committee, University of Washington, Seattle, WA

1/10-6/10 Scientific Review Committee, Institutional Review Board, Trainee Member, Dana-Farber/Harvard Cancer Center, Boston, MA

**Research Funding:**

2005-2006 Notch signaling in hematopoietic stem cell renewal and differentiation (mentor: Irwin Bernstein M.D.); Howard Hughes Medical Institute Research Training Fellowship for Medical Students ($34,000)

2009-2010 Use of radiation therapy for central nervous system metastases in the SEER-Medicare database: population based practices, 1995-2005 (mentor: Rinaa Punglia M.D., M.P.H.); Joint Center for Radiation Therapy Foundation ($7500)

**Bibliography:**

*Manuscripts in Refereed Journals:*

1. Yao MC, Yao CH, **Halasz LM**, Fuller P, Rexer CH, Wang SH, Jain R, Coyne RS, Chalker DL. Identification of novel chromatin-associated proteins involved in programmed genome rearrangements in Tetrahymena. J Cell Sci. 2007 Jun 15; 120 (Pt 12): 1978-1989. PMID: 17519286.
2. **Halasz LM**, Bussiere MR, Dennis ER, Niemierko A, Chapman PH, Loeffler JS, Shih HA. Proton stereotactic radiosurgery for the treatment of benign meningiomas. Int J Radiat Oncol Biol Phys. 2010 Oct 7. PMID: 20934263.

3. Mak RH, **Halasz LM**, Schultz DJ, Tanaka C, Ancukiewicz M, Russell AH, Viswanathan AN. Outcomes After Radiation Therapy with Concurrent Weekly Platinum-Based or 5-Fluorouracil-Based Chemotherapy for Squamous Cell Carcinoma of the Vulva. Gynecol Oncol. 2011 Jan;120(1):101-107. PMID: 20950845.

4. Varnum-Finney B*, **Halasz LM*,** Sun M, Radtke F, Gridley T, Bernstein ID. Notch2 promotes self renewal of hematopoietic stem and progenitor cells during marrow regeneration. J Clin Invest. 2011 Mar 1;121(3):1207-1216. PMID: 21285514. (*co-first authors)

5. **Halasz LM,** Sreedhara M, Chen Y, Bellon JR, Punglia RS, Wong JS, Harris JR, Brock JE. Improved outcomes of breast-conserving therapy for ductal carcinoma in situ. Int J Radiat Oncol Biol Phys. 2012 Mar 15;82(4):e581-6. PMID: 22208975.

6. **Halasz LM,** Catalano PJ, Mauch PM, Ng AK. Favorable outcomes of combined modality treatment for non-Hodgkin lymphoma despite positive mid- or post-chemotherapy PET. Int J Radiat Oncol Biol Phys. 2012 Aug 1;83(5):e647-54. PMID: 22607911.

7. **Halasz LM,** Weeks JC, Neville BA, Taback N, Punglia RS. Use of stereotactic radiosurgery for brain metastases from non-small cell lung cancer in the United States. Int J Radiat Oncol Biol Phys. 2012 Oct 9. PMID: 23058058.

*Other Publications:*

1. **Halasz LM**, Choi NC. Does prophylactic cranial irradiation reduce the incidence of brain metastases in extensive small-cell lung cancer? Nat Clin Pract Oncol. 2008 Jun; 5(6): 308-309. PMID: 18431375.

2. Brock JE, **Halasz LM.** A new pathological system for grading DCIS with improved prediction of local recurrence: results from the UKCCCR/ANZ DCIS trial: Pinder SE, Duggan C, Ellis IO, et al. Br J Cancer. 103: 94-100. Breast Diseases: A Year Book Quarterly. 2011; 22(1): 47-49.

3. **Halasz LM**, Rockhill JK. Stereotactic radiosurgery and stereotactic radiotherapy for brain metastases. Surg Neurol Int 2013;4:S185-91.

*Abstracts not mentioned previously:*

**Halasz LM**, Uno H, Zornosa C, D'Amico T, Dexter E, Hayman J, Otterson G, Pisters K, Weeks JC, Punglia RS. Comparative effectiveness of stereotactic radiosurgery versus whole brain radiation therapy (WBRT) for patients with brain metastases from non-small cell lung cancer. Oral Presentation. Annual Meeting of the American Society for Therapeutic Radiation Oncology. September 23, 2013. Atlanta, Georgia.

**Invited Talks:**

UW Department of Radiation Oncology Grand Rounds. "Evaluating new technology in Radiation Oncology using outcomes research." January 23, 2013.

Discussant for joint tumor board between Uganda Cancer Institute and Fred Hutchinson Cancer Research Center. "Cases from Kampala: CNS tumors." November 14, 2013.

UW Palliative Care Grand Rounds. "Palliative Radiation Therapy." January 21, 2014.

Harborview Medical Center Chief of Medicine Rounds. "Urgent Radiation Oncology." March 4, 2014.

Washington State Health Care Authority
*Health Technology Assessment*

## Public Comments: Proton Beam Therapy

| | Name |
|---|---|
| 1 | **Shannon MacDonald**, MD<br>Assistant Professor, Harvard Medical School<br>Department of Radiation Oncology, Massachusetts General Hospital |
| 2 | **Don Denton** |
| 3 | **Ralph Ermoian**, MD<br>Assistant Professor, Department of Radiation Oncology<br>University of Washington |
| 4 | **George E. Laramore** PhD, MD<br>Peter Wootton Professor of Radiation Oncology<br>University of Washington |
| 5 | **George Sandison**, PhD, FCCPM, FAAPM<br>Professor & Director of Medical Physics, Department of Radiation Oncology<br>Adjunct Professor Department of Radiology<br>University of Washington |
| 6 | **Shilpen Patel**, MD, FACRO<br>Associate Professor, University of Washington<br>Medical Director of the Clinical Outcomes Assessment Program/Foundation for Health Care Quality<br>Chief of Thoracic Radiation Oncology/Stereotactic Body Radiation Therapy Program Lead |
| 7 | **Ed Kim,** MD<br>Assistant Professor, Department of Radiation Oncology<br>University of Washington |
| 8 | **Nina A. Mayr,** MD, FASTRO, FAAAS<br>Professor & Chair, Department of Radiation Oncology<br>University of Washington |
| 9 | **Jason K. Rockhill,** MD, PhD<br>Associate Professor, Departments of Radiation Oncology & Neurological Surgery<br>Co-Director, Gamma Knife Center<br>Co-Director, UW Medicine Clinical Neuro Oncology<br>Associate Residency Program Director, Department of Radiation Oncology University of Washington |
| 10 | **Ramesh Rengan** MD, PhD<br>Associate Professor, Department of Radiation Oncology<br>University of Washington<br>Associate Member, Fred Hutchinson Cancer Research Center<br>Medical Director, SCCA Proton Therapy |
| 11 | **Smith "Jim" Apisarnthanarax**, MD<br>Associate Professor, Department of Radiation Oncology<br>University of Washington |
| 12 | **Jing Zeng,** MD<br>Assistant Professor, Department of Radiation Oncology<br>University of Washington |

| | Name |
|---|---|
| 13 | **Wui-Jin Koh**, MD<br>Professor Department of Radiation Oncology<br>University of Washington |
| 14 | **Eugen B. Hug**, M.D.<br>Professor of Proton-Radiotherapy<br>Medical Director, ProCure Proton Therapy Centers<br>Chief Medical Officer, ProCure |
| 15 | **Robin Baird**, ProCure patient |

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| 5. | Research funding. | | X |
| 6. | Any other relationship, including travel arrangements. | X | |

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

travel funds only to attend meeting in US from decimal (amt ~ 700$, < 1K)

| | Potential Conflict Type | Yes | No |
|---|---|---|---|
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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.

X [redacted] 4.28.14 Shannon MacDonald

*Signature* *Date* *Print Name*

**For questions contact:** Christine Masters
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360-725-5126

Harvard Medical School

# Rationale for the use of Proton RT for Select Patients with Breast Cancer

Shannon MacDonald, MD

HTCC Public Meeting

May 16, 2014

## LABC: Rationale for use

- Breast cancer patients are often cured of their disease, but may experience late side effects as a result of radiation therapy and late cardiac toxicity may negate or decrease survival benefit from RT and lead to chronic and costly morbidity
- Many patients requiring RT also receive cardiotoxic chemotherapy
- Patients undergoing mastectomy and reconstruction often have reconstruction deferred until after requiring a second surgery due to limitations in standard RT planning

# Cardiac Toxicity

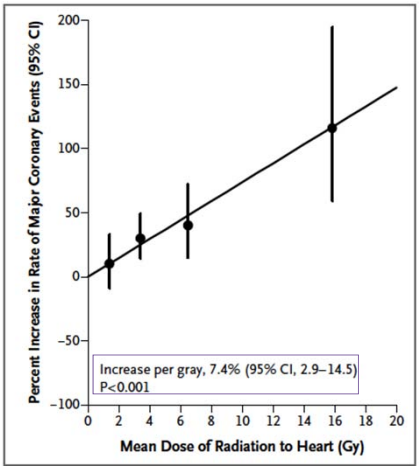


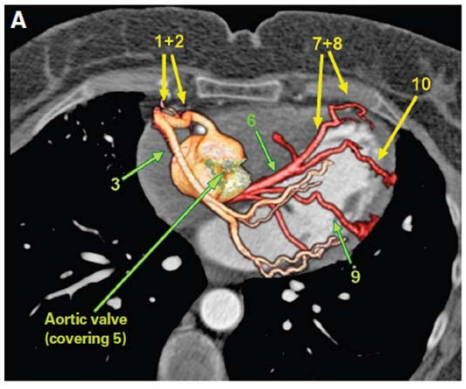

**Table 3. Percentage Increase in the Rate of Major Coronary Events per Gray, According to Time since Radiotherapy.**

| Time since Radiotherapy* | No. of Case Patients | No. of Controls | Increase in Rate of Major Coronary Events (95% CI)† |
|---|---|---|---|
| | | | *% increase/Gy* |
| 0 to 4 yr | 206 | 328 | 16.3 (3.0 to 64.3) |
| 5 to 9 yr | 216 | 296 | 15.5 (2.5 to 63.3) |
| 10 to 19 yr | 323 | 388 | 1.2 (−2.2 to 8.5) |
| ≥20 yr | 218 | 193 | 8.2 (0.4 to 26.6) |
| 0 to ≥20 yr | 963 | 1205 | 7.4 (2.9 to 14.5) |

- Myocardial infarction
- Coronary revascularization tx
- Death from ischemic heart disease
- Major coronary events increased by 7.4% for each increase of 1 Gy

Darby et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *NEJM* 2013

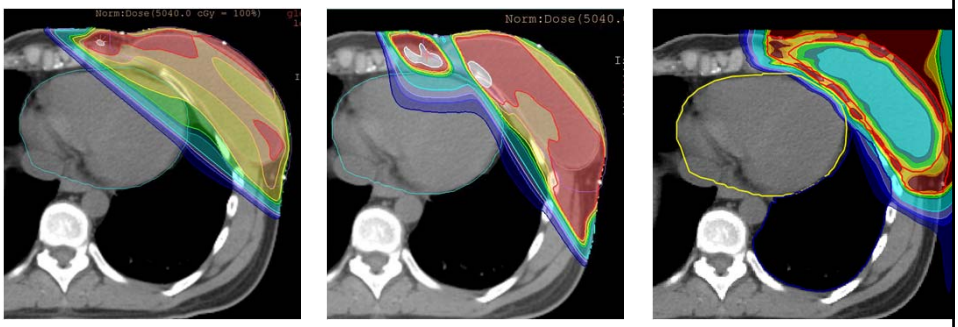
# LAD: Major Vessels




Patients undergoing L-sided radiation for breast cancer were more vulnerable to stenosis of **mid and distal branches of LAD** subsequently found on angiogram.

Nilsson et al. Distribution of coronary artery stenosis after radiation for breast cancer. *JCO* 2011.

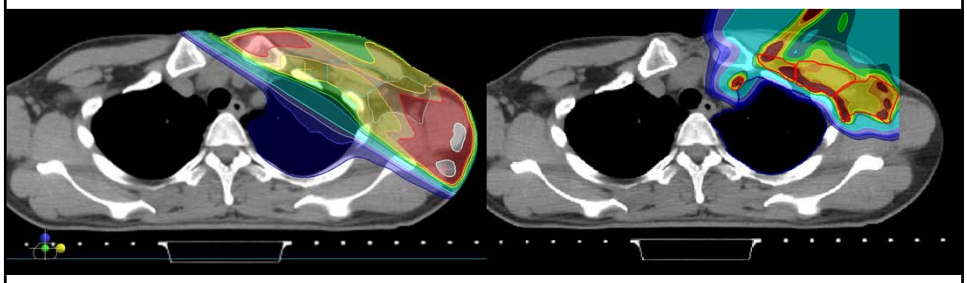
# Protons with implants



Photons Photon/Electron Proton(IMPT)

Jimenez RB et al, *Radiother Oncol* , 2013

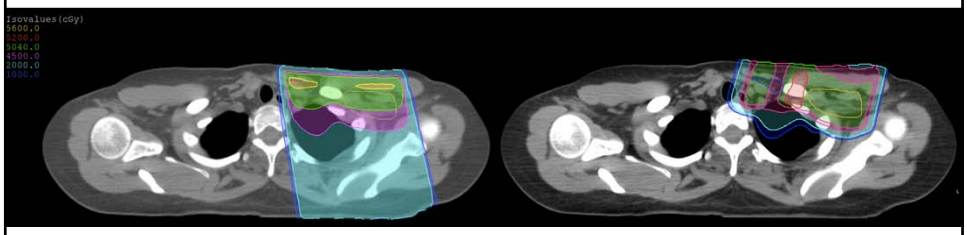
# Lymphatic region comparison



Photons Proton(IMPT)

Jimenez RB et al, *Radiother Oncol* , 2013

# SCV region

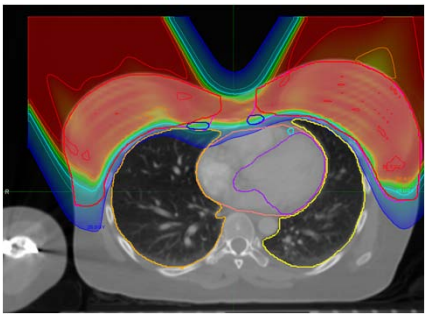



Photons Protons

Could sparing of soft tissue decrease the risk of lymphedema?

# Appropriate Patients to Evaluate for Benefit from Proton RT

- Advanced disease
- Treatment after mastectomy
- IMN involvement
- Cardiotoxic chemo
- Young age
- Permanent implants
- Poor cardiac anatomy
- LIQ tumors
- Pre-existing cardiac disease
- Decreased arm mobility



*Thank you*

## Disclosure

Any unmarked topic will be considered a "Yes"

| | Potential Conflict Type | Yes | No |
|---|---|---|---|
| 1. | Salary or payments such as consulting fees or honoraria in excess of $10,000. | | X |
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| 3. | Status or position as an officer, board member, trustee, owner. | | X |
| 4. | Loan or intellectual property rights. | | X |
| 5. | Research funding. | | X |
| 6. | Any other relationship, including travel arrangements. | | X |

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

| | Potential Conflict Type | Yes | No |
|---|---|---|---|
| 7. | Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government). | | X |

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

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 [redacted] 4/24/14 Don Denton

*Signature* *Date* *Print Name*

**For questions contact:** Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126

Name:  Don Denton
Organization:  Representing myself

My comment relates to Proton Beam Therapy being considered by the Health Technology Clinical Committee (HTCC).  Living in east Tennessee, I am unable to attend May's public hearing, so I am providing these written comments for consideration.

I am a prostate cancer survivor.  When diagnosed 3-1/2 years ago, my urologist recommended robotic surgery--he called it the *Gold Standard*.  With this treatment, he opined that my probability of survival for 10 years at 65%, but accompanied by permanent incontinence and impotence and a high probability of recurrence.  He also speculated that radiation and Lupron injections would follow the surgery.

Fortunately I discovered proton therapy.  Initially my insurance company rejected this treatment option, which should have never happened.  I had to fight it to gain the benefits for which I had paid, but unfortunately, most people simply roll over and take what the insurance company offers.

Proton therapy's benefits include no surgery, no recovery time, no permanent side effects, no quality of life issues, and no cancer.  My 3-year check-up occurred in early April, and my oncologist opined that my cancer is history, and my probability of survival with no recurrence is 99.5%.

Not only did proton therapy preserve my life, it also preserved my quality of life.  Conventional treatment options could not have accomplished this result.  What's the point of being alive but wishing I were dead and wondering when my cancer would return?

Health insurance companies should not be allowed to reject one's choice of proton therapy. Their arguments that other treatment options are equally effective are bogus.  A recent peer-reviewed study of prostate cancer patients confirmed a 99% success rate at five years, which is clearly superior.  Also, insurers claims that it's much more expensive are untrue.  Shortened treatment programs offered by some proton centers are priced favorably--much more so than just a couple of years ago.

I urge the HTCC to provide its strong endorsement and support to proton therapy.  It represents a major paradigm shift in the way cancer will be cured in the future.  Washington State should be progressive in embracing this phenomenal technology.  Allowing insurance companies to avoid paying benefits would be a giant step in the wrong direction.

If there is anything that I can address from a proton therapy patient's perspective, please do not hesitate to contact me.

Thank you for your consideration of my comments.

Don Denton
104 Sunshine Way  Phone:  865-437-9545
Townsend, TN  37882  E-mail:  kinzelsprings@comcast.net

## Disclosure

Any unmarked topic will be considered a "Yes"

| | Potential Conflict Type | Yes | No |
|---|---|---|---|
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| 3. | Status or position as an officer, board member, trustee, owner. | | X |
| 4. | Loan or intellectual property rights. | | X |
| 5. | Research funding. | | X |
| 6. | Any other relationship, including travel arrangements. | | X |

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

I treats some of my patients at the Proton Center in Seattle

| | Potential Conflict Type | Yes | No |
|---|---|---|---|
| 7. | Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government). | | X |

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

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 [redacted] _____

*Signature* *Date*

Ralph Ermoian, MD

*Print Name*

**For questions contact:** Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126

## Disclosure

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| 7. | Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government). | | X |

If yes to #7, provide name and funding Sources: I AM A FACULTY MEMBER IN THE DEPARTMENT OF RADIATION ONCOLOGY AT THE UNIVERSITY OF WASHINGTON. I USE PROTON RADIOTHERAPY TO TREAT SELECTED PATIENTS IN MY CLINICAL PRACTICE

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. - see above

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 [redacted] 4/18/2014 GEORGE E. LARAMORE PHD, MD

*Signature* *Date* *Print Name*

**For questions contact:** Christine Masters
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Olympia, WA 98504-2712
360-725-5126

## Disclosure

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X [redacted] 04/16/14 GEORGE A. SANDISON

*Signature* *Date* *Print Name*

**For questions contact:** Christine Masters
Health Technology Assessment
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360-725-5126

## Disclosure

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| 5. | Research funding. | | X |
| 6. | Any other relationship, including travel arrangements. | | X |

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

I work as medical director for the Clinical outcomes Assessment Program + ~~work at~~ treat pts at the Proton Center / Procure

| | Potential Conflict Type | Yes | No |
|---|---|---|---|
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If yes to #7, provide name and funding Sources: University of Washington

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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.

X [redacted] 4/16/14 Shilpen Patel

*Signature* *Date* *Print Name*

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

I work at the University of Washington. and Seattle Cancer Care Alliance.

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X [redacted]

*Signature* *Date*

EDWARD KIM

*Print Name*

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| 5. | Research funding. | | X |
| 6. | Any other relationship, including travel arrangements. | | X |

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

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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.

X [redacted] 4/16/14 Nina A. Mayer, MD.

*Signature* *Date* *Print Name*

**For questions contact:** Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126

## Disclosure

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[redacted] 4/16/14 Jason Rodl

*Signature* *Date* *Print Name*

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

Medical Director, SCCA Proton Therapy

→ no interest or salary from proton center

- I am a faculty member of UW Department of Radiation Oncology

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X [redacted] 4/16/14 Ramesh Rengan

*Signature* *Date* *Print Name*

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| 4. | Loan or intellectual property rights. | | ✓ |
| 5. | Research funding. | | ✓ |
| 6. | Any other relationship, including travel arrangements. | | ✓ |

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

I work at a medical institution that treats patients with protons.

| | Potential Conflict Type | Yes | No |
|---|---|---|---|
| 7. | Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government). | | ✓ |

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X [redacted] 4/16/14 Smith Apisarnthanarax

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

I am employed by the University of Washington Medical Center, and work part of the week at the SCCA/ProCure Proton Radiation Center.

| | Potential Conflict Type | Yes | No |
|---|---|---|---|
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X [redacted] 4/18/14 Jing Zeng

*Signature* *Date* *Print Name*

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360-725-5126

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_____

_____

_____

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X [redacted] 4/16/14 Wui-Jin Koh

*Signature* *Date* *Print Name*

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I work at the University of Washington

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X [redacted] 4/16/14 Stephen Bowen

*Signature* *Date* *Print Name*

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X [redacted]

*Signature* *Date*

JUERGEN MEYER

*Print Name*

**For questions contact:** Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126

# Proton Beam Radiotherapy: Presentation to the Washington HTCC

HTCC Public Meeting

May 16, 2014

SeaTac Airport







## UW Department of Radiation Oncology Faculty Titles:

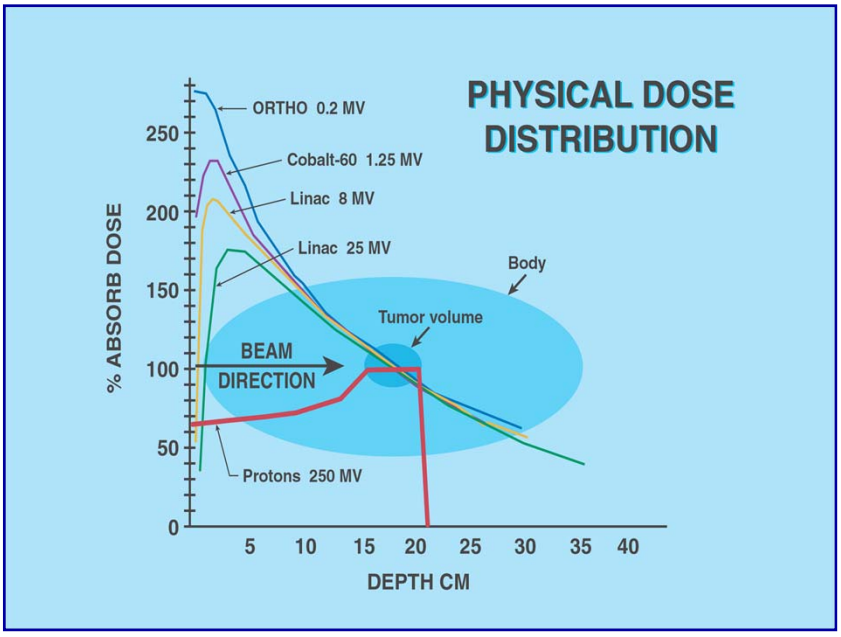
1. Nina Mayr MD, Professor and Chair
2. **George Laramore MD PhD, Founding medical director, SCCA Proton Therapy, Peter Wooten Professor and Former Chair**
3. **Ramesh Rengan MD PhD, Medical Director, SCCA Proton Therapy, Associate Professor, Associate Member FHCRC**
4. **Jim Apisarnthanarax MD, Associate Professor**
5. George Sandison PhD, Professor and Chief of Medical Physics
6. Juergen Meyer PhD, Associate Professor, Medical Physicist
7. Jason Rockhill MD PhD, Associate Professor
8. Edward Kim MD, Assistant Professor
9. Ralph Ermoian MD, Assistant Professor
10. Jing Zeng MD, Assistant Professor
11. Lia Halasz MD, Assistant Professor
12. Shilpen Patel MD, Associate Professor
13. Wui-Jin Koh MD, Professor
14. Steve Bowen PhD, Assistant Professor, Medical Physicist

Faculty have conceded their allotted time to the three speakers highlighted above

# Therapeutic Advantages –Background and Rationale

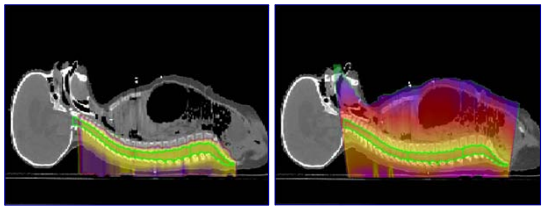




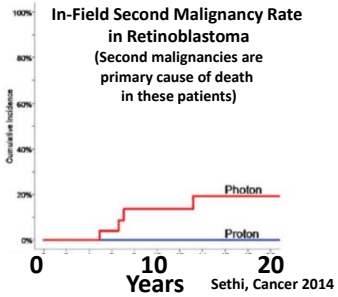


Slide 5

## Proton vs Photon Dosimetric Comparisons



Protons Photons




- Universal coverage recommendations for pediatrics in most plans
  - HTA Finding was of incremental benefit vs comparators
- Protons implemented in pediatric practice on the basis of dosimetric comparative superiority
  - Benefits accrue and persist for decades
  - Cannot be quantified through standard clinical trial mechanism
- Dosimetric studies and comparisons are essential for clinical decision making in radiation treatment and fundamental to our practice
  - Should not be excluded from any meaningful analysis of radiation benefit vs harm

## Proton Beam Radiotherapy: Need for Clinical Evidence

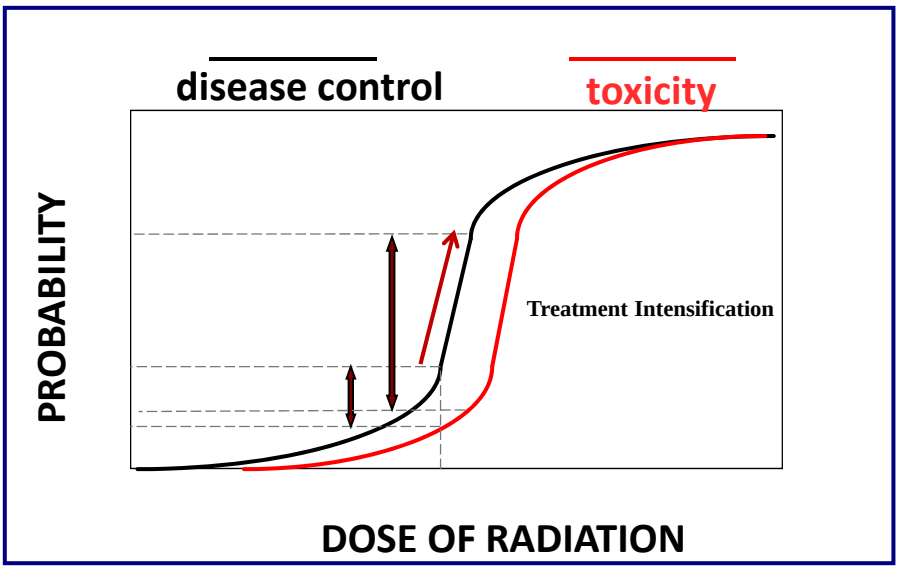
## The need for clinical data to evaluate proton beam radiotherapy

- Clinical data is lacking for many sites
  - 8/16 cancers surveyed in HTA report had no evidence
  - Additional 7/16 had low evidence including prostate
- Ongoing initiatives that UW/SCCA are participating in
  - **PartiQOL: Phase III randomized trial of IMRT vs proton in prostate cancer**
  - **PCG Registry**
    - All patients treated at center are enrolled (unless they decline) in our prospective registry to track near and long-term clinical outcomes
  - **PCORI Proton vs Photon Pragmatic Clinical Trial Grant Submission**
    - UW/SCCA participating in proton consortium grant submission to PCORI
    - Prospective clinical trials in
      - Post-prostatectomy prostate
      - Post-operative lung
      - Breast Cancer
- Clinical data (especially long-term endpoints) are resource and cost intensive to obtain
- **Clinical Evidence cannot be obtained without payer support**
  - Industry partnership paradigm for drug clinical trials does NOT apply to new technologies
  - Washington HTA can provide the **essential backing required** to obtain these data through their recommendations

# Proton Beam Radiotherapy: Lung

Slide 9

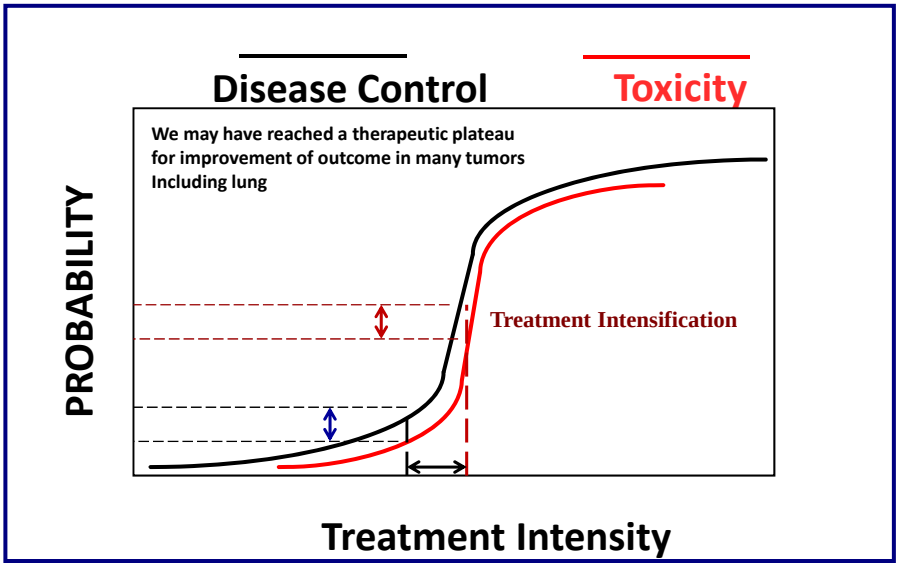
## Proton Radiotherapy: Lung





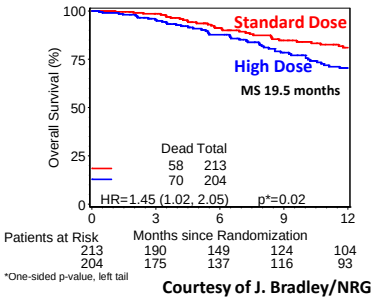

Slide 10

## Proton Radiotherapy: Lung

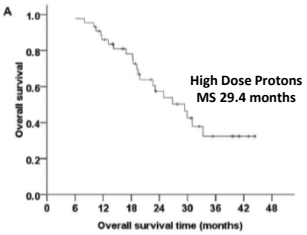


Slide 11

# Proton Radiotherapy: Lung




Courtesy of J. Bradley/NRG

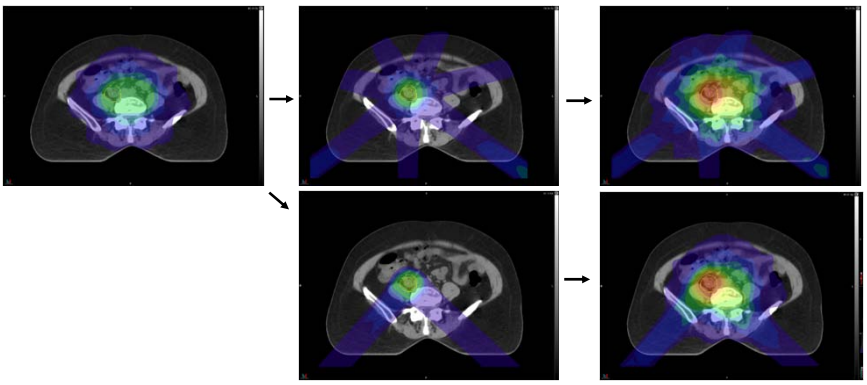



Chang et al Cancer 2011

- No clear role for dose intensification beyond 1970's standard with **photon beam radiotherapy**
- Proton beam may be especially beneficial in narrow therapeutic window tumors
- Clinical Data: Randomized trial of IMRT vs Protons
  - **UW/SCCA will participate in RTOG 1308 once NRG membership approved**

# Proton Beam Radiotherapy: Patients in whom photons are contra-indicated

## Proton beam radiotherapy for Re-irradiation




- Emerging patient population
- No viable photon or surgical options for these patients
- Limited clinical to date shows value of protons for these patients
- Clinical Evidence gathering
  - UW Thoracic Re-irradiation trial (PI:Zeng)
  - Penn trial
  - Need payer partnership
- **HTA Report is silent on this group of patients for whom protons may be the only viable therapeutic option**

## Proton Beam Radiotherapy– GI

Slide 15

# Curative Treatment of GI Cancers is Toxic

- Combined treatment with surgery, radiation, and chemotherapy is common
- Pancreatic and rectal cancer: severe GI toxicities up to 20-25%
  - Toxicities related to radiation dose to bowel
- Esophageal cancer: postoperative pulmonary complications up to 33-46%
  - Toxicities related to radiation to lungs

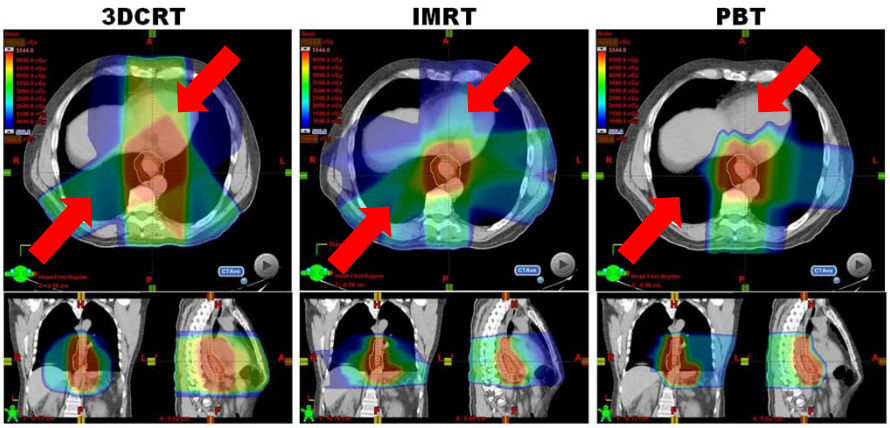
Sauer et al. NEJM 2004, Regine et al. JAMA 2008, INT 0116: MacDonald et al. NEJM 2001, Wei et al. IJROBP 2008, Gayed et al. JNM 2006, Hsu et al. Ann Surg Oncol 2009, Wang et al. IJROBP 2006, Tepper et al. JCO 2008 (CALGB), CROSS trial 2012

1



Slide 16

# Esophageal cancer: Protons spare more lungs and heart

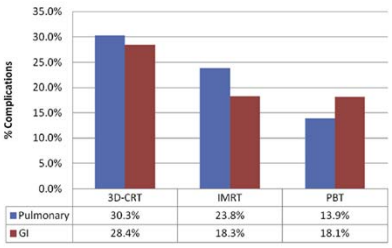



**3DCRT:** 4-field static photons; **IMRT:** 5-field modulated photons; **PBT:** 2-field passive scatter protons (PA/LPO)

Welsh et al. IJROBP 2011, Wang et al. IJROBP 2013

## Esophageal Cancer: MD Anderson Experience

- 62 esophageal cancer patients treated with protons
- Postoperative heart and lung complications 15%
  - Compared to 32-67% in large prospective trials
- Compared to other radiation techniques, protons reduced lung complications




| | 3D-CRT | IMRT | PBT |
|---|---|---|---|
| Pulmonary | 30.3% | 23.8% | 13.9% |
| GI | 28.4% | 18.3% | 18.1% |

- The technique of radiation therapy is a major modifiable factor for postoperative complications
- **MDACC Phase III Randomized Trial of Proton Beam Therapy Versus Intensity-Modulated Radiation Therapy for the Treatment of Esophageal Cancer**

Lin et al. IJROBP 2012, Wang et al. IJROBP 2013

## Proton Beam Radiotherapy: Conclusions

# Conclusions

- Recommend expanded payer coverage policies for patients enrolled on clinical trials and prospective outcome registries
- Include dosimetric studies where clinical data are lacking
  - Fundamental component of radiation oncology clinical practice
- Expand coverage for patients in tumors where current state-of-the-art X-rays (IMRT) offer suboptimal clinical outcome
  - Lung/ GI
- Include language to address patients for whom photon treatment is contra-indicated
  - Re-irradiation patients
  - Patients with syndromes associated with radiosensitivity (Crohns, A-T, Lupus, etc)

## Disclosure

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I AM CHIEF MEDICAL OFFICER OF PROCURE TREATMENT CENTERS, INC. I RECEIVE FULL SALARY AND HAVE STOCK OPTIONS FROM PROCURE.

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SEE ABOVE

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X [redacted] 4/26/2014 EUGEN B. HUG, M.D.

*Signature* *Date* *Print Name*

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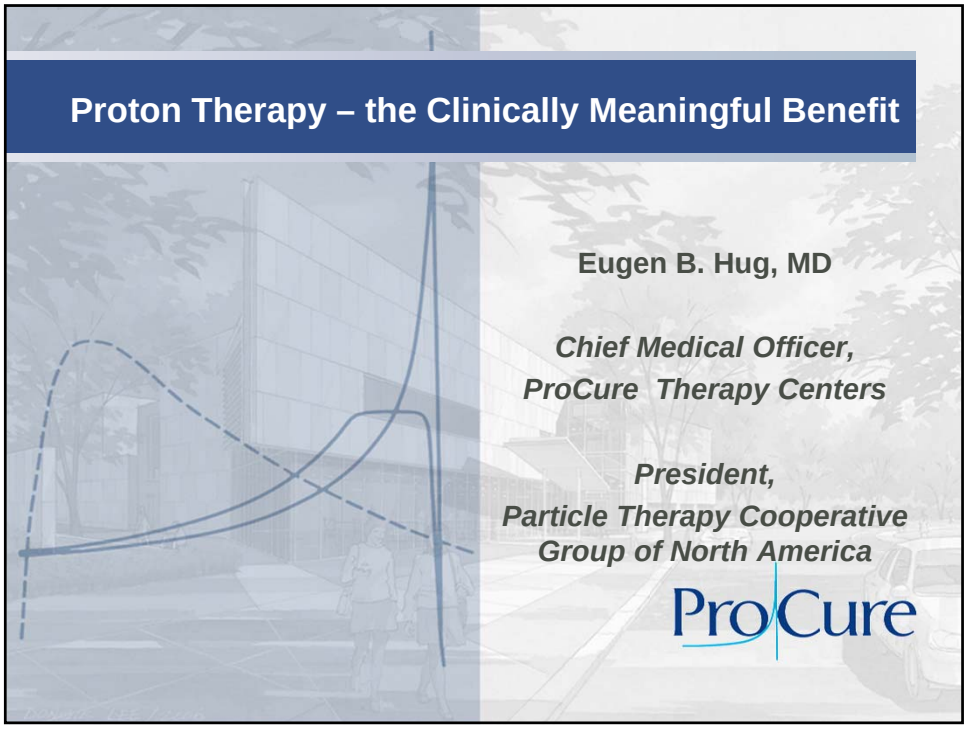



## Central Paradigm of Radiation Oncology

***"Increase dose to tumor – decrease dose to normal organs"***

= Increased cure – Decreased side effects

= Technological solution:
from 2-dimensional delivery, to 3-D, to 4-D

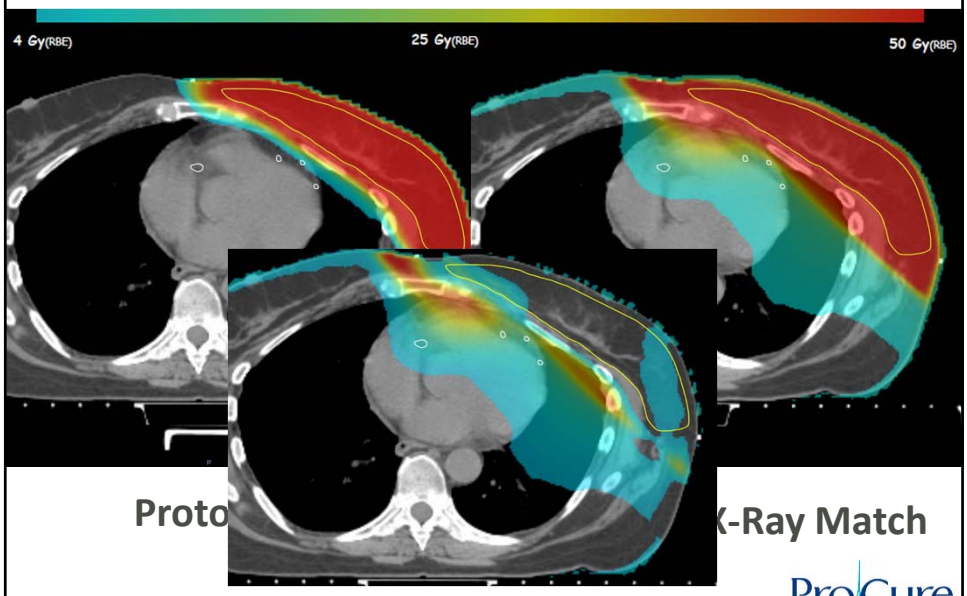
= A technology that delivers less radiation to normal organs while focusing dose in tumor is the superior technology

= Proton Therapy is the next evolutionary step

ProCure

2

## Protons for avoidance of coronary artery and contralateral breast dose

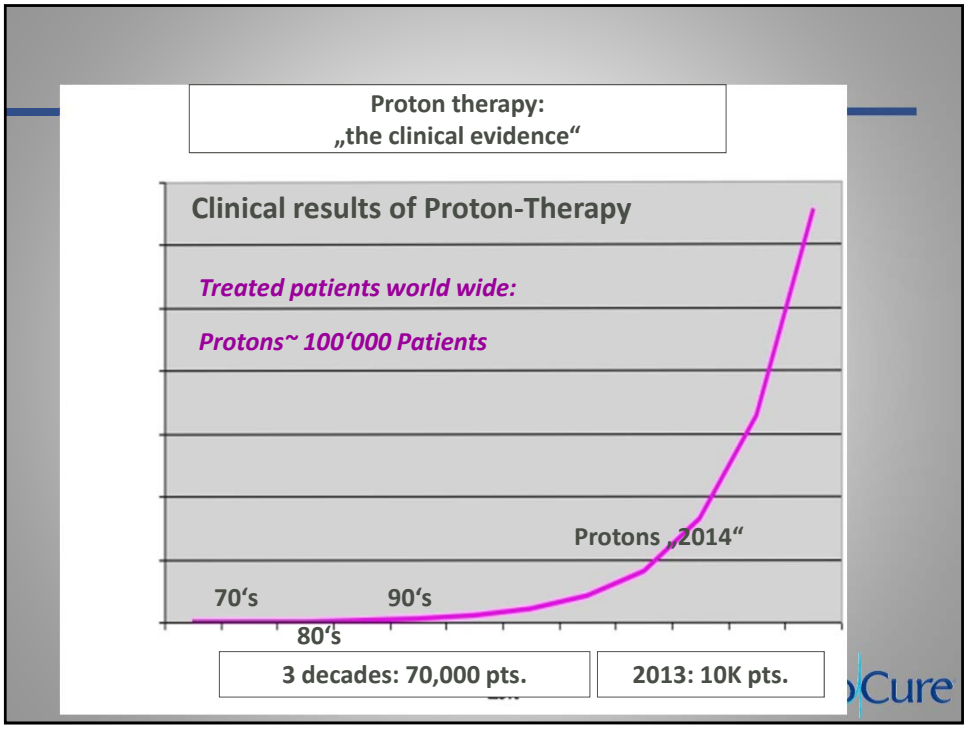


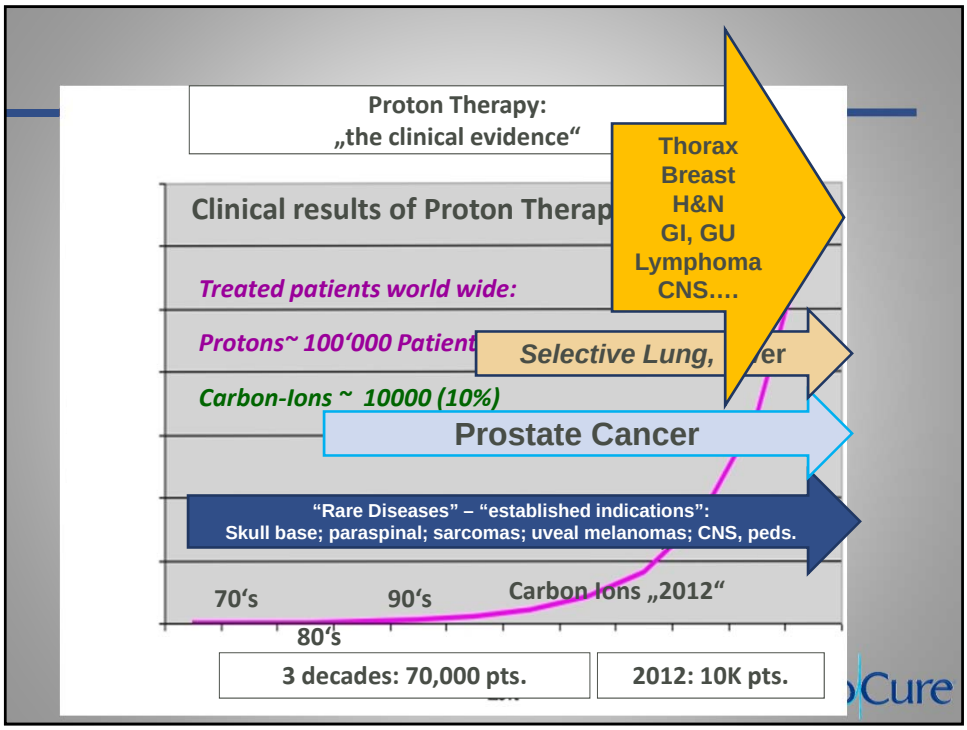

## Proton Therapy

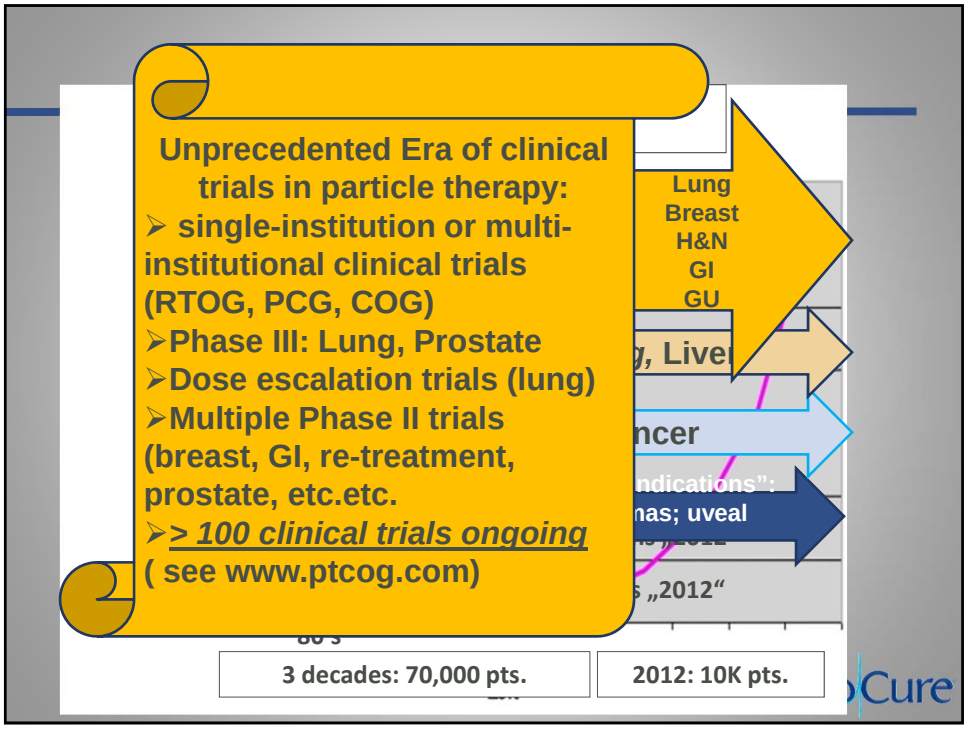
- No radiation dose = no radiation damage
- Less radiation dose = less radiation damage

ProCure

4


Proton therapy:
„the clinical evidence“
Clinical results of Proton-Therapy
Treated patients world wide:
Protons~ 100‘000 Patients
Protons „2014“
70‘s
80‘s
90‘s
3 decades: 70,000 pts.
2013: 10K pts.


Proton Therapy:
„the clinical evidence“
Clinical results of Proton Therap
Treated patients world wide:
Protons~ 100‘000 Patient
Carbon-Ions ~ 10000 (10%)
Thorax
Breast
H&N
GI, GU
Lymphoma
CNS....
Selective Lung,
Prostate Cancer
“Rare Diseases” – “established indications”:
Skull base; paraspinal; sarcomas; uveal melanomas; CNS, peds.
Carbon-Ions „2012“
70‘s
80‘s
90‘s
3 decades: 70,000 pts.
2012: 10K pts.




## Proton Therapy

- **Emerging Technology = Emerging Evidence**
- **How can we possibly judge the role/quality/benefits of emerging medical technology by the availability of mature clinical evidence?**
- **As surrogate, inclusion of pre-clinical data (i.e. dosimetric comparisons) and early clinical data are paramount**
- **Economical support the bona fide effort of the proton community to develop clinical evidence necessary to objectively judge proton therapy.**

8

ProCure

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| 6. | Any other relationship, including travel arrangements. | ✓ | |

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

#6. Received proton therapy for Breast cancer. There was no reimbursement for treatment

| | Potential Conflict Type | Yes | No |
|---|---|---|---|
| 7. | Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government). | ✓ | |

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

Same as #6 above

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 [redacted] 4/25/14 Robin J. Baird

*Signature* *Date* *Print Name*

**For questions contact:** Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126

Washington State Health Care Authority

Agency Medical Director Comments

# Proton Beam Therapy

Daniel Lessler MD, MHA
Chief Medical Officer
Washington State Health Care Authority
May 16, 2014

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## Ionizing Radiation for the Treatment of Malignant & Non-Malignant Tumors

- 3D-conformal RT 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

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## Theoretical Advantages

- Protons deliver most of their radiation energy at the point of greatest penetration of the protons in the tissue
- Normal tissues beyond the target receive little or no radiation

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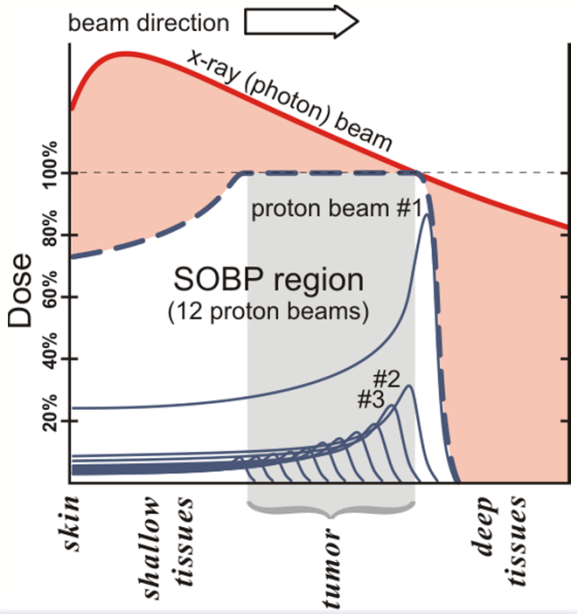


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## Uncertainties

- Uncertainty around the end of the dose range when deep-seated tumors are considered
- Lateral spread of the beam develops at the end of the beam (penumbra); may affect adjacent normal tissue
- Protons are sensitive to tissue heterogeneity; beam precision may be disturbed as it passes through different types of tissue

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## Uncertainties

- Neutrons are produced by passively-scattered proton beams and result in additional radiation to the patient (location of neutron production and biologic significance is debated)
- Relative biologic effectiveness (RBV) values of protons in relation to photons are not known with absolute certainty for all tissues and fractionation schemes

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Proton Beam Therapy

## Key Questions

- What is the comparative impact of PBT with curative intent on survival, dz progression, HRQOL, and other pertinent outcomes vs XRT alternatives and other cancer specific treatment options?
- What is the comparative impact of salvage treatment with PBT versus major alternatives on survival, dz progression, HRQOL and other patient outcomes vs XRT alternatives and other cancer-specific treatment options?
- What are the comparative harms associated with the use of proton beam therapy relative to its major alternatives, including acute and late toxicities, systemic effects such as fatigue and erythema, toxicities specific to each cancer type and risks of secondary malignancy?

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Proton Beam Therapy

## Key Questions

- What are the differential effectiveness and safety of proton beam therapy according to factors such as age, sex, race/ethnicity, disability, presence of comorbidities, tumor characteristics and treatment protocol?
- What is the costs and cost-effectiveness of proton beam therapy relative to XRT alternatives and other cancer-specific options?

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Proton Beam Therapy

## Cancers

- Bone
- Brain, spinal, paraspinal
- Breast
- Esophageal
- GI
- Gynecological
- Head and Neck
- Liver
- Lung
- Lymphoma
- Ocular
- Pediatric
- Prostate
- Sarcoma
- Seminoma
- Thymoma

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Proton Beam Therapy

## Non-Cancerous Conditions

- Arteriovenous malformations
- Hemangiomas
- Other benign tumors
  (e.g. acoustic neuromas, pituitary adenomas)

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Proton Beam Therapy

## Agency Medical Directors' Concerns

**Safety** = **Medium**
Adverse effects from any type of radiotherapy may be severe, including the risk of secondary cancers. PBT has theoretical advantages, but do these translate into actual clinical benefit?

**Efficacy** = **High**
PBT theoretically enables focused delivery of higher doses of radiation to diseased tissue, but does this lead to better clinical outcomes compared to standard XRT?

**Cost** = **High**
Cost may be up to 2X standard treatments

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## Evaluating Net Health Benefit: Issues

- Insufficient evidence for 8 cancers to evaluate net health benefit vs. comparators
  - Breast, esophageal, GI, gynecologic, lymphomas, sarcomas, seminoma, thymomas
- For pediatric cancers, only 1 poor quality clinical study; other described studies were decision-analyses informed by clinical outcomes derived from dosimetric and modeling studies

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## Cancers with Potential Incremental Benefit

- Ocular cancer: improved outcomes with comparable rates of harm, *moderate strength of evidence*
- Brain, spinal, and paraspinal tumors: equal outcomes with possibly less harm, *low strength of evidence*

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## Cancers with Comparable Treatment Outcomes

- Bone
- Head/neck
- Liver
- Lung
- Prostate

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## Non-Cancerous Conditions

- Insufficient evidence
  - AVMs and other benign tumors (acoustic neuromas; pituitary adenomas)
- Comparable treatment outcome
  - Hemangiomas

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Proton Beam Therapy

## Current State Agency Policy

| Description | Medicaid | UMP | DOC | LNI |
|---|---|---|---|---|
| **Proton Beam Therapy** | PA | PA | PA | PA |

**C:** Covered
**NC:** Not covered
**PA:** Prior authorization required

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Proton Beam Therapy

## State Agency Utilization

| PEB Proton Beam Patients | 2009 | 2010 | 2011 | 2012 | 4 Yr Overall Total** | Avg Annual Chnge |
|---|---|---|---|---|---|---|
| PEB Average Annual Members | 210,501 | 213,487 | 212,596 | 212,684 | | 0.3% |
| Total Proton Beam Patients | 7 | 5 | 7 | 4 | 20 | -10.6% |
| Total Paid (PEB Primary only) (Imaging/planning included) | $290,083 | $53,639 | $37,133 | $83,088 | $463,943 | 3.8% |
| % of total for direct day of treatment costs | 94.3% | 62.4% | 98.2% | 90.6% | 90.2% | |
| Average Paid per Patient (PEB Primary only) | $96,694 | $26,820 | $18,567 | $83,088 | $66,278 | |

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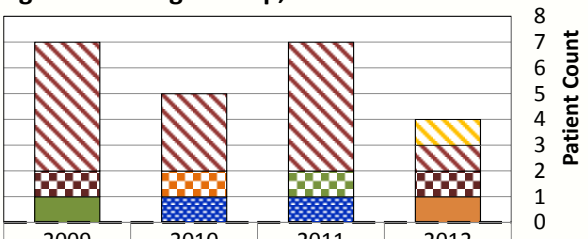
State Agency Utilization

### PEB/UMP Proton Beam Therapy Patients by Diagnosis and Age Group, 2009-2012

All patients are male.
**Matching color** indicates same diagnosis.
**Matching pattern** indicates same age group..

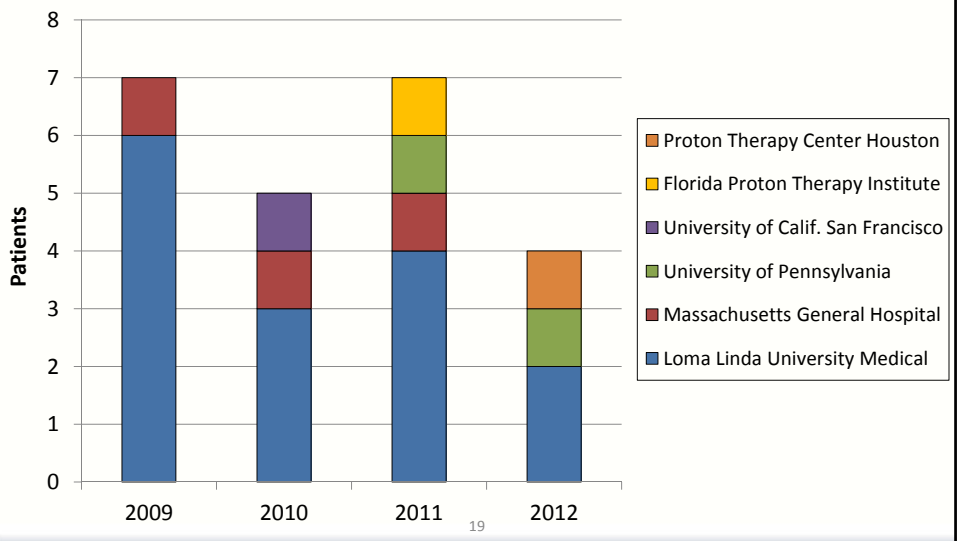
**Note:** Younger patients are shown lower and with more solid patterns.




| | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|
| Lung 66-85 | 0 | 0 | 0 | 1 |
| Prostate 66-85 | 5 | 3 | 5 | 1 |
| Prostate 51-65 | 1 | 0 | 0 | 1 |
| Eye 51-65 | 0 | 1 | 0 | 0 |
| Brain 51-65 | 0 | 0 | 1 | 0 |
| Spinal 35-50 | 0 | 1 | 1 | 0 |
| Eye 0-20 | 0 | 0 | 0 | 1 |
| Brain 0-20 | 1 | 0 | 0 | 0 |

State Agency Utilization

**PEB Proton Beam Therapy Patients 2009-2012**
**Treatment Centers by Year**

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Proton Beam Therapy

# Summary:

- The available literature that looks at the comparative effectiveness and safety of PBT is limited and generally fair to poor quality
- Available evidence suggests that proton and photon treatments are either equivalent or that benefits of proton therapy are uncertain
- Any theoretical advantage comes at double the cost of available, covered alternatives
- Evidence that PBT is possibly superior is best for ocular tumors
- Studies of PBT in pediatric populations with cancer are especially lacking

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Proton Beam Therapy

## Private Payer Examples

| Condition | Premera BC | Aetna | UnitedHC |
|---|---|---|---|
| Uveal Melanoma | May be Medically Necessary | Medically Necessary | Proven |
| Chordomas & Chondrosarcomas | May be Medically Necessary | Medically Necessary | Proven |
| Pediatric Cancers (some limit to CNS) | May be Medically Necessary | Medically Necessary | Covered under 19 years of age |
| Prostate | Not medically Necessary | Not Medically Necessary | Not Medically Necessary |
| NSCLC | Investigational | Experimental/ Investigational | Unproven |
| Head & Neck (other than skull-based chordoma or chondrosarcoma) | Investigational | Experimental/ Investigational | Unproven |

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Proton Beam Therapy

## Centers for Medicare & Medicaid Services (CMS)

- No national coverage determination
- Local coverage determination covers for the following if life expectancy > 2 yrs
  - Unresectable benign or malignant tumors of the CNS, including glioblastoma, acoustic neuroma and AVMs
  - Intraocular melanomas
  - Pituitary neoplasms
  - Advanced, unresectable tumors of head and neck
  - Malignant tumors of the paranasal and other accessory sinuses
  - Unresectable retroperitoneal sarcoma
  - Solid tumors in children

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Proton Beam Therapy

## State Agency Recommendation

**Cover for the following conditions:**

- Ocular tumors
- Pediatric populations (age < 21 yrs), undergoing treatment in the context of evidence collection/submission of outcome data (e.g., registry; observational study)

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Proton Beam Therapy

## State Agency Recommendation

**Non-covered for the following conditions:**

- AVMs
- Bone
- Brain/spinal
- Breast
- Esophageal
- GI
- Gynecological
- Head/neck
- Hemangiomas
- Liver
- Lung
- Lymphoma
- Prostate
- Sarcoma
- Seminoma
- Thymomas
- Other non-cancerous conditions

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## State Agency Recommendation

**If covered, conditions should include, for example:**

- Undergoing treatment in the context of evidence collection/submission of outcome data (e.g., registry, observational study).



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## Questions?

**More Information:**
http://www.hca.wa.gov/hta/Pages/neurotomy.aspx

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Washington State Health Care Authority

# Proton Beam Therapy

An Assessment of
Comparative Clinical Effectiveness
& Comparative Value

**Presented to the Washington State Health Care Authority by**
**Daniel A. Ollendorf, MPH**
**May 16, 2014**

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## Overview

- Project Scope, Comparators, Outcomes of Interest
- Systematic Review of Published Evidence
- Comparative Value
- Evidence Ratings
- Clinical Guidelines
- Payer Coverage Policies
- Summary

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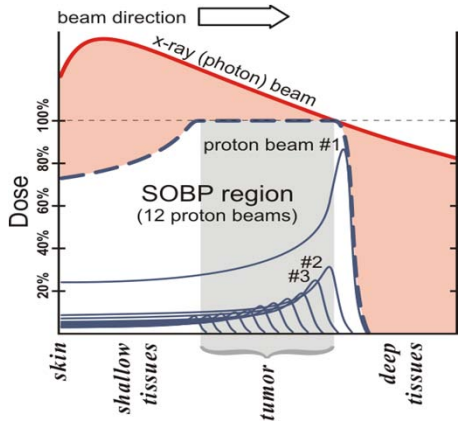
## Background

- Protons in clinical use for >60 years
- Clinically appealing physical attributes ("Bragg peak")

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Source: Adapted from Levin WP, Kooy H, Loeffler, DeLaney TF. Proton beam therapy. *Br J Cancer.* 2005;93(8):849-854.

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## Background

- General comparison to photon radiation:
  - Lower radiation dose at body entry/shallow tissue depths
  - Lack of exit dose (i.e., after target) vs. photons
- Early adoption in:
  - Pediatric cancers (increased radiation sensitivity, secondary malignancy, impacts on development)
  - Cancers at or adjacent to critical anatomic structures (e.g., brain stem, eye, spinal cord)

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## Background

- Relative rarity of these cancers and construction expense ($150-$200 million): <5 facilities 10 years ago
- More recent use in prevalent cancers:


5 Source: The National Association for Proton Therapy. http://www.proton-therapy.org/map.htm; Particle Therapy Co-Operative Group. http://www.ptcog.ch/

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## Uncertainties with PBT

- Lack of clarity re: end of dose range for deep-seated tumors
- PBT "penumbra" formation
- Neutron production
- Lack of precision in estimates of "relative biological effectiveness" vs. photons for some tumor types
- Continued evolution of photon therapy
- Cost and cost-effectiveness

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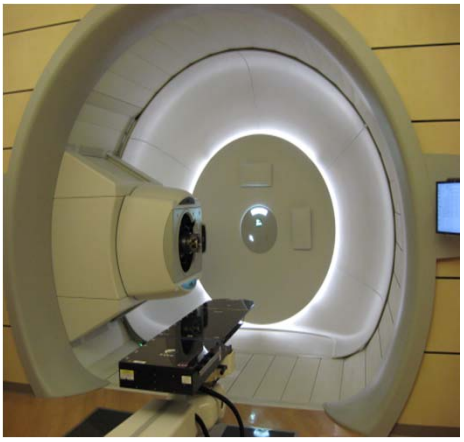
## PBT: What Patients Can Expect



- Initial treatment planning and simulation session
- Daily treatment fractions (5 days/wk, 15-60 mins per session)
- Up to 8 weeks of treatment
- Potential systemic SE, anatomy-specific SE, secondary cancer risks

Source: ProCure Proton Therapy Centers. http://www.procure.com/Portals/1/Media/Gantry-New_1_display.jpg

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## Radiation Alternatives

| Modality | Type | Approx. Cost* |
|---|---|---|
| IMRT | External beam | $18-20K |
| 3D-CRT | External beam | $10-12K |
| Brachytherapy | Seed implant procedure | $8-10K |
| Stereotactic Radiosurgery | External beam | $10-15K |
| Proton beam | External beam | $30-35K |

*Based on cited Medicare estimates for prostate cancer treatment

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## Key Questions

1) **What is the comparative impact of proton beam therapy 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 multiple cancer types and noncancerous conditions?**

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 multiple cancer types and noncancerous conditions?**

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## Key Questions

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)?**

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## Key Questions

5) **What are the costs and cost-effectiveness of proton beam therapy relative to radiation therapy alternatives and other cancer-specific treatment options (e.g., surgery, chemotherapy)?**

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## Project Scope

**Population:**

- Patients who are candidates for external beam radiation therapy for one of 16 cancer types or 3 noncancerous conditions
- Treatment of primary cancer for curative intent or recurrent cancer (palliative treatment excluded)
- Adults and children

**Interventions/Comparators:**

- Proton beam therapy (alone and in combination with other treatments)
- Primary comparators: other forms of radiation therapy
- Other disease-specific comparators assessed if studies found

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## Conditions of Interest

| Condition Category | Specific Condition Types | |
|---|---|---|
| | | |
| **Cancer** | Bone cancer | Lung cancer |
| | Brain, spinal, & paraspinal tumors | Lymphomas |
| | Breast cancer | Ocular tumors |
| | Esophageal cancer | Pediatric cancers |
| | Gastrointestinal cancers | Prostate cancer |
| | Gynecologic cancers | Soft Tissue Sarcomas |
| | Head & neck cancers | Seminoma |
| | Liver cancer | Thymoma |
| **Noncancerous Conditions** | Arteriovenous malformations | Other benign tumors |
| | Hemangiomas | |

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## Project Scope

### Clinical Outcomes:

- Disease-free and/or overall survival
- Disease-related and/or all-cause mortality
- Measures of tumor regression and control
- Incidence of metastases
- Tumor recurrence (including intermediate measures such as biochemical recurrence)
- Health-related quality of life (HrQoL)
- Requirements for subsequent therapy

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## Project Scope

**Potential Harms:**

- Radiation-Induced Toxicity
  - Acute (<90 days)
  - Late (≥90 days)
  - Recorded using standardized grading system such as that of Radiation Therapy Oncology Group (e.g., 0=no toxicity, 4=seizures, paralysis, or coma for radiation to the brain)*
- Secondary Malignancy
- Rates of specific adverse events (e.g., urinary retention in prostate cancer, pneumonitis in breast or lung cancer)

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*Source: http://www.rtog.org/ResearchAssociates/AdverseEventReporting/RTOGEORTCLateRadiationMorbidityScoringSchema.aspx

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## Literature Search

- Published studies Jan 1990 – Feb 2014
- Focus on *comparative* studies:
  - RCTs and observational (including contemporaneous and noncontemporaneous comparisons)
  - No a priori limits on sample size or duration
- Simulation/dosimetric comparisons not included
- Case series abstracted and available in evidence tables but not a focus of assessment conclusions

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## Quality & Strength of Evidence

- Quality of Individual Studies:
  - USPSTF Criteria: based on comparability of study arms, control for confounding, intent-to-treat analysis, etc. (Good/Fair/Poor)
- Overall Strength of Evidence:
  - Risk of bias: study design and quality
  - Consistency: direction and magnitude of findings
  - Directness: direct comparison of major interventions and/or direct measurement of key outcomes
  - Precision: confidence interval around estimates of intervention effect

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## Judgment of Overall Net Health Benefit

- From ICER's evidence rating matrix:
  - *Superior:* Moderate-to-large net health benefit vs. comparator(s)
  - *Incremental:* Small net health benefit vs. comparators(s)
  - *Comparable:* Given tradeoffs in effectiveness and/or harms, comparable net health benefit vs. comparator(s)
  - *Inferior:* 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)

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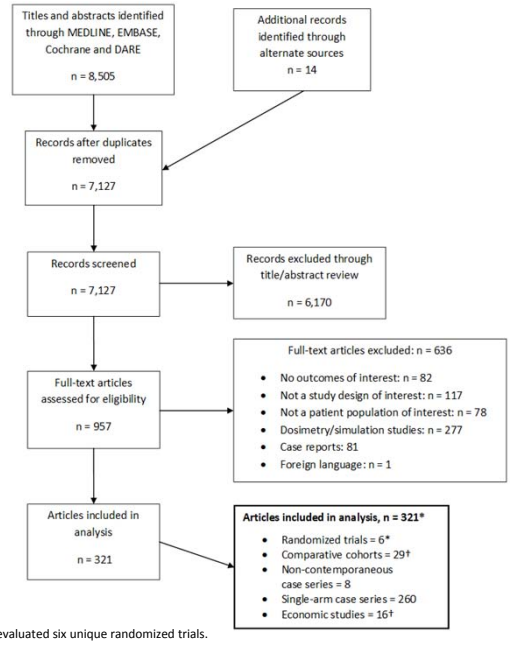
## PRISMA flowchart showing results of literature search

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* Nine studies evaluated six unique randomized trials.
† One study reported on clinical and economic outcomes.

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## Findings

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## Quality & Type of Evidence

- 6 RCTs ***but only 1*** with explicit comparison of PBT-based strategy to alternative treatment
- 37 comparative cohort studies, none of which was judged to be of good quality
  - 21 fair, 16 poor
- Evidence base considered to be insufficient (completely or essentially absent of comparative study) for 12 of 19 conditions of interest
- Focus in this presentation on remaining 7 conditions

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## KQ1: PBT with Curative Intent, Impact on Patient Outcomes

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| Condition | RCT/CC (N) | Comparator(s) | Survival | Tumor Control | SOE |
|---|---|---|---|---|---|
| Brain/Spinal Ca | 0/2 (72) | IMRT, photon | ⟺ | ND | Low |
| Liver Ca | 0/2 (385) | PBT+chemo, carbon ion | ND | ND | Low |
| Lung Ca | 0/3 (563) | IMRT, 3D-CRT, carbon ion | ND | ND | Moderate |
| Ocular Ca | 1/6 (1545) | PBT+TTT or chemo, enucleation | ⇧ | ⇧ | Moderate |
| Prostate Ca | 1/9 (2072) | IMRT, photon, RP, WW | ND | ⟺ | Moderate |
| Hemangiomas | 0/1 (44) | Photon | --- | ND | Low |

ND: No difference
⟺: Mixed evidence

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## Lung studies

- Three fair-quality comparative cohorts:
  - Two retrospective comparisons of PBT (74 Gy) to IMRT or 3D-CRT in 452 patients with NSCLC treated at MD Anderson and followed for 1-1.5 years (Sejpal, 2011; Lopez-Guerra, 2012)
    - No differences in survival between groups
    - PBT superior to 3D-CRT in preserving diffusing capacity of lung for carbon monoxide
  - One prospective comparison to carbon-ion therapy (another heavy-particle therapy in use in Europe and Asia) (Fuji, 2013)
    - 111 patients with NSCLC followed for median of 3.5 years
    - No differences in 3-year estimates of tumor control, progression-free survival, or overall survival

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## Ocular studies

- 1 RCT and 3 cohort studies that did not explicitly compare PBT to an alternative
- Evidence from 3 fair-quality retrospective cohort studies in uveal melanoma vs. surgical enucleation:
  - Largest study (n=1,051) found statistically-significant reductions of 60% for PBT in cancer-related and all-cause mortality up to 2 years, but nonsignificant differences thereafter (Seddon, 1990)
  - Smaller study in France (n=67) showed significantly higher overall (79% vs. 40%) and metastasis-free (59% vs. 39%) Cox-adjusted survival at 5 years for PBT (Bellmann, 2010)
  - Italian study (n=132) showed nominal survival differences for PBT, but groups somewhat imbalanced on age, stage, and tumor thickness (Mosci, 2012):
    - After regression adjustment for these variables, differences were no longer significant

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## Prostate cancer studies

- Fair-quality RCT (Shipley, 1995):
  - PBT+photons (75 Gy) vs. photons alone (67 Gy) in advanced prostate cancer; median f/u 5 years, n=202, treated between 1982-1992
  - No differences in tumor control or survival in overall cohort or study "completers"
    - Better tumor control at 8 years in men with poorly-differentiated tumors (85% vs. 40%, p=.0014)
- 2 fair-quality comparative cohorts:
  - Prospective evaluation of QoL showed no differences in overall scales, some benefits of PBT, vs. surgery, photons, or watchful waiting on individual domains (Galbraith, 2001)
  - Retrospective, matched comparison to brachytherapy showed no differences in survival, metastasis, or biochemical failure (Coen, 2012)

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## Other conditions

- No or insufficent comparative study for KQ1:
  - Bone, breast, esophageal, GI, gynecologic, head/neck cancers
  - Lymphomas, soft tissue sarcomas, seminomas, thymomas
  - Arteriovenous malformations, other benign tumors
- No comparative pediatric studies for KQ1:
  - Widespread belief that comparative study unethical in children based on increased sensitivity to radiation and theoretical benefits of PBT

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## KQ2: PBT for Recurrent Conditions, Impact on Patient Outcomes

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| Condition | RCT/CC (N) | Comparator(s) | Survival | Tumor Control | SOE |
|---|---|---|---|---|---|
| Liver Ca | 0/2 (385) | PBT+chemo, carbon ion | ND | ND | Low |
| Ocular Ca | 0/1 (73) | PBT+TTT or chemo, enucleation | ⇑ | ⇑ | Low |

ND: No difference
⇔: Mixed evidence

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## Ocular study

- Single, fair-quality retrospective cohort study of 73 patients with recurrent uveal melanoma after initial course of PBT:
  - Treated with second course of PBT or surgical enucleation at MGH and followed for 5-7 years (Marucci, 2011)
  - Overall survival (63% vs. 36%) and metastasis-free survival (66% vs. 31%) at 5 years significantly in favor of PBT
    - Findings unchanged after Cox PH adjustment

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## Other conditions

- No or insufficent comparative study for KQ2:
  - Bone, brain/spinal, breast, esophageal, GI, gynecologic, head/neck, prostate cancers
  - Lymphomas, soft tissue sarcomas, seminomas, thymomas
  - Arteriovenous malformations, hemangiomas, other benign tumors
- No comparative pediatric studies for KQ2

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## KQ3: Potential Harms of PBT

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| Condition | RCT/CC (N) | Comparator(s) | Toxicity | Dis.Specific Harms | SOE |
|---|---|---|---|---|---|
| Brain/Spinal Ca | 0/2 (72) | IMRT, photon | ⇩ | ⇩ | Low |
| Esophageal Ca | 0/2 (519) | IMRT, 3D-CRT | --- | ⟺ | Low |
| Lung Ca | 0/3 (965) | IMRT, 3D-CRT, carbon ion | ND | ⟺ | Moderate |
| Ocular Ca | 1/2 (283) | PBT+TTT or chemo, enucleation | --- | ⇩ | Low |
| Prostate Ca | 1/3 (32512) | IMRT, photon, RP, WW | ⟺ | ⟺ | Moderate |
| Hemangiomas | 0/1 (44) | Photon | ND | ND | Low |

ND: No difference
⟺: Mixed evidence

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# Lung studies

- Three fair-quality cohort studies:
  - Significantly lower rates of severe acute esophagitis (up to 6 months) vs. IMRT (6% vs. 28%) in 652 patients treated at MD Anderson for NSCLC and analyzed retrospectively (Gomez, 2012)
  - Significantly lower rates of esophagitis (5% vs. 39%) and pneumonitis (2% vs. 6%) vs. IMRT in previously-described retrospective MD Anderson cohort (Sejpal, 2011)
    - But higher rates of severe dermatitis (24% vs. 17% for IMRT)
  - Third, prospective study (vs. carbon-ion) showed no differences in dermatitis, pneumonitis, or rib fracture between modalities (Fuji, 2013)

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## Prostate cancer studies

- Previously-described RCT (Shipley, 1995) found significantly higher rates of mild-moderate rectal bleeding in PBT+photon group (32% vs. 12% for photons alone, p=.0002)
  - No differences seen in any grade 3 or higher toxicities as well as hematuria, urethral stricture, incontinence, and loss of potency
- Three fair-quality retrospective database comparisons:
  - Analysis of ~30,000 men in Medicare-SEER database found Cox-adjusted rates of GI morbidity 2-14 times higher for PBT vs. IMRT, 3D-CRT, and conservative management (Kim, 2011)
  - Higher GI toxicity also seen in matched Medicare-SEER study of ~1,400 patients treated with PBT or IMRT (17.8 vs. 12.2 per 100 person-years, p<.05) (Sheets, 2012)
    - No differences in urinary morbidity, ED, hip fracture, or need for add'l cancer therapy
  - Matched study using Chronic Conditions Warehouse found lower urinary morbidity for PBT at 6 months (6% vs. 10% for IMRT, p=.03) but no difference at 12 months (Yu, 2013)

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## Secondary Malignancy

- Chung, 2013:
  - Matched PBT-photon retrospective cohort study using SEER-Medicare dataset (n=1,116); median f/u 6.4 yrs
  - No 2nd cancers detected in 88 pediatric cases
  - No statistical difference in unadjusted comparisons
  - Cox PH adjustment for age, sex, tumor site, yr of diagnosis, etc.: Hazard Ratio: 0.52 (95% CI: 0.32, 0.85, p=0.009)
  - However:
    - When solid tumors occurring within 5 years of treatment excluded, NO differences between modalities
    - Comparisons primarily to older-generation photon therapy, not IMRT

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## Secondary Malignancy

- Sethi, 2013:
  - Retrospective cohort study of 86 infants treated for retinoblastoma and followed for 7-13 years
    - Seven of 31 photon patients got stereotactic radiotherapy or IMRT
  - Numeric but non-significant difference in overall rate of secondary malignancy (5% vs. 14% for photon, p=0.12)
  - Significant differences in favor of PBT when malignancies restricted to "in-field" or thought to be radiation-induced (0% vs. 14%, p=0.015)
  - However:
    - Adjustments only made for differential follow-up, not confounding

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## Other conditions

- No or insufficent comparative study for KQ3:
  - Bone, breast, GI, gynecologic, head/neck, liver cancers
  - Lymphomas, soft tissue sarcomas, seminomas, thymomas
  - Arteriovenous malformations, other benign tumors
- Single poor-quality comparative pediatric study for KQ3

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# KQ4: Differential Impact of PBT in Key Patient Subgroups

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## Impact of PBT in Key Subgroups

- **Demographics:**
  - Data from 2 fair-quality retrospective cohort studies suggesting reduced rates of metastasis (vs. enucleation) and secondary malignancy (vs. photons) with advanced age (Chung, 2013; Seddon, 1990); no differences seen in a fair-quality retrospective cohort study vs. enucleation in recurrent uveal melanoma (Marucci, 2011)
- **Clinical Characteristics:**
  - Reduced rates of secondary malignancy in infants with hereditary form of retinoblastoma in poor-quality retrospective cohort (Sethi, 2013)
- **Tumor Characteristics:**
  - 8-year estimate of local tumor control significantly better with PBT in fair-quality prostate cancer RCT among patients with poorly-differentiated tumors (Shipley, 1995)
  - No differences seen in 3 other fair-quality retrospective cohort studies of PBT vs. IMRT/3D-CRT in lung cancer (Sejpal, 2011), enucleation in uveal melanoma (Mosci, 2012), or brachytherapy in prostate cancer (Coen, 2012)

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## Impact of PBT in Key Subgroups

- **Treatment Protocol:**
  - Data available on different PBT dosing regimens in 4 RCTs (2 in prostate cancer, 1 in melanoma of choroid or ciliary body, 1 in chordomas and skull base tumors)
  - Improved disease control with higher-dose PBT+photon (79 Gy vs. 70 Gy PBT+photon) in 1 good-quality prostate cancer RCT, but also greater severe acute GI toxicity (Zietman, 2010)
  - No major differences in effectiveness or harm in other RCTs

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## KQ5: Economic Impact of PBT

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## Economic Impact of Proton Beam Therapy: Prior Published Evidence

- 16 studies identified, mostly decision-analytic models with results derived from dosimetric findings
- Breast Cancer (3 studies):
  - Results sensitive to assumptions regarding underlying risk of cardiac disease (and assumed effects of PBT vs. photons)
- Head and Neck Cancers (2 studies):
  - Assumption of lower mortality based on potentially higher curative dose from dosimetry studies
- Lung Cancer (2 studies):
  - PBT found to be superior to conventional radiation but clinically inferior to and more expensive than carbon-ion and stereotactic radiation in inoperable NSCLC (based on clinical data from meta-analysis of case series)

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## Economic Impact of Proton Beam Therapy: Prior Published Evidence

- Pediatric Cancers (3 studies):
  - Lifetime costs of PBT lower in patients with medulloblastoma, and PBT more effective than photon radiation (based on dosimetry findings)
- Prostate Cancer (4 studies):
  - Results sensitive to assumptions regarding reductions in cancer recurrence (not demonstrated in clinical study) as well as urinary and GI toxicity (mixed evidence in clinical study)
- Facility Assessments (4 studies):
  - Studies focusing on debt coverage suggest that larger (3-4 gantry) PBT facilities will require treatment of “noncomplex” prevalent cancers to service debt

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## Budget Impact Analysis

- Straightforward assessment of prostate and lung cancer radiation therapy volume at PEBB in 2012
- Replacing brachytherapy, IMRT, and radiosurgery with PBT would increase treatment costs by 75% (from ~$2 million to $3.5 million) in PEBB radiation therapy patient population
- Findings similar when typical Medicare payment rates for planning, simulation, and treatment used instead

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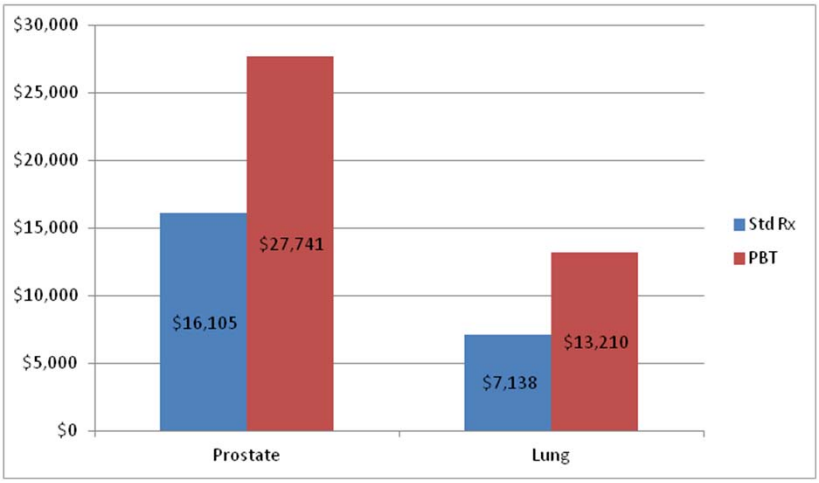
## Budget Impact Analysis




NOTE: "Std Rx" refers to the current mix of radiation treatments used in each population (IMRT and brachytherapy for prostate cancer, IMRT and radiosurgery for lung cancer)

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## Clinical Practice Guidelines

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## Practice Guidelines

- Sources:
  - National Comprehensive Cancer Network (2013-2014)
  - American Society of Radiation Oncology (ASTRO) (2013)
  - American College of Radiology (ACR) (2011-2013)

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## Practice Guidelines

- Not recommended for routine use in prostate cancer (outside of a clinical trial or registry)
- Appropriate for ocular tumors
- Appropriate (in some) for CNS lesions
- Appropriate (in some) for non-small cell lung cancer
- Appropriate for unresectable chondrosarcomes of the skull base and axial skeleton
- May be appropriate for certain lymphomas and soft tissue sarcomas, pending long-term studies of benefits and harms

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## Payer Coverage Policies

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## CMS

- LCD for the state provides coverage for the following (if life expectancy >2 years):
  - Unresectable benign or malignant tumors of the CNS, including glioblastoma, acoustic neuroma and arteriovenous malformations
  - Intraocular melanomas
  - Pituitary neoplasms
  - Chordomas and chondrosarcomas
  - Advanced, unresectable tumors of the head and neck
  - Malignant tumors of the paranasal and other accessory sinuses
  - Unresectable retroperitoneal sarcoma
  - Solid tumors in children

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## CMS

- Additional coverage for patients enrolled in a clinical trial or registry with:
  - 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

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## Private Payers

- Consistent coverage regionally and nationally for:
  - Uveal melanoma
  - Chordomas and chondrosarcomas
  - Pediatric cancers (limited to CNS and retinoblastoma by some)
- Coverage by some payers for:
  - CNS tumors close to vital structures in adults
  - Arteriovenous malformations
  - Pituitary tumors
- Most private payers do not cover PBT for prostate cancer due to lack of proven effectiveness over radiation alternatives

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## Ongoing Studies

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## Ongoing RCTs of PBT

- GI (2, vs. IMRT)
- Glioblastoma (1, vs. IMRT)
- Liver (2, 1 vs. sorafenib, 1 vs. RF ablation)
- Lung (3, 2 vs. conventional photon, 1 vs. SBRT)
- Meningiomas (1, vs. carbon-ion)
- Prostate (2, vs. IMRT)

- Completion dates: 2015-2023

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## Notable PBT Registries

- Proton Collaborative Group (PCG)
  - Initiated in 2009; ongoing data collection for proton-treated patients at 4 sites (Illinois, New Jersey, Oklahoma, Washington)
- Pediatric Proton Consortium Registry (PPCR)
  - Initiated in 2012; ongoing data collection for proton-treated patients age ≤21 at 5 sites (Florida, Illinois, Massachusetts, Missouri, Pennsylvania)
- Long-term Follow-up Registry
  - Initiated in 2013; attempt to maintain lifetime contact with proton-treated patients at 2 sites (Indiana, Tennessee)
- Re-irradiation Registry Study for NSCLC
  - Initiated in 2013; data collection on patients receiving thoracic re-irradiation with PBT or IMRT (Texas)

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# Overall Evidence Summary

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| Condition | Incidence (per 100,000) | Net Health Benefit vs. Comparators | Type of Net Health Benefit | Strength of Evidence | Guideline Recommendations | Coverage Policies |
|---|---|---|---|---|---|---|
| ***Cancer*** | | | | | | |
| **Bone** | 1.3 | Insufficient | --- | + | M | M |
| **Brain/spinal** | 9.6 | Incremental | B: = H: ↓ | + | U | U |
| **Breast** | 97.7 | Insufficient | --- | o | NM | NR/NC |
| **Esophageal** | 7.5 | Insufficient | --- | o | NM | NR/NC |
| **GI** | 100.6 | Insufficient | --- | o | NM | NR/NC |
| **Gynecologic** | 38.2 | Insufficient | --- | o | NM | NR/NC |
| **Head/neck** | 17.2 | Insufficient | --- | + | NM | M |
| **Liver** | 12.8 | Comparable | B: = H: = | + | NM | M |
| **Lung** | 95.0 | Comparable | B: = H: = | ++ | M | M |
| **Lymphomas** | 32.9 | Insufficient | --- | o | NR/NC | NR/NC |
| **Ocular** | 1.2 | Superior | B: ↑ H: ↓ | ++ | U | U |
| **Pediatric** | 9.1 | Incremental | B: = H: ↓ | o* | U | U |
| **Prostate** | 99.4 | Comparable | B: = H: = | ++ | M | M |
| **Sarcomas** | 4.8 | Insufficient | --- | o | NM | M |
| **Seminoma** | 4.0 | Insufficient | --- | o | NM | NM |
| **Thymoma** | 0.2 | Insufficient | --- | o | NM | NM |
| | | | | | | |
| ***Noncancerous*** | | | | | | |
| **AVMs** | 1.0 | Insufficient | --- | o | NM | M |
| **Hemangiomas** | 2.0 | Comparable | B: = H: = | + | NM | NM |
| **Other** | 2.0 | Insufficient | --- | o | NM | M |

*Rating based on widespread acceptance rather than evidence base
B: Benefits; H: Harms
Strength of Evidence: Low=+; Moderate=++; High=+++; No evidence=o
Legend: U=Universally recommended or covered; M=Mixed recommendations or coverage policies; NM=Not mentioned in guidelines or coverage policies; NR/NC=Not recommended or not covered

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## Summary & Conclusions

- Comparative evidence generated to date for PBT is sparse and of generally lower quality:
  - Moderate evidence of superior net health benefit only available for ocular cancers
  - Judgment of incremental benefit for brain and spinal tumors, but with low strength of evidence
  - Acceptance of PBT for pediatric cancers based on assumption of benefit from dosimetry and simulation, not clinical study
  - Even situations with evidence suggesting "comparable" performance to alternatives (liver, lung, and prostate cancer, hemangiomas), strength of evidence was low or moderate
- Ongoing RCTs and registries will provide opportunity to revisit evidence base as it emerges

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## Backup Slides

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# Quality Ratings: USPSTF criteria

**Outcome Studies:**

- **"Good":**
  - Comparable groups with no or low attrition; intent-to-treat analysis used in RCTs
  - Reliable and valid measurement instruments used
  - Clear description of intervention and comparator(s)
  - All important outcomes considered
  - Attention to confounders in design and analysis
- **"Fair":**
  - Generally comparable groups, some differential follow-up may occur; intent-to-treat analysis used in RCTs
  - Acceptable measurement instruments used
  - Some but not all important outcomes considered
  - Some but not all potential confounders are accounted for
- **"Poor":**
  - Noncomparable groups and/or differential follow-up; lack of intent-to-treat analysis for RCTs
  - Unreliable or invalid measurement instruments used (including not masking outcome assessment)
  - Key confounders given little or no attention

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# 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 Benefits

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.

[1] Based on Legislative mandate: See RCW 70.14.100(2).

[2] The principles and standards are based on USPSTF Principles at: Hhttp://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

[3] The principles and standards are based on USPSTF Principles at: Hhttp://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

- 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.
- 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[4] 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.

| Not Confident | Confident |
|---|---|
| Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence. | Very certain of evidentiary support. Further information is unlikely to change confidence |

[4] Based on GRADE recommendation: http://www.gradeworkinggroup.org/FAQ/index.htm

***1. 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.

## Medicare Coverage and Guidelines

**[from page 14 of the evidence report]**

### *Centers for Medicare and Medicaid Services (CMS)*

Local Coverage Determination (LCD)

While there is no current National Coverage Determination (NCD) for PBT, an LCD involving Washington State provides coverage of PBT for treatment with curative intent or for advanced disease (if life expectancy is greater than two years) for the following indications (Group 1):

- Unresectable benign or malignant tumors of the CNS, including glioblastoma, acoustic neuroma and arteriovenous malformations
- Intraocular melanomas
- Pituitary neoplasms
- Chordomas and chondrosarcomas
- Advanced, unresectable tumors of the head and neck
- Malignant tumors of the paranasal and other accessory sinuses
- Unresectable retroperitoneal sarcoma
- Solid tumors in children

Coverage of PBT is provided for the following investigational conditions (Group 2) as long as patients are enrolled in a clinical trial or registry:

- 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

**[from page 11 of the evidence report]**

## 3. Clinical Guidelines and Training Standards

Major guideline statements as well as competency and/or accreditation standards regarding proton beam therapy can be found in the sections that follow below. Documents are organized by the organization or association.

### *National Comprehensive Cancer Network (NCCN) (2013 – 2014)*

http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site

PBT is considered appropriate for use in the treatment of non-small-cell lung cancer (NSCLC). For unresectable high- and low-grade chondrosarcomas of the skull base and axial skeleton, PBT may be indicated to allow for high-dose treatment. PBT may be appropriate for patients with Hodgkin and Non-Hodgkin lymphoma as well as soft tissue sarcomas; however, long-term studies are necessary to confirm benefits and harms.

Currently, PBT is not recommended for use in prostate cancer, as superior or equivalent effects have not been demonstrated in comparison to conventional external-beam therapy. For ethmoid and maxillary sinus tumors, PBT is an investigative therapeutic technique only.

Guidelines for treatment options in ocular tumors are under development. No other cancer types of interest for this review are described in NCCN guidelines.

### *American Society for Radiation Oncology (ASTRO) (2013)*

https://www.astro.org/Practice-Management/Reimbursement/Proton-Beam-Therapy.aspx
http://www.choosingwisely.org/doctor-patient-lists/american-society-for-radiation-oncology/

In a position statement, ASTRO concludes that the evidence supporting the use of PBT in prostate cancer continues to develop and define its role among current alternate treatment modalities. ASTRO strongly supports the provision of coverage with evidence development to evaluate the comparative effectiveness of PBT relative to other options including IMRT and brachytherapy.

As part of the Choosing Wisely® campaign, ASTRO provided a list of items that physicians and patients should discuss, including the topic of PBT, listed below:

“Don’t routinely recommend proton beam therapy for prostate cancer outside of a prospective clinical trial or registry.”

### *American College of Radiology (ACR) (2011-2013)*

http://www.acr.org/Quality-Safety/Appropriateness-Criteria

The ACR Appropriateness Criteria® consider PBT for treatment planning in T1 and T2 prostate cancer to be appropriate but with lower ratings than for IMRT (6-7 versus 8-9, based on a 1-9 scale). PBT-based treatment plans are considered inappropriate (rated 1-2) in spinal and non-spinal bone metastases, and for NSCLC patients with poor performance status or requirements for palliative treatment. The use of PBT as boost therapy in cervical cancer is not considered to be appropriate by the ACR. The ACR appropriateness criteria do not evaluate PBT in the treatment of other cancers or noncancerous conditions.

### *American Cancer Society (ACS) (2013)*

In a detailed patient guide, the ACS concludes that use of protons in prostate cancer may theoretically cause less damage to normal tissue surrounding the area of focus, but no current studies demonstrate the advantages of PBT over photon therapy. More comparative studies are necessary to evaluate the outcomes between the different modalities, with identification of the appropriate therapy for different kinds of cancer.

http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-treating-radiation-therapy
http://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/radiation/radiationtherapyprinciples/radiation-therapy-principles-how-is-radiation-given-external-beam-rad

### *Alberta Health Services (2013)*

http://www.albertahealthservices.ca/hp/if-hp-cancer-guide-rt002-proton-beam-RT.pdf

PBT is recommended as a therapeutic option in patients with ocular melanoma, CNS lesions (including craniopharyngioma, germ cell tumors and low-grade gliomas), sarcomas (including chordoma and chondrosarcoma), and benign conditions such as arteriovenous malformations (AVMs) and meningiomas. Additional pediatric conditions that may be considered for PBT are ependymomas, rhabdomyosarcoma, Ewing's sarcoma, pineal tumors, and patients requiring craniospinal irradiation. Treatment with PBT for adults with acoustic neuromas, and paranasal sinus and nasal cavity tumors is recommended, as well as for lymphoma in patients less than 30 years of age. PBT is not recommended for the treatment of prostate cancer, NSCLC or other lymphomas.

### *Training Standards*

In documents published by the ACR, and in joint publications with ASTRO and the American Association of Physicists in Medicine (AAPM), qualifications for radiation oncologists and qualified medical physicists are specified. Specific criteria are described below:

- Radiation oncologist
    - certification in Radiology by the American Board of Radiology (ABR); or
    - certification in Radiation Oncology or Therapeutic Radiology by the ABR, the American Osteopathic Board of Radiology, the Royal College of Physicians and Surgeons of Canada (RCPSC) or the Collège des Médecins du Québec; or
    - satisfactory completion of a radiation oncology residency program approved by the American Council of Graduate Medicine Education, the

RCPSC, the Collège des Médecins du Québec or the American Osteopathic Association; and
    - specific training in proton therapy; and
    - completion of continuing medical education

- Qualified medical physicist
    - certification in Therapeutic Medical Physics by the ABR, the Canadian College of Physicists in Medicine, or the American Board of Medical Physics; and
    - meet state/local radiation control agency qualifications to practice radiation oncology physics and/or provide oversight of a facility; and
    - specific training in proton therapy including treatment planning, quality assurance and equipment configuration; and
    - completion of continuing medical education

http://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/Radiation_Oncology.pdf
http://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/Rad_Onc_Proton_Therapy.pdf
http://www.acr.org/~/media/ACR/Documents/PGTS/standards/ProtonTherapy.pdf

ProCure, a company that develops and manages proton therapy centers in the U.S., operates a Training and Development Center in Bloomington, IN. Clinical and technical training programs focused on proton therapy are offered for radiation oncologists, medical physicists, dosimetrists, radiation therapists and other support staff.

http://www.procure.com/Media/SeattleCenterMedia/ProCureTrainingandDevelopmentCenter.aspx

## Health Technology Evidence Identification

Discussion Document:
What are the key factors and health outcomes and what evidence is there?

| Safety Outcomes | Safety Evidence |
|---|---|
| Radiation-induced toxicity- Acute | |
| Radiation-induced toxicity- Late | |
| Secondary malignancy | |
| Disease specific harm, e.g., incontinence, pulmonary complications | |
| Abnormal Bowel function | |
| Abnormal Bladder function | |
| Abnormal Sexual function | |
| Difficulty walking | |
| Return to work | |
| Weight loss | |
| Suppression of WBC | |
| Decreased hemoglobin | |
| Grade > 3 late toxicities | |

| Efficacy – Effectiveness Outcomes | Efficacy / Effectiveness Evidence |
|---|---|
| Mortality | |
| Progression free survival | |
| Tumor control | |
| Metastases | |
| Local failure | |
| Survival | |

| Special Population / Considerations Outcomes | Special Population Evidence |
|---|---|
| Age | |
| Sex | |
| Race | |
| Disability | |
| Comorbidities | |
| Tumor characteristics | |
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| | |
| **Cost** | **Cost Evidence** |
| Cost effectiveness | |
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## 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.

**Is there sufficient evidence under some or all situations that the technology is:**

| | **Unproven** (no) | **Equivalent** (yes) | **Less** (yes) | **More** (yes) |
|---|---|---|---|---|
| **Effective** | | | | |
| **Safe** | | | | |
| **Cost-effective** | | | | |

**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?

## Clinical Committee Findings and Decisions

**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.

***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?