



# Comparative Effectiveness of Proton Irradiation Treatment

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## PREFACE

Quality Enhancement Research Initiative's (QUERI) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) clinicians, managers and policymakers as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout the VA, and some evidence syntheses inform the clinical guidelines of large professional organizations.

QUERI provides funding for four ESP Centers and each Center has an active university affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence;
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of HSR&D Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at [Nicole.Floyd@va.gov](mailto:Nicole.Floyd@va.gov).

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## EXECUTIVE SUMMARY

### BACKGROUND

Maximizing target tumor dose while minimizing healthy tissue damage continues to be a challenge in radiation therapy. Because of its appealing dosimetric characteristics, proton beam therapy (PBT) has held the clinical promise of allowing for higher doses of radiation to be delivered more safely, especially for ocular, skull base, and spinal tumors that require exceptional precision. But the role of protons is less clear for more common tumors, like prostate, where their dosimetric advantages may be diminished and for which intensity-modulated radiation therapy (IMRT) can now safely deliver optimally high radiation doses.

To help consider the increased number of offers from University Affiliates to provide contracted off-site proton irradiation therapy, the VA Radiation Oncology Program requested that the Evidence-based Synthesis Program Coordinating Center (ESP CC) synthesize the most recent literature on the comparative effectiveness of PBT in various cancers. This report of that synthesis focuses on the following questions:

How does PBT compare with conventional X-ray-based external beam treatments and state-of-the-art therapies with regard to benefits and harms for both new patients and those who have locally recurrent tumors after irradiation?

How do the comparative effects of proton and photon beam therapies differ according to variation in tumor motion?

### METHODS

Our research librarian searched MEDLINE® (via PubMed®), the Cochrane Clinical Register of Controlled Trials, and ClinicalTrials.gov using the terms “proton beam” and “cancer” to identify articles relevant to the key questions. We also hand-searched reference lists, consulted experts, requested information from proton therapy system manufacturers and centers, and searched ClinicalTrials.gov.

We selected studies that compared benefits (survival, quality of life, functional capacity, local tumor control, delivery of planned chemotherapy and radiation regimens) and harms (toxicity and secondary malignancies) for PBT versus other modalities in adults with any cancer type (except ocular). We used standardized methods to assess internal validity and the overall strength of evidence for each outcome.

### RESULTS

We reviewed a total of 2,774 citations. From these, we included 25 relevant primary comparative studies and 6 systematic reviews. Requests to manufacturers and proton beam facilities did not identify any additional published or unpublished comparative studies, but only 6 manufacturers affirmed they weren't aware of any additional studies.

Most existing systematic reviews are outdated, as their literature searches were conducted prior to the publication of most of the comparative studies. The 2014 review produced by the Institute

for Clinical and Economic Review (ICER)<sup>1</sup> for the Washington State Health Care Authority Health Technology Assessment Program (HTA) included 22 of the 25 comparative studies. The ICER review was useful for its accurate data abstraction, but we couldn't rely on its conclusions.

## COMPARATIVE EFFECTIVENESS OF PBT (KEY QUESTIONS 1, 2, & 4)

### Breast

There is low-strength evidence of comparable 7-year cumulative local recurrence for single field PBT versus photon-based 3D conformal accelerated partial-breast irradiation for patients with stage I breast cancer, but various 7-year skin toxicities were more common in the proton therapy group (range, increased from 15-28% to 54-90%). However, there was no difference in patients' ratings of good or excellent for 7-year overall cosmetic outcomes or in local failure rates. This evidence came from one fair-quality prospective trial of 98 patients with stage I breast cancer treated between October 2003 and April 2006 at Massachusetts General Hospital.<sup>2</sup>

### Esophageal

There is low-strength evidence that, when used in trimodal therapy (neoadjuvant chemoradiation followed by surgical resection), IMRT and proton beam have comparable risk of postoperative pulmonary complications (OR: 2.23; 95% CI: 0.86-5.75) and GI complications (OR: 1.02; 95% CI: 0.47-2.25), 3-dimensional conformal radiation therapy (3D-CRT) and proton beam have comparable risk of GI complications (OR: 2.31; 95% CI: 0.69-7.74; 28.4% vs 18.1), but that 3D-CRT has a higher risk than proton beam of pulmonary complications (OR: 9.13; 95% CI: 1.83-45.42; 30.3% vs 13.9%). When given alone, there is low-strength evidence that proton therapy is associated with a higher risk of acute pneumonitis compared with IMRT/3D-CRT (33% vs 15%; P=.04).

### Medulloblastoma

There is low-strength evidence that PBT 54.6 GyE and photon therapy 52.9 Gy have comparable 2-year overall and progression-free survival, proportion of patients with treatment breaks, and locoregional failure, but some 1-month toxicities were less common in the proton beam therapy group, including medical management of esophagitis (5% vs 57%; P<.001), > 5% weight loss (16% vs 64%; P=.004), and Grade  $\geq$  2 nausea/vomiting (26% vs 71%; P=.004). This evidence came from a fair-quality retrospective cohort study of 40 adults with medulloblastoma treated at the MD Anderson Cancer Center from 2003 to 2011.<sup>3</sup>

### Non-small cell lung cancer

In patients with locally-advanced NSCLC, there is low-strength evidence that, even at a higher dose (74 Gy), acute risk of severe esophagitis (grade  $\geq$  3) at 6 months for PBT is similar to 3D-CRT 63 Gy, but lower than with IMRT 63 Gy (6% vs 28%; P<.0001).<sup>4</sup> This evidence came from one cohort study of 652 patients with NSCLC, mostly clinical stage IIIA-B and mean age of 66 years, who were treated at MD Anderson Cancer Center between 2000 and 2008. Evidence on survival and 15-17 month toxicity in a subgroup of those patients given concurrent chemotherapy was insufficient to draw conclusions. There is also insufficient evidence to draw conclusions about proton-based stereotactic ablative therapy for early-stage lung cancer compared with photon-based stereotactic ablative therapy.

## Prostate

Table 1 summarizes the numbers and types of comparative studies and our conclusions for each different comparison of PBT to IMRT, 3D-CRT, brachytherapy, and conventional photon therapy, respectively.

**Table 1. Conclusions for Comparative Studies in Prostate Cancer**

<b>Comparator</b>	<b>Benefits (Strength of Evidence Grade)</b>	<b>Harms (Strength of Evidence Grade)</b>
PBT vs IMRT	Similar Quality of Life (QOL) (low SOE): 2 historically-controlled cohorts (N=1695): <sup>5,6</sup>	Transiently lower GU toxicity at 0-6 months for PBT (low SOE), <sup>7</sup> but similar GI and GU toxicity at 12-24 months (low to moderate), <sup>7,8</sup> and increased GI toxicity with PBT at 4-5 years (low SOE): 4 retrospective cohorts <sup>8-10</sup> N=34,185
PBT vs 3D-CRT	Similar QOL (insufficient SOE), but survival vs 3D-CRT remains unknown: 1 historically-controlled cohort <sup>5</sup> ; N=218	Increased acute GI toxicity with PBT (low SOE): 1 retrospective cohort <sup>9</sup> ; N=NR
PBT vs brachytherapy	Similar 8-yr survival and distant metastasis (low SOE): 1 historically-controlled cohort <sup>11</sup> ; N=282	No evidence
PBT+photon vs photon alone	Similar overall 5-8 year survival and QOL (low SOE): (1 RCT, 2 cohort studies; N=567) <sup>12-14</sup>	Increased 8-year rectal bleeding and urethral stricture (low SOE): 1 RCT <sup>14</sup> ; N=202

## Spinal cord glioma

There is low-strength evidence that use of PBT may be disadvantageous for highly infiltrative tumors such as intermedullary spinal cord gliomas, as demonstrated by a reduced chance of 5-year overall survival (photon vs proton, aHR: 55.82; 95% CI: 1.34-2316.8).<sup>15</sup> This conclusion is based on one retrospective cohort study of 32 patients treated for intramedullary gliomas at Massachusetts General Hospital with either PBT (N=10) or IMRT (N=22) at an average dose of 51 Gy in 1.8 median daily fractions over 29 treatments.

## Mixed cancer types – secondary malignancies

There is insufficient evidence to draw conclusions about how PBT compares to other radiation modalities in the risk of secondary malignancy. While secondary cancer risk for PBT patients was half that of photon patients in a retrospective cohort of patients with a variety of non-metastatic cancers, this study had numerous methodological limitations.<sup>16</sup>

## Other cancer types

Although we found comparative studies in giant cell tumors of the bone, head and neck cancer, uveal hemangiomas, and meningiomas, they provided insufficient evidence for drawing conclusions.

### KEY QUESTION 3: PATIENTS WITH LOCAL RECURRENCES

There is insufficient evidence to draw conclusions about the comparative effects of PBT versus other radiation modalities among patients with recurrent tumors. We identified 2 comparative studies on recurrent tumors, one among patients with recurrent malignant brain tumors<sup>17</sup> and one among patients with recurrent liver cancer,<sup>18</sup> but both studies were rated poor quality due to their failure to account for potentially important confounding.

### KEY QUESTION 4A: EFFECTS OF TUMOR MOTION VARIABILITY

There is insufficient evidence to determine how the comparative effects of proton and photon beam therapies differ according to variation in tumor motion. Although dosimetric studies comparing methods of accounting for respiratory motion in treatment planning report that 4-dimensional computed tomography (4DCT) imaging decreases doses to normal structures compared with other multiphase,<sup>19</sup> free-breathing,<sup>20</sup> or 3-dimensional computed tomography (3DCT) imaging,<sup>21</sup> how this translates to clinical outcomes is not clear. We did not identify any studies that evaluated clinical outcomes of interest based on variability in tumor motion, imaging and planning methods used to account for respiratory motion, or quality assurance standards.

## DISCUSSION

For the cancer sites and types reviewed here, there are no reliable data from long-term randomized trials on survival, quality of life, or functional capacity of patients who underwent PBT compared with any other modality. We could not fully assess the overall net health benefit of proton beam therapy versus its comparators because comparative observational studies did not consistently report many outcomes of greatest interest. Comparative risk of secondary malignancies was only evaluated by one poor-quality retrospective cohort study of non-metastatic cancer patients treated with PBT or photon modalities for a variety of cancers.<sup>16</sup> Ability to deliver planned treatments was only reported by one small retrospective cohort study.<sup>3</sup> No studies reported functional capacity outcomes or overall severe late toxicity. Table 2 summarizes the key findings on comparative benefits and harms that are supported by low-strength evidence. Although we found comparative studies in giant cell tumors, head and neck cancer, uveal hemangiomas, and meningiomas, they provided insufficient evidence for drawing conclusions. There is insufficient evidence to draw conclusions about the comparative effects of PBT versus other radiation modalities among patients with recurrent tumors or how the comparative effects of proton and photon beam therapies differ according to variation in tumor motion.