A Systematic Review of the Cost and Cost-Effectiveness Studies of Proton Radiotherapy

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

BACKGROUND: Economic analyses of new technologies, such as proton-beam radiotherapy (PBT), are a public health priority. To date, no systematic review of the cost-effectiveness of PBT has been performed. METHODS: Systematic searches of PubMed, EMBASE, abstracts from American Society for Radiation Oncology and American Society of Clinical Oncology meetings, and the Cost-Effectiveness Analysis Registry were conducted (2000-2015) along with abstracts from the Particle Therapy Co-Operative Group of North America for both years of existence (2014-2015). Eighteen original investigations were analyzed. RESULTS: The cost-effectiveness for prostate cancer—the single most common diagnosis currently treated with PBT—was suboptimal. PBT was the most cost-effective option for several pediatric brain tumors. PBT costs for breast cancer were increased but were favorable for appropriately selected patients with left-sided cancers at high risk of cardiac toxicity and compared with brachytherapy for accelerated partial breast irradiation. For non-small cell lung cancer (NSCLC), the greatest cost-effectiveness benefits using PBT were observed for locoregionally advanced—but not early stage—tumors. PBT offered superior cost-effectiveness in selected head/neck cancer patients at higher risk of acute mucosal toxicities. Similar cost-effectiveness was observed for PBT, oncolysis, and plaque brachytherapy in patients with uveal melanoma. CONCLUSIONS: With greatly limited amounts of data, PBT offers promising cost-effectiveness for pediatric brain tumors, well-selected breast cancers, locoregionally advanced NSCLC, and high-risk head/neck cancers. Heretofore, it has not been demonstrated that PBT is cost-effective for prostate cancer or early stage NSCLC. Careful patient selection is absolutely critical to assess cost-effectiveness. Together with increasing PBT availability, clinical trial evidence, and ongoing major technological improvements, cost-effectiveness data and conclusions from this analysis could change rapidly. Cancer 2016;00:000--000. © 2016 American Cancer Society.

KEYWORDS: cost-effectiveness, health care economics, operational costs, proton radiation therapy.

The clinical application of proton-beam radiotherapy (PBT) for the treatment of various cancers is growing rapidly. Ten years ago, there were only 4 operational PBT facilities in the United States; as of the writing of this article, 16 US centers had become operational, and it is estimated that by 2020, there will be 91 operational facilities worldwide.1 The dosimetric benefits of PBT are well established—the absence of an exit dose beyond the Bragg peak spares normal tissue that otherwise would receive an exit dose if a photon beam were used2—and this reduces the whole-body integral dose. Although such data provide convincing rationale for the use of PBT, the clinical significance of these findings has not been clearly demonstrated. Currently, PBT is being used increasingly for the treatment of pediatric,3 skull base,4,5 hepatocellular,6 head/neck,7 and central nervous system tumors as well as selected breast and lung cancers, prostate cancer,8 pancreatic carcinoma, and ocular tumors.9

Because of the rising costs of cancer care, there is concern that conventional PBT centers may not be sustainable in the future.10,11 Others have argued that, because the clinical and toxicity data for PBT are incomplete compared with data for photons, it will be difficult to truly assess the cost-effectiveness of PBT.12,13 Furthermore, because PBT technology and delivery are quickly being better optimized, presumed cost variables themselves have become inaccurate, rendering previous cost comparisons obsolete.14,15

Studying the cost-effectiveness of PBT is difficult, in part because there is great reliance on clinical outcomes and toxicity data, and there is a clear dearth of such data for PBT. Cost-effectiveness (CE) studies commonly consist of 2 types of analyses: modeling studies and nonmodeling studies. Modeling studies involve probabilistic input of various future

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occurrences (e.g., outcomes and toxicities) in the natural history of hypothetical patients with newly diagnosed cancer. These probabilities are not used in nonmodeling studies (thus, these are only "cost" analyses); so, although nonmodeling studies are technically easier to perform, the reliability of data from such studies is relatively less.

Two common techniques used to execute modeling analyses involve population-based (Markov) or individual-based (Monte Carlo) modeling and simulation. In either technique, various parameters of the analyzed individuals are specified (e.g., tumor stage, age, radiation therapy [RT] dose, systemic therapy). Costs of intervention typically are calculated from insurance reimbursement figures and often are used as comparator arms (e.g., protons vs photons). After the intervention takes place in the simulated population, probabilities of adverse effects (and costs of supportive management thereof) with each RT modality, along with corresponding medical costs (e.g., from literature estimates), come into effect as time progresses through successive modeling iterations. Similarly, costs associated with acute/late toxicities, treatment complications, length of hospital stay, and disease course (all based on literature estimates) come into play probabilistically as the lifetime of the simulated individuals progresses until a finite time point or death (from cancer or any cause). Thereafter, RT modalities are compared for overall costs, taking into account not only treatment costs but also all aftereffects. Major outcomes of these studies include the quality and quantity of further survival, termed quality-adjusted life-years (QALYs), as well as the costs associated with each QALY gained from each RT modality, termed the incremental cost-effectiveness ratio (ICER). The ICER is a substitute for whether a particular intervention is labeled "cost-effective" by various parties and has historically estimated to be $50,000/QALY, also known as the "willingness-to-pay" (WTP) threshold. Sensitivity analyses are performed thereafter to measure variability in computed costs associated with changes in input parameters. In this truly contentious and rapidly evolving environment, evidence-based justification for using new treatment modalities is crucial. Herein, we provide the first known comprehensive review analyzing all available data regarding the cost-effectiveness of proton RT. Sources of information included PubMed, EMBASE, abstracts from annual meetings of the American Society for Radiation Oncology and the American Society of Clinical Oncology, the Cost-Effectiveness Analysis Registry (available at: https://research.tufts-nemc.org/cear4/, Accessed August 10, 2015), abstracts from the Particle Therapy Cooperative Group of North America for both years of its existence (2014 and 2015), those in reference lists from the major articles identified, and articles known to the authors. Searches were conducted to identify all articles addressing the cost-effectiveness and economics of proton RT with the following headings: protons, proton facility, proton radiation, cost, cost-effectiveness, value, economics, policy, monetary, reimbursement, and medical insurance. Search terms were restricted from 2000 to 2015 in efforts to include more recent data; all searches were completed by June 1, 2015. On the basis of initial searches, 563 articles/abstracts were identified (Fig. 1). Articles were reviewed by all 3 authors; the resolution of discrepancies favored adding the particular article into the analysis, and there was no standard data-abstraction form. Care was taken to ensure that inclusion criteria were sufficiently broad such that possibly pertinent publications were excluded by individual screening rather than by the initial database search. If an abstract and corresponding journal publication were from the same group, then the abstract was excluded. After duplicates were removed, each of the 555 remaining eligible items was independently screened for the criteria described below, and 497 were further excluded. Specifically, articles without specific assessments/reflectors on costs of proton RT, thus being outside the scope of this review, were excluded. In addition, editorials/commentaries were excluded. Of the 58 publications remaining, 30 were review articles; although many were cited, they were not included in the primary analysis. An additional 7 original articles and 3 abstracts prominently addressed the cost-effectiveness of PBT but did not directly assess monetary aspects; these are cited but not discussed in depth. Thus, 18 original investigations (3 abstracts and 15 articles) were identified that had sufficient focus and relevance to be incorporated.

MATERIALS AND METHODS
This systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.16 Eligibility criteria included published work in English evaluating the cost-effectiveness of proton RT. Sources of information included PubMed, EMBASE, abstracts from annual meetings of the American Society for Radiation Oncology and the American Society of Clinical Oncology, the Cost-Effectiveness Analysis Registry (available at: https://research.tufts-nemc.org/cear4/, Accessed August 10, 2015), abstracts from the Particle Therapy Co-Operative Group of North America for both years of its existence (2014 and 2015), those in reference lists from the major articles identified, and articles known to the authors. Searches were conducted to identify all articles addressing the cost-effectiveness and economics of proton RT with the following headings: protons, proton facility, proton radiation, cost, cost-effectiveness, value, economics, policy, monetary, reimbursement, and medical insurance. Search terms were restricted from 2000 to 2015 in efforts to include more recent data; all searches were completed by June 1, 2015. On the basis of initial searches, 563 articles/abstracts were identified (Fig. 1). Articles were reviewed by all 3 authors; the resolution of discrepancies favored adding the particular article into the analysis, and there was no standard data-abstraction form. Care was taken to ensure that inclusion criteria were sufficiently broad such that possibly pertinent publications were excluded by individual screening rather than by the initial database search. If an abstract and corresponding journal publication were from the same group, then the abstract was excluded. After duplicates were removed, each of the 555 remaining eligible items was independently screened for the criteria described below, and 497 were further excluded. Specifically, articles without specific assessments/reflectors on costs of proton RT, thus being outside the scope of this review, were excluded. In addition, editorials/commentaries were excluded. Of the 58 publications remaining, 30 were review articles; although many were cited, they were not included in the primary analysis. An additional 7 original articles and 3 abstracts prominently addressed the cost-effectiveness of PBT but did not directly assess monetary aspects; these are cited but not discussed in depth. Thus, 18 original investigations (3 abstracts and 15 articles) were identified that had sufficient focus and relevance to be incorporated.

RESULTS
Prostate Cancer
Prostate cancer is currently the most common cancer in the United States for which PBT is used. Peeters et al17 counterintuitively reported that PBT was slightly cheaper
than intensity-modulated RT (IMRT) in a nonmodeling study of patients with prostate cancer ($16,090 [$19,469] versus $18,160 [$21,974]). Before an early Swedish study demonstrated an increase of $7,952 ($8,731) and 0.297 QALYs gained for PBT, prostate cancer initially was studied from a CE perspective in 2007. Intermediate-risk disease was modeled using Markov methodology. Because the ability of PBT to spare dose to organs-at-risk allows for dose-escalation to the tumor, the authors assumed that the prescribed prostate dose could be safely escalated with PBT from 81 to 91 Gray (Gy) while still keeping the organ-at-risk dose under tolerance limits, which is questionable in light of dose-outcome data from weaker single-institutional data. Despite this assumption and the lack of toxicity accountability in the Markov model, PBT was not as cost effective as IMRT. In a man aged 70 years, mean costs were judged as $63,511 (€56,734) for PBT and $36,808 (€32,880) for IMRT, with 8.54 and 8.12 QALYs gained, respectively; whereas, in a man aged 60 years, the costs were $64,989 (€58,054) and $39,835 (€35,156) with 9.91 and 9.45 QALYs gained, respectively. Subset analysis, albeit with very few PBT patients, of elective PBT for low-risk cancer using Surveillance, Epidemiology, and End Results and 2010 Medicare data indicated that the average cost was $42,772 (€38,208) for PBT compared with $29,616 (€26,456) for IMRT, approximately $14,000 (€12,506) for prostatectomy, $16,883 (€15,082) for brachytherapy, and $2,766 (€2,471) for watchful waiting.

Modeling analysis comparing IMRT, stereotactic body radiotherapy (SBRT), and PBT was conducted using Markov methodology in men aged 65 years who either were eligible for RT or declined surgery, which presumably incorporated all 3 major risk groups to some degree. There were salient methodological flaws, including lack of probabilistic multivariate sensitivity analyses and assumption of a 1-time cost for toxicities without reassessment thereafter. By using Radiation Therapy Oncology Group (RTOG) toxicity criteria and systematic searches of acute/late toxicity data, payer's perspective costs were $24,873 (€22,219) and 8.11 QALYs gained for SBRT, $33,068 (€29,540) and 8.05 QALYs gained for IMRT, and $69,412 (€62,005) with 8.06 QALYs gained for PBT. However, those data failed to take into account that PBT can be used to deliver SBRT—another technique by which PBT costs could decrease.

Yu and colleagues used 2008 and 2009 Medicare reimbursement data and identified 27,647 patients who received prostate RT (553 patients received PBT and the remainder received conventionally fractionated IMRT). At a median 12-month follow-up, there were no differences in genitourinary (IMRT vs PBT: 17.5% vs 18.8%, respectively), gastrointestinal (10.2% vs 9.9%, respectively), or other (5.6% vs 4.5%, respectively) toxicities. The median Medicare reimbursement was $32,428 (€28,968) for PBT and $18,575 (€16,593) for IMRT; the authors concluded that PBT was not sufficiently cost-effective at similar toxicity levels experienced by both groups. This is important in light of other Markov data estimating a need to decrease composite toxicity by 41% for PBT to be comparably cost effective with IMRT. These data are depicted in Table 1. It is important to consider this lack of a proven CE benefit for prostate cancer given the relative ubiquity of patients receiving prostate PBT treatments throughout the United States and around the world.

Breast Cancer

A Swedish report that used Markov modeling analyzed 2 groups of patients with left-sided breast cancer who received either PBT or conventional whole-breast irradiation (WBI). Total costs were €11,248 ($13,610) for PBT and €5,001 ($6,051) for WBI, with 12.35 and 12.25 QALYs gained, respectively. This was consistent with another Markov analysis by the same researchers.
<table>
<thead>
<tr>
<th>Reference, Country, Year of Cost Analysis</th>
<th>Methodology</th>
<th>Key Assumptions of Model</th>
<th>Cancer Details</th>
<th>Therapy Comparisons</th>
<th>Total Costs</th>
<th>QALYs</th>
<th>ICER</th>
<th>Conclusions and Criticisms</th>
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</thead>
<tbody>
<tr>
<td>Lundkvist 2005, Sweden, 2002</td>
<td>Markov</td>
<td>• Adverse events were GU and GI</td>
<td>Men aged 65 y with prostate cancer undergoing PBT or 35 fractions of CRT</td>
<td>PBT vs CRT</td>
<td>$7,952 ($8,902) higher for PBT</td>
<td>0.297 paired from PBT</td>
<td>$26,800 ($30,001)/QALY</td>
<td>• PBT not cost-effective and showed increased costs at all levels</td>
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<td>• Costs based on &quot;standard treatments&quot; without managing physician costs</td>
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<td>• Yearly excess mortality rate of 2.5% because prostate cancer was used for all patients uniformly</td>
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<td>• PBT has 30% of the risk of adverse events as CRT</td>
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<td>• Assumed that PBT would be delivered at a higher target radiation dose than conventional radiation, and thereby increases the tumor control&quot; with arbitrary 20% improvement in tumor control and 20% reduction in mortality with PBT</td>
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<td>• No capital investment, labor, or operational costs included</td>
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<td>• No RT dose correlation given</td>
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<td>• Posttreatment health state includes progression, responsive (or lack thereof) to hormones</td>
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<td>• Assumed that 50 prostate patients were treated per y (same as the number of head/neck patients)</td>
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<td>• Assumed PBT could increase dose by 10 Gy to 61 Gy safely with 10% decrease in biochemical failure</td>
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<td>• Adverse event of sexual dysfunction not noted</td>
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<td>• QOL analysis incorporated into model</td>
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<td>• Sensitivity analysis: appropriate variability in costs</td>
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<td>• No capital investment, labor, or operational costs included</td>
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<td>• PBT not as cost-effective as IMRT, but could be so for younger patients</td>
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<td>Intermediate-risk patients aged either 60 y or 70 y</td>
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<td>PBT vs IMRT</td>
<td>Aged 70 y: PBT, $63,511 ($55,734) IMRT, $36,829 ($32,880)</td>
<td>9.91 and 9.45, respectively</td>
<td>Aged 70 y: $63,578 ($56,794)/QALY</td>
<td>Aged 60 y, $55,726 ($49,789)</td>
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<td>• PBT with increased costs unless its costs at $29,000 ($36,744) or below</td>
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<td>• Did not directly deal with toxicity/adverse effects in Markov model (only survival)</td>
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<td>• Authors acknowledge that essentially all conclusions rely on whether extra 10 Gy could be delivered</td>
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<td>• Utility values remained the same between IMRT and PBT (because of the dearth of data)</td>
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<td>• Arbitrary assumption that all hormone-refractory patients die in 1 y</td>
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<td>Konski 2007, USA, 2005</td>
<td>Markov</td>
<td>• Assumed facility of either 2-room photons or 3-room PBT, or PBT/carbon-ion (8 rooms) with average lifetime 30 y</td>
<td>No stratification for risk category of prostate cancer</td>
<td>PBT vs IMRT</td>
<td>PBT, $15,090 ($13,450) IMRT, $16,160 ($21,974)</td>
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<td>• Compared with proton facility costs, PBT costs increase by 3.2, and particle facility costs increase by 4.8</td>
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<td>Poots 2010, Holland, 2007</td>
<td>Cost estimates from literature</td>
<td>• Investment capital, operational, and labor costs from literature and existing business plan, including interest and replacing linacs every 10 y</td>
<td>No stratification for risk category of prostate cancer</td>
<td>PBT vs IMRT</td>
<td>PBT, $15,090 ($13,450) IMRT, $16,160 ($21,974)</td>
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<td>• Assumed linear correlation between cost/fraction and number of fractions</td>
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<td>• Lack of clarity on types of tumors treated at certain frequencies (or lack thereof)</td>
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<td>• Not a &quot;cost-effectiveness&quot; analysis, without assessment of outcomes or toxicities</td>
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<td>• Sensitivity analysis: performed for operational costs and not cancer specifically; appropriate variability in costs; treatment timing/capacity potentially most variable</td>
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<td>Alzer 2010; USA, 2010</td>
<td>Medicare and SEER data</td>
<td>Survival per Social Security Life Table; Cost per Medicare payments for inpatient/outpatient services with diagnosis as prostate cancer; no patients on hormones; no capital investment, labor, or operational costs included</td>
<td>Subset of 21 low-risk patients who received PBT</td>
<td>PBT vs IMRT vs surgery vs cryotherapy vs SBRT vs brachytherapy vs ADT</td>
<td>PBT: $42,772 ($38,208) IMRT: $23,515 ($22,659) surgery: $27,755 ($24,871) cryotherapy: $14,000 ($12,505) SBRT: $26,850 ($24,025) brachytherapy: $16,883 ($15,062) ADT: $7070 ($5318)</td>
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<td>• PBT more costly in low-risk disease • Applicability greatly limited, only to Medicare patients and with very low sample size for PBT • Only a small “cost” (not “cost-effectiveness”) analysis with essentially no accountability for outcomes and toxicities between groups, especially PBT group • Sensitivity analysis: none</td>
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<td>Yu 2013; USA, 2009-2009</td>
<td>Medicare estimates</td>
<td>Toxicities included GI, GU, and other IMRT; Matched PBT and IMRT patients for equitability; No capital investment, labor, or operational costs included</td>
<td>27,647 patients ages 66-94 y undergoing prostate radiation; 27,094 IMRT and 503 PBT</td>
<td>PBT vs IMRT</td>
<td>PBT: $52,428 ($29,068) IMRT: $18,575 ($15,503)</td>
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<td>• PBT not cost-effective • Relative increase in risk of composite toxicity needs to be 40%-60% for PBT to be cost-effective at the $100,000/QALY level • PBT group more likely to be younger, Caucasian, wealthier, home very close or very far from facility • At 12 mo, no differences in GI (IMRT, 17.5%; PBT, 18.8%); GI (IMRT, 10.2%; PBT, 9.9%); short (IMRT, 5.6%; PBT, 4.5%) toxicities • Did not examine outcomes (only toxicity) • Only applicable to Medicare patients • Only a “cost” analysis with no “cost-effectiveness” measures • Lack of accountability at specific disease states (e.g., recurrence) or RT doses • Sensitivity analysis: none</td>
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<td>Goyal 2012; USA, 2011</td>
<td>SEER and Medicare data</td>
<td>Equal disease control with PBT and IMRT; Utility values based on Medicare and literature; No capital investment, labor, or operational costs included</td>
<td>Patients aged ≥ 66 y</td>
<td>PBT vs IMRT</td>
<td>—</td>
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<td>• PBT not cost-effective • PBT needs to have 41% reduction in overall toxicity to be considered cost-effective (threshold $100,000/QALY) • Currently in abstract form without precise methodologies reported • Unclear whether QOL included • Sensitivity analysis: quality of analysis unverifiable</td>
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</table>

Abbreviations: ADT, androgen-deprivation therapy; CRT, conventional radiotherapy; GI, gastrointestinal; GU, genitourinary; Gy, Gray; ICER, incremental cost-effectiveness ratio; IMRT, intensity-modulated radiation therapy; linacs, linear accelerators; PBT, proton-beam radiotherapy; QALYs, quality-adjusted life-years; QOL, quality of life; RT, radiation therapy; RTOG, Radiation Therapy Oncology Group; SBRT, stereotactic body radiation therapy; SEER, Surveillance, Epidemiology, and End Results; WW, watchful waiting; y, years.
demonstrating an increase of €5,920 ($7,163) and 0.17 QALYs gained for PBT. However, when examining a specific population with twice the estimated risk of nonradiotherapy-related cardiac disease (owing to baseline hypertension, obesity, hypercholesterolemia, cardiac disease history, etc.), the average cost for PBT per QALY gained was nearly halved from €66,608 ($80,596) to €34,290 ($41,491), primarily because of reductions in anticipated cardiac morbidity. However, the applicability of this study is uncertain in light of the modern techniques used for cardiac dose sparing in photon-based RT (eg, dose modulation, active breathing control, deep inspiratory breath hold, and respiratory gating). In addition, the assumption of a 14% risk of severe RT pneumonitis is too high for the modern era. Therefore, similar analyses with more modern comparisons would be of great interest.

Together with dosimetric data for PBT in accelerated partial breast irradiation (APBI), an analysis used 2003 Medicare estimates to estimate costs for WBI with electron boost (50 Gy in 25 fractions plus 10 Gy in 5 fractions), PBT, and mixed photon-electron (3-field arrangement) treatment. Although the latter cost €5,300 ($4,734), PBT was only modestly more expensive ($13,200 [€11,792]) than WBI ($10,600 [€9,469]). However, that study did not account for costs secondary to potential cardiopulmonary side effects and, hence, was not strictly a “cost-effectiveness” analysis but rather only a “cost” analysis, which is solely applicable to US Medicare patients.

A more recent CE analysis for APBI, albeit without methodological details available, was presented at the Particle Therapy Co-Operative Group of North America annual meeting in 2015 and used 2014 Medicare allowable charges. Although IMRT was the most expensive treatment and linear accelerator-based, 3-field arrangement conformal RT (3DCRT) APBI was the least expensive ($6,771 [€6,049]), Medicare allowable charges for PBT APBI were $13,883 (€12,402), which were only marginally greater than those for conventional WBI ($13,149 [€11,746]). APBI using PBT also was less expensive than stratum-adjusted volume implant applicators ($14,859 [€13,265]) and was only slightly more expensive than MammoSite APBI27 ($12,245 [€10,938]) (Hologic, Inc, Marlborough, Mass). Hence, current research examining APBI versus WBI could have implications for the potential incorporation of PBT. These data are summarized in Table 2.

Non-small Cell Lung Cancer

Grutters et al analyzed patients with inoperable stage I non-small cell lung cancer (NSCLC) who received treatment with PBT, carbon-ion RT, 3DCRT, and SBRT, which cost €27,567 ($33,356), €19,215 ($23,250), €22,696 ($27,462), and €13,871 ($16,784), respectively; and the corresponding QALYs gained were 2.33, 2.67, 1.98, and 2.59, respectively. Thus, the costs per QALY gained were lowest for SBRT and carbon-ion RT, although the latter cannot be adequately modeled/compared (true US costs for this modality are unavailable). A critique of that report included large assumptions of similar utility figures for acute and chronic afteffects as well as lack of assessment beyond 5 years, both because of the dearth of available clinical data. Furthermore, the report did not segregate patients into those with central versus peripheral tumor locations and, thus, could not identify possible subsets that could benefit. However, the data are consistent with a nonmodeling study (with corresponding limitations) published by the same group in which literature-based costs were calculated. SBRT was identified as the cheapest at €3,720 ($4,501) compared with €8,150 ($9,862) for 3DCRT and €16,090 ($19,469) for PBT.

Markov analysis of concurrent chemoradiotherapy for locally advanced NSCLC using PBT, IMRT, and 3DCRT demonstrated that PBT increased the QALYs gained by 0.549 and 0.452 compared with 3DCRT and IMRT, respectively. Although such data are hypothesis-generating, future studies are required to determine the cost-effectiveness of PBT for advanced-stage lung cancers. These data are depicted in Table 3 and are further reinforced by additional recent clinical data, which need to be considered in parallel.

Head/Neck Cancers

Markov modeling in the Swedish study mentioned above for head/neck cancers illustrated that the cost of PBT was just €3,887 ($4,703) higher, with a relatively large 1.02 QALYs gained from PBT. This indicates that the cost-effectiveness of PBT for head and neck cancer could be substantial, although the lack of toxicity data for PBT in head/neck cancers at the time of publication renders its applicability questionable. A nonmodeling study calculated literature-based costs for head/neck cancers, and the estimated cost of IMRT was €11,520 ($13,939), whereas PBT was more than triple the cost at €39,610 ($47,928); however, without a toxicity analysis, definitive conclusions remain elusive.

A Markov report from Holland specifically examined patients with stage III and IV oral cavity, laryngeal, and pharyngeal cancers. Cohorts were divided into 3 groups: IMRT for all patients, intensity-modulated proton therapy (IMPT) for all patients, and mixed IMPT/IMRT with IMPT only if it was “expected to be
<table>
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<tr>
<th>Reference, Country, Year of Cost Analysis</th>
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<th>Key Assumptions of Model</th>
<th>Cancer Details</th>
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<th>QALYs</th>
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<th>Conclusions and Criticisms</th>
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<tr>
<td>Lundqvist 2005&lt;sup&gt;54&lt;/sup&gt;, Sweden, 2002</td>
<td>Markov</td>
<td>• Patients at risk of all-cause death every year • Tumor-related death in first 10 y • Mortality rates per Swedish life tables • Population risk for cardiac disease based on national registry based on age • Did not count patients who received regional lymph node irradiation and hence assumed 10y survival of 65% • No capital investment, labor, or operational costs included</td>
<td>Woman aged 55 y with left-sided breast cancer, secondary analysis of subpopulation assumed to have double the cardiac disease risk</td>
<td>PBT vs WBI</td>
<td>PBT, $11,248 ($13,860) IMRT, $6001 ($9251)</td>
<td>$66,608 ($80,596)/QALY for general patients; $64,280 ($64,491)/QALY for subpopulation</td>
<td>PBT potentially economically beneficial in select patients at high risk of cardiac toxicity • Arbitrary assumptions of 14% pneumonitis risk, and 75% of those patients taking indeterminate amount of sick leave from work (productivity loss) • Simulated younger patients aged 55 y despite average age of 63 y for Swedish breast cancer patients, but many costs/ utilities were based on national averages • Sensitivity analysis: appropriate variability in costs; variations in estimated risk of cardiac disease most related to changes in costs of PBT vs WBI</td>
<td></td>
</tr>
<tr>
<td>Lundqvist 2005&lt;sup&gt;55&lt;/sup&gt;, Sweden, 2002</td>
<td>Markov</td>
<td>• Patients at risk of all-cause death every year • Tumor-related death in first 10 y • Cardiac diseases categorized as fatal (death-inducing) or nonfatal • Base incidence of cardiac disease were age/gender-matched • No capital investment, labor, or operational costs included</td>
<td>Woman aged 55 y with left-sided breast cancer; PBT vs CRT in 25 fractions</td>
<td>PBT vs CRT</td>
<td>$5,820 ($7,163) Higher for PBT</td>
<td>0.17 gained from PBT</td>
<td>$34,200 ($30,651)/QALY</td>
<td>PBT not cost-effective • Used outdated RT techniques, including no breast boost and assumption of 14% risk of severe pneumonitis, no corresponding utility reductions • Adverse events included only cardiopulmonary toxicities and no others, including second cancers • Little data for risk of cardiac events after breast cancer RT • Sensitivity analysis: wide variability in costs; cardiac risk reduction most related to variability in costs</td>
</tr>
<tr>
<td>Taghian 2006&lt;sup&gt;56&lt;/sup&gt;, USA, 2003</td>
<td>Medicare estimates</td>
<td>• Costs (professional/technical) assumed to be for 25 fractions with 5-fraction boost without chemohormone therapy • No capital investment, labor, or operational costs included</td>
<td>Breast cancer in a general representative population, without further details</td>
<td>PBT vs WBI (30 Gy in 25 fractions + 10 Gy in 5 fractions) vs mixed photon-electrons (opposed isocenter photons, electron beams)</td>
<td>PBT, $13,200 ($11,768) WBI, $10,600 ($9,469) Mixed, $5,300 ($4,734)</td>
<td>—</td>
<td>—</td>
<td>PBT only modestly more cost-effective than conventional WBI • &quot;Cost&quot; analysis and not a &quot;cost-effectiveness&quot; analysis without comparison for outcomes, toxicities, etc • Only applicable to USA Medicare patients because of the specific source of cost data • Sensitivity analysis: none; technical components of treatment provide most sources of cost variations</td>
</tr>
<tr>
<td>Ovall 2014&lt;sup&gt;57&lt;/sup&gt;, USA, 2015</td>
<td>Medicare estimates</td>
<td>• Costs strictly based on Medicare figures without other salient parameters • No capital investment, labor, or operational costs included</td>
<td>Early stage breast cancer patients suitable for APBI</td>
<td>APBI vs WBI: APBI using SAVI, MammoSite, linear accelerator-based 3D CRT WBI using 3DFF, hypofractionation, IMRT, hypofractionated IMRT</td>
<td>PBT APBI, $13,883 ($12,402) SAVI APBI, $14,860 ($13,265) MammoSite APBI, $12,245 ($10,506) 3D CRT APBI, $5,777 ($5,049) 3D FF WBI, $13,149 ($11,746) Hypofractionated WBI, $15,070 ($13,395) IMRT APBI, $19,599 ($17,558) Hypofractionated IMRT WBI, $11,747 ($10,494)</td>
<td>—</td>
<td>—</td>
<td>Currently in abstract form without precise methodologies reported • Also used Medicare estimates without data on several other parameters as above • Sensitivity analysis: none</td>
</tr>
</tbody>
</table>

Abbreviations: 3DCRT, 3-dimensional conformal radiotherapy; 3DFF, 3-dimensional field-in-field; APBI, accelerated partial breast irradiation; CRT, conventional radiotherapy; Gy, Gray; ICER, incremental cost-effectiveness ratio; IMRT, intensity-modulated radiation therapy; NSCLC, nonsmall cell lung cancer; PBT, proton-beam radiotherapy; QALYs, quality-adjusted life-years; RT, radiation therapy; SAVI, stratum-adjusted volume implant; SBRIT, stereotactic body radiation therapy; SRS, stereotactic radiosurgery; WBI, whole breast irradiation; y, years.
<table>
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<tr>
<th>Reference, Country, Year of Cost Analysis Methodology</th>
<th>Key Assumptions of Model</th>
<th>Cancer Details</th>
<th>Therapy Comparisons</th>
<th>Total Costs (95% CI)</th>
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</thead>
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<tr>
<td>Guttens 2010&lt;sup&gt;15&lt;/sup&gt;; Holland, 2007 Markov</td>
<td>• Health states included grade 2–3 RT pneumonitis or esophagitis with corresponding quality of life • Second malignancies or cardiac events not counted • Estimates of nearly all event probabilities based on meta-analysis; • Discounting of future effects and costs performed at 1.5% and 4%, respectively (within Dutch context) • Incomplete operational costs • No capital investment or labor costs included</td>
<td>Inoperable stage I NSCLC</td>
<td>PBT vs CRT vs CRT vs SBRT</td>
<td>PBT, 22.567 ($52,213–62,385); CRT, 19.215 ($41,273–21,479); CRT, 1.38 ($0.95–2.06) BRRT, 1.29 ($0.89–2.09)</td>
<td>(15.97–30,864)</td>
<td>(11,124–16,784)</td>
<td>(15,421–91,494)</td>
</tr>
<tr>
<td>Peeters 2010&lt;sup&gt;15&lt;/sup&gt;; Holland, 2007 Cost estimates from literature</td>
<td>• Assumed facilities of either 3-room photon, 3-room PBT, or PBT/carbon ion (3 rooms) with average lifetime 30 y • Investment capital, operational, and labor costs from literature and existing business plans, including interest and replacing linacs every 10 y</td>
<td>Inoperable stage I NSCLC</td>
<td>PBT vs SBRT vs SBRT</td>
<td>PBT, 12.386 ($12,881)</td>
<td>BRRT, 0.52 ($0.48–0.57); 3DCRT, 6.150 ($8,621)</td>
<td>(4.50–5.01)</td>
<td>(5.30–5.03)</td>
</tr>
<tr>
<td>Liwers 2010&lt;sup&gt;20&lt;/sup&gt;; Belgium, 2012 Markov</td>
<td>• Defined for 10 y with disease states of controlled disease, locoregional or distant progression, and death • No capital investment, labor, or operational costs included</td>
<td>Locally advanced NSCLC, concurrent chemotherapy</td>
<td>PBT vs IMRT vs 3DCRT</td>
<td>PBT with $15,587 ($15,587–16,587) increase from 3DCRT and $14,257 ($15,587–16,587) increase from IMRT</td>
<td>PBT with 0.064 QALY increase from 3DCRT and 0.054 increase from IMRT</td>
<td>PBT with $34,396 ($34,396–$35,095)/QALY from 3DCRT and $31,541 ($35,095–$35,095)/QALY from IMRT</td>
<td>• PBT is &quot;borderline cost-effective in the Belgian health care context&quot; • Currently in abstract form without precise methodologies reported, including chemotherapy details, costs, and complications/adverse effects • Sensitivity analysis: none</td>
</tr>
</tbody>
</table>

Abbreviations: 3DCRT, 3-dimensional conformal radiation therapy; CI, confidence interval; CRT, carbon-ion radiation therapy; CRT, conventional radiotherapy; ICER, incremental cost-effectiveness ratio; IMRT, intensity-modulated radiation therapy; linacs, linear accelerators; NSCLC, nonsmall cell lung cancer; PBT, proton-beam radiotherapy; QALYs, quality-adjusted life-years; RT, radiation therapy; SBRT, stereotactic body radiation therapy; y, years.
cost-effective” (which was calculated based on the estimated 6-month risk of xerostomia). RTOG grades of normal tissue complications were specifically used to define toxicities. At 12 months, xerostomia and dysphagia rates were 22% and 18%, respectively, with IMPT; 36% and 21%, respectively, with mixed IMPT/IMRT; and 44% and 22%, respectively with IMRT. Although all 3 groups had similar gains in QALYs (IMRT, 6.52; IMPT, 6.62; mixed IMPT/IMRT, 6.56), costs were €50,989 ($61,697) for IMPT, €41,038 ($49,656) for IMRT, and €43,650 ($52,816) for mixed IMPT/IMRT. This is the strongest evidence to date suggesting that select patients with head/neck cancer may have decreased side effects during treatment with nearly the same RT costs as standard-of-care IMRT. However, the lack of clinical data continues to hamper interpretations from this study; utility scores were based on a poorly performed cross-sectional analysis, and probabilities of disease progression were also based on outdated studies. Nevertheless, despite incomplete characterization of toxicities (eg, need for gastrostomy tube), this report remains the only study to date that has demonstrated a CE benefit from PBT in head/neck cancers. Therefore, further characterization of the population of patients with head/neck cancer who can benefit most from PBT is of great clinical interest not only for future toxicity analyses but also for CE analyses. These data are depicted in Table 4.

Recent clinical data in oropharyngeal and nasopharyngeal cancers using matched-cohort (PBT vs IMRT) methodology have demonstrated an approximate 50% reduction in the use of gastrostomy feeding tubes for the PBT cohort. The potential of PBT for improving cost-effectiveness and QALYs for this event would be expected to be considerable; a phase 2 trial in oropharyngeal cancer is currently underway. This group has recently conducted a modeling study to evaluate episodic costs of care, including management of acute toxicities in head/neck cancer, and the data favorably support PBT. Therefore, if prospective studies confirm a meaningful improvement in long-term outcomes with PBT, then the cost-effectiveness of PBT may reach an acceptable threshold for more routine implementation in select patients with head and neck cancer. Although more subgroups could economically benefit most from PBT, attention also must be paid to those patients who are not likely to derive this benefit so that a more complete and balanced economic assessment can be developed.

**Pediatric Cancers**

Table 5 summarizes data for the cost-effectiveness of PBT in pediatric cancers. The aforementioned Swedish study assessed the cost-effectiveness of PBT for medulloblastoma, although the assessment was performed before dose de-escalation. By using Markov modeling, a cohort of children (aged 5 years) with medulloblastoma was assessed comparing PBT versus IMRT. Although the initial costs of PBT were estimated at €10,218 ($12,364) compared with €4,239 ($5,129) for conventional RT (2.4-fold increase), total costs of adverse effects were estimated at €4,232 ($5,121) and €33,857 ($40,967), respectively (8-fold difference in favor of PBT), yielding total costs of €14,450 ($17,484) and €38,096 ($46,096), respectively (2.6-fold increase over PBT). Analysis revealed that the greatest factors contributing to adverse event costs were IQ, hearing loss, and growth hormone deficiency. QALYs were similar in both groups, with 12.778 and 12.095 QALYs gained, respectively. The same group performed another Markov analysis in medulloblastoma illustrating that PBT dominated the cost analyses (€23,647 [$28,613] per patient saved; 0.683 QALYs gained from PBT). However, a flaw in the study limiting reliability was the generalization of using similar PBT costs per fraction for all types of cancer (regardless of treatment time and other parameters).

In a similar study of medulloblastoma using Monte Carlo methodology, children aged 5 years received PBT or IMRT. Whereas the lifetime (including morbidity management) IMRT cost was estimated at €112,790 ($100,755), the PBT cost was estimated at €80,211 ($71,652), and total QALYs gained favored the PBT-treated patients (17.37 vs 13.91, respectively). Because the study was designed to assess costs throughout a lifetime, posttreatment costs were not tracked until the children reached age 18 years. Although not consistent with the previous report in terms of QALYs (which was attributed to different actual costs of IQ loss), the report corroborated the finding that a decrease in adverse effects from PBT offered cost benefits.

Another report that specifically examined growth hormone deficiency in pediatric patients with brain tumors used Markov simulation to compare PBT and IMRT and concluded that the advantages of PBT were maintained across an entire dosing range, with greater differences in hypothalamic dose between photons and protons creating larger CE spreads. Similar results were obtained by Hirano and colleagues when examining only hearing loss because of cochlear dose reduction with PBT versus IMRT. The applicability of these data is limited because the costs for all potential major adverse effects were not assessed, including costs of ancillary treatment equipment such as anesthesia.
### TABLE 4. Summaries of Available Studies Examining Cost-Effectiveness for Head and Neck Tumors

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<tr>
<th>Reference, Country, Year of Cost Analysis</th>
<th>Methodology</th>
<th>Key Assumptions of Model</th>
<th>Cancer Details</th>
<th>Therapy Comparisons</th>
<th>Total Costs</th>
<th>QALY's</th>
<th>ICER</th>
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</table>
| Lundqvist 2005<sup>10</sup>, Sweden, 2002 | Markov      | - Mortality data for first 9 years from national registry  
- Thereafter, assumed to have normal age-specific mortality  
- Used constant utility score from quality-of-life studies  
- No capital investment, labor, or operational costs included | Patients aged 65 y with head and neck cancers treated with PBT vs 35 fractions CRT ( Including hyperfractionation) | PBT vs CRT | €9,867 ($4,703) higher for PBT | Gained 1.02 from PBT | €9,800 ($4,254)/QALY | - PBT potentially can be cost-effective, especially in light of side effects  
- Questionable use of hyperfractionation  
- Data used but not incorporated into costs  
- Calculated constant dentistry costs, unclear on relation to dose/fractionation/modality  
- No data on toxicities/quality of life after PBT in existence for use at the time, thus inherently inaccurate comparison  
- IMRT largely not used for these cancers at time of publication, limiting toxicity data  
- Sensitivity analysis: appropriate variability in costs |
| Peeters 2010<sup>7</sup>, Holland, 2007 | Cost estimates from literature | - Assumed facilities of either 2-room photon, 3-room PBT, or PBt/carbon ion (8 rooms) with average lifetime 30 y  
- Investment capital, operational, and labor costs from literature and existing business plans, including interest and replacing linacs every 10 y | No stratification for type or stage of head and neck cancer | PBT vs IMRT | PBT, €69,610 ($47,020); IMRT, €111,520 ($13,839) | - | - | - PBT not cost-effective  
- Compared with photon facility costs, PBT costs increased by 3.2 and particle facility costs increased by 4.6  
- Assumed linear correlation between cost/fraction and number of fractions  
- Lack of clarity on types of tumors treated at certain frequencies (or lack thereof)  
- Not a “cost-effectiveness” analysis, without assessment of outcomes or toxicities  
- Sensitivity analysis: performed for operational costs and not cancer specifically; appropriate variability in costs |
| Raemakers 2013<sup>5</sup>, Holland, 2010 | Markov | - Many diverse health states, depending on disease status and RTOG grade ≥2 dysphagia and/or xerostomia  
- IMRT "of deficient" (mixed) group calculated based on ICERs on case-by-case basis and probability of xerostomia linear, probability for this group was 37% vs 26% for IMRT and 45% for CRT  
- Assumed that toxicities within first 6 mo were partly reversible but irreversible thereafter  
- No capital investment, labor, or operational costs included | Stage III/IV oral cavity, laryngeal, pharyngeal | IMRT vs IMRT vs mixed | IMRT: €50,690 ($61,607)  
IMRT, €41,038 ($40,656)  
Mixed, €43,650 ($52,815) | IMRT, €6,52; MRT, €6,52; mixed, €6,56 | Mixed vs IMRT, €50,278 ($57,478)/QALY  
137,345 ($143,228)/QALY | - IMRT-only had increased costs at all examined levels, but was only compared with IMRT-only (mixed group not analyzed)  
- Xerostomia/dysphagia rates at 12 mo were 22%/16% IMRT, 35%/21% mixed, 44%/23% CRT  
- Individual calculation of cost-effectiveness and toxicity risk very important to determine optimal modality  
- Disease progression statistics based on old study with CRT  
- Utility scores for disease states based on relatively weak cross-sectional analysis  
- Vague methodology on time course and frequency of time points used to assess toxicities  
- Not all toxicities and costs assessed (eg, odynophagia requiring pain medications, gastrostomy tube, etc)  
- Sensitivity analysis: appropriate variability in costs |

**Abbreviations:** 3DCRT, 3-dimensional conformal radiation therapy; CRT, conventional radiotherapy; ICER, Incremental cost-effectiveness ratio; IMRT, intensity-modulated proton therapy; IMRT, intensity-modulated radiation therapy; linacs, linear accelerators; NSCLC, non-small cell lung cancer; PBT, proton beam radiotherapy; QALYs, quality-adjusted life-years; RTOG, Radiation Therapy Oncology Group; SBRT, stereotactic body radiation therapy; y, years.
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</table>
| Lundkvist 2005<sup>16</sup>; Sweden, 2002 | Markov      | • 25% of IQ loss attributable to RT  
• 75% of patients with hearing loss incur only 1-time cost of hearing aid  
• Capital investment costs distributed evenly among all patients treated at facility  
• Operational/labor costs not included | Children aged 5 y with medulloblastoma | PBT vs IMRT | PBT: $14,450 ($17,484); IMRT: $28,096 ($36,096) | PBT: 12,778; IMRT: 12,093 | — | • PBT superior because of less IQ loss, hearing loss, GH deficiency  
• Used same utility values for pediatric and adult life  
• Did not account for QOL secondary to IQ and hearing loss  
• Little mention of RT doses, was performed before dose de-escalation to neuraxis  
• Sensitivity analysis: appropriate variability in costs |
| Lundkvist 2005<sup>16</sup>; Sweden, 2002 | Markov      | • IQ loss of 25% attributable to RT  
• Average IQ loss, 17 points  
• Risk of hearing loss, around 13%  
• No capital investment, labor, or operational costs included | Children aged 5 y with medulloblastoma who received PBT or 25 fractions CRT | PBT vs CRT | $23,647 ($28,613) lower for PBT | Gained 0.583 from PBT | —$25,610  
(—$26,419/QALY) | • PBT superior  
• Costs per fraction of RT used for all types of cancers (including palliation)  
• Accounted for travel/lodging costs for some but not all cancer types  
• Did not account for QOL secondary to IQ and hearing loss  
• Little mention of RT doses, was performed before dose de-escalation to neuraxis  
• Sensitivity analysis: appropriate variability in costs; variations in estimated risk of adverse effects (IQ loss and GH deficiency) most related to changes in costs of PBT vs CRT |
| Malhotra-Vega 2013<sup>16</sup>; USA, 2012 | Monte Carlo | • Linear correlation between IQ reduction (average 10 points) and wage decrease (productivity)  
• No other diseases impact death other than heart disease and second cancer  
• No capital investment, labor, or operational costs included | Children aged 5 y with medulloblastoma | PBT vs IMRT | PBT: $60,211 ($71,355); IMRT: $91,790 ($100,765) | PBT: 17.37; IMRT: 13.91 | — | • PBT superior owing to decrease in adverse effects  
• Started to track posttreatment health benefits/costs at age 19 y  
• Did not take other endocrine disorders from neuraxis radiation into account  
• No pediatric QOL data  
• Sensitivity analysis: appropriate variability in costs |
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<tr>
<td>Hirano 2014&lt;sup&gt;11&lt;/sup&gt;; Japan, 2012</td>
<td>Markov</td>
<td>• Cochlear RT doses calculated based on institutional data • QOL data used for hearing loss • Used general death rates to account for other mortality • Operational costs included, but no capital investment or labor costs</td>
<td>Children aged 6 y with medulloblastoma</td>
<td>PBT vs IMRT</td>
<td>—</td>
<td>PBT, 23.44; IMRT, 22.46</td>
<td>$11,773 ($10,517)/QALY, $20,150 ($18,000)/ QALY, or $31,716 ($18,269)/QALY depending on QOL scale used</td>
<td>• Specifically assessed cochlear dose-related hearing loss • Did not include IQ, productivity/wage loss • Operational costs were simply median costs in Japanese facilities regardless of type/area of treatment • Sensitivity analysis relatively high variability; although PBT is appropriately cost-effective, widest variability based on discount rate (3% used in study with range 0%-7%)</td>
</tr>
<tr>
<td>Matlhot Vega 2016&lt;sup&gt;27&lt;/sup&gt;; USA, 2012</td>
<td>Markov</td>
<td>• Linear correlation between hypothalamic RT dose and risk of GH deficiency • GH costs included those for medications and office visits • PBT costs were $190,000 cut-of-pocket more than photons • GH deficiency does not impact death whatsoever • No capital investment, labor, or operational costs included</td>
<td>Children ages 4 and 12 y with brain tumors requiring hypothalamic RT dose</td>
<td>PBT vs IMRT</td>
<td>Various costs, depending on age and hypothalamic dose/GH deficiency</td>
<td>Various QALYs, depending on age and hypothalamic dose/GH deficiency</td>
<td>Various ICERs, depending on age and hypothalamic dose/GH deficiency</td>
<td>• PBT more superior if hypothalamic dose difference greater between IMRT and PBT • PBT is more cost-effective unless its costs are $580,000/654,761 (for a child aged 12 y) or $725,000/ 683,414 (for a child aged 4 y) higher than IMRT • Assumed same costs for GH in adulthood and childhood • Did not include IQ or productivity/wage loss • Analysis limited to GH deficiency only without accounting for survival outcomes (toxity only) • Sensitivity analysis: appropriate variability in costs</td>
</tr>
</tbody>
</table>

Abbreviations: CRT, conventional radiotherapy; GH, growth hormone; ICER, incremental cost-effectiveness ratio; IMRT, intensity-modulated radiotherapy; PBT, proton-beam radiotherapy; QALYs, quality-adjusted life-years; QOL, quality of life; RT, radiotherapy; y, years.
Emerging data suggest dosimetric superiority and/or reduced toxicities with PBT for several pediatric tumors, including retinoblastoma, brain tumors and cranio- 
aryngiomas, rhabdomyosarcoma, ependymoma, and esthesioneuroblastoma. However, to date, CE analyses for these tumors have not been performed.

Esophageal Cancer
Although data examining the efficacy and favorable dosimetry of PBT for esophageal cancers have been published/presented, there are currently no data examining cost-effectiveness in esophageal cancer. Data from a multi-institutional, retrospective cohort of neoadjuvant chemoradiotherapy followed by resection in 582 patients who received treatment with photons (n = 471) or protons (n = 111) revealed that the postoperative hospital length of stay was shorter for patients in the proton group (9 vs 12 days; P < .0001), largely attributable to the fewer cardiopulmonary and wound toxicities. Ninety-day mortality rates were also lower for the PBT group. A more detailed analysis of this data set is currently underway, including a CE analysis.

Skull Base Cancers
The previously discussed Dutch nonmodeling analysis also included patients with skull base chordomas. Conventionally fractionated stereotactic RT for chordomas cost an estimated €13,970 ($16,904) compared with €30,530 ($36,941) for PBT, and no toxicities were discussed. Because skull base tumors are currently a relatively agreed-upon indication for PBT, and because this was only a "cost" study that failed to consider decreases in toxicity with PBT, CE studies are clearly needed. These data are presented in Table 6.

Uveal Melanoma
Markov-modeled results were recently published from the Mayo Clinic comparing PBT, enucleation, and plaque brachytherapy. The authors demonstrated similar costs of $22,772 ($20,342) for enucleation, $24,894 ($22,238) for PBT, and $28,662 ($25,604) for plaque brachytherapy. The QALYs gained were nearly identical at 2.918, 2.938, and 2.994, respectively. There were wide numerical variations based on estimated observations on 1-way sensitivity analysis, and a dubious model assumption was that all recurrences necessarily led to metastases or death. The analysis did not stratify tumors for size and also did not use recent data indicating that PBT produces superior survival compared with enucleation and improved vision preservation compared with plaque brachytherapy.

In addition to established data, improved outcomes with PBT against brachytherapy in phase 3 trials are emerging, and future CE analyses correspondingly could be more favorable. The results are summarized in Table 6.

CRITIQUES AND APPLICABILITY
Primarily, it is important to mention that there is no "perfect" CE analysis. It is nearly impossible to account for every salient logistical and economic variable in modeling; examples include the initial capital investment of PBT facilities (real estate/construction), hours of operation, employee labor costs, adjustment for monetary value over time, taxes, interest rates, treatment time per patient, patient commuting costs, and machine maintenance. Moreover, very few studies use prospectively-collected data as the basis for utilities, costs, and other assumptions, and this can be a major detriment to the quality of available CE analyses. In addition, no study in this review took into account all commonly encountered, major adverse events, including secondary malignancies (although these are less important for poor-prognosis tumors). Furthermore, costs of adverse events (and worsening of pre-existing comorbidities) are substantially uncertain owing to the enormous possibilities of treatments/procedures (and physician visits) to ameliorate a given adverse effect. Hence, because no CE study can assess all of the aforementioned parameters, it is important for readers to critically evaluate the scope of included variables in each study to determine practical applicability.

There are several other factors to be discussed with regard to applicability. Although CE analyses rely heavily on established clinical data and an unavoidable assortment of assumptions, older CE reports (eg, see Lundkvist et al) often rely on studies with outdated forms of RT, techniques, and technologies. Often in CE reports, the time point of CE calculations after therapy is ambiguous; although there is often adjustment for the value of money over time (some studies do not perform this), some studies only adjust select variables for this factor. Furthermore, different health care systems in other countries can have vastly different costs of goods/services as well as WTP thresholds (eg, see Geurts et al), thus leading to potentially different economic conclusions.

It has been postulated by the Panel for Cost-Effectiveness in Health and Medicine that these conditions as well as others are necessary for high-quality and reliable CE analyses. Other discussion points set forth include the necessary inclusion of quality-of-life data (of which there are very little for PBT to date, although many
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<tr>
<td>Peeters 2010; Holland, 2007</td>
<td>• Assumed facilities of either 2-room photons, 3-room PBT, or PBT/carbon ion (3 rooms) with average lifetime 30 y • Investment capital, operational, and labor costs from literature and existing business plans, including interest and replacing linacs every 10 y</td>
<td>Cost estimates from literature</td>
<td>Skull base chordomas</td>
<td>PBT vs CSRT</td>
<td>PBT, €30,530 ($38,941); CSRT, €13,970 ($16,904)</td>
<td>—</td>
<td>—</td>
<td>• PBT not cost-effective • Compared with photon facility costs, PBT costs increase by 3.2 and particle facility costs increase by 4.8 • Assumed linear correlation between cost/fraction and number of fractions • Lack of clarity on types of tumors treated at certain frequencies (or lack thereof) • Not a “cost-effectiveness” analysis, without assessment of outcomes or toxicities • Sensitivity analysis: performed for operational costs and not cancer specifically; appropriate variability in costs; treatment timings/capacity potentially most variable</td>
</tr>
<tr>
<td>Moriarty 2015; USA, 2011</td>
<td>• Posttreatment health states of recurrence, distant metastases, and death from cancer/any cause(s) • All patients with metastasis die of disease; QOL analysis incorporated, but no data available for QOL for recurrence/metastatic disease states • No capital investment, labor, or operational costs included</td>
<td>Markov</td>
<td>10,000 patients aged 59 y with ocular melanomas</td>
<td>PBT vs plaque brachytherapy vs enucleation</td>
<td>PBT, $24,094 ($22,236); Brachytherapy, $28,662 ($25,504); Enucleation, $22,772 ($20,342)</td>
<td>PBT, 2,338; Brachytherapy, 2,304; Enucleation, 2,518</td>
<td>Compared with enucleation; brachytherapy, $77,500 ($69,230)/ QALY; PBT, $106,100 ($94,779)/ QALY</td>
<td>• Wide variations in results • Minimal differences in QALY and little cost-differences • Effects only analyzed for 5 y posttreatment • Assumed that local recurrences were not salvageable and necessarily led to metastases and/or death • Sensitivity analysis: high variability with different scenarios presenting each option as most cost-effective in various settings; used only one-way without multivariate analysis</td>
</tr>
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Abbreviations: CSRT, conventionally fractionated stereotactic radiation therapy; ICER, incremental cost-effectiveness ratio; linacs, linear accelerators; PBT, proton-beam radiotherapy; QALYs, quality-adjusted life-years; QOL, quality of life.
ongoing clinical trials are assessing this issue), because patients may not be in “perfect-quality” health for the QALYs calculated. Although the panel also recommends the use of high-quality and diverse data as the basis of study assumptions, such data clearly do not exist at this time for PBT (eg, prospective PBT publications). There are also controversies regarding whether the costs of preexisting diseases that could be impacted by RT should be added (eg, chronic obstructive pulmonary disease exacerbation in post-RT lung cancer patients). Next, although the panel recommended a 3% discount on costs to adjust for the value of money, this may not be applicable in other countries, which often adjust them differently (eg, Grutters et al29). Finally, the panel also noted that very few studies account for the costs associated with mortality, and no article in this review did so. Taken together, according to these guidelines, it is clear on multiple counts that no study included this review met the appropriate criteria set forth by the panel. Nevertheless, despite the overall low level of evidence, we suggest that a more reliable method of ascertaining the applicability of CE studies is to evaluate corroboration between results and conclusions of repeated CE or even “cost-only” studies (eg, prostate and pediatric brain cancer CE studies). In addition, we encourage readers to use this overall low quality of evidence to comprehensively assess which tumors could be good candidates for further CE study. Replicative studies are greatly encouraged to validate claims and conclusions.

DISCUSSION AND CONCLUSIONS
Greater availability of PBT has necessitated the generation of a larger body of clinical data to support its efficacy and utility. Not only are clinical data needed, economic analyses are also crucial; these largely depend on currently sparse outcomes research, although this is rapidly changing. We reviewed all known data from CE analyses of PBT; and, although the paucity of data permitted few robust conclusions, no previous summative reviews are currently in existence to guide medicoeconomic decisions.

The clinical use of PBT has been limited to date; capacity constraints have precluded the conduct of large-scale trials, which are required to evaluate the comparative effectiveness of PBT versus conventional RT modalities.61 Meanwhile, because of increased up-front investments and operational costs, initial costs of PBT are higher; these must be contextualized by recognizing that within the last couple years, smaller, single-room solutions have become available. These reduce both up-front costs and some operational costs, suggesting that going forward, the ratios generated for CE comparisons will be relatively improved for PBT compared with the historic data presented herein.

There are numerous additional limitations of the data analyzed in this review, including the need to use caution when interpreting any results based on several assumptions (including the scope of costs encompassed in each study, not limited to initial capital investment, labor, and operational/maintenance costs, which were included in only one article17) made in modeling, but also because some conclusions are from nonmodeling studies (eg, Medicare estimates) or theoretical/hypothetical studies that were not explicitly discussed in this review.62,63 Furthermore, different health care systems can have radically different estimates of costs, and applicability to health economics in other countries can be predictably limited. In addition, time points of CE measurement (as designated by authors) after treatment can have large impacts on QALY and ICER values and hence the conclusions of a particular analysis. Moreover, even newer methods of modeling cost-effectiveness are emerging64 and will necessitate cross-corroboration of data between different methods to remain confident in data, results, and conclusions.

The arbitrary WTP threshold of $50,000 ($44,665) per gained QALY has been heavily criticized as a historical remnant, and many have argued for increases, especially in light of inflation and newer economic times.65 Studies generally use thresholds from $20,000 ($17,866) to $100,000 ($89,330) per QALY gained; however, according to a review of the Tufts CE registry, although most studies still use the so-called “historical threshold,” $100,000 per QALY as well as both $50,000 and $100,000 per QALY are more frequently being used.66 Complicating matters is that WTP depends on perspective (patient/practitioner/payer): type of insurance company, specific clinical circumstance of the patient, “clinical aggressiveness” of the managing physician, and location of the particular market (competing facilities/referral patterns). There are several other factors that influence this parameter, including the country/society/economic system, noteworthy socioeconomic events therein, and several other factors, even involving the global economy. Although having similar values aids in study standardization, this is misleading secondary to several other nonstandardized variables between studies. Therefore, by integrating and prioritizing these variables, perhaps it is most appropriate to create several different WTP thresholds that can—and should—fluctuate with time.

Available evidence suggests that PBT for unselected populations with early-stage lung cancer and prostate cancer is economically suboptimal. It is crucial to recognize
that historical PBT approaches for prostate cancer have used opposed lateral fields, which do not spare the anterior rectal wall; however, recent developments, such as the availability of rectal gel spacers and the ability to perform in vivo Bragg-peak range verification, would allow the use of anterior or anterior-oblique PBT beam arrangements, which would be substantially superior from a dosimetric perspective and could improve the CE profile of PBT, albeit to an unknown degree.\textsuperscript{67,68} Conversely, PBT is likely the economic standard of care for a significant proportion of pediatric patients, although CE evidence only exists for pediatric brain tumors. Many other cancers with the potential for significant radiation-induced toxicities, such as head/neck cancers, esophageal cancer, advanced NSCLC, brain tumors, skull base neoplasms, ocular cancers, and certain left-sided breast cancers as well as certain soft tissue sarcomas are all potential candidates for cost-effective PBT. Data for these indications and also for reirradiation in multiple anatomic sites are rapidly emerging and will likely result in radical revision of many current conclusions.

The ability of PBT to reduce cardiopulmonary morbidity cannot be overlooked. Darby et al\textsuperscript{69} demonstrated a linear correlation between mean heart dose and cardiac morbidity, with the greatest risk among patients who have baseline cardiac risk factors. Therefore, the ability of PBT to effectively reduce cardiac doses in patients with left-sided breast cancer,\textsuperscript{70} especially if utilizing techniques such as regional nodal irradiation,\textsuperscript{71} may lead to decreased cardiac morbidity and mortality, although increased experience and longer follow-up times with PBT are necessary for corroboration. This suggests that PBT can yield improved cost-effectiveness if certain high-risk subsets of breast cancer patients are selected.

Similarly, data are needed for patients with advanced NSCLC in whom cardiopulmonary tolerance doses have a major impact on outcome, including survival, and they represent a patient population in which the potential for toxicity-related medical costs also increase. The RTOG 0617 trial demonstrated inferior survival in the higher dose arm that was linked to probable cardiopulmonary toxicities associated with higher dose.\textsuperscript{72} Multivariate analyses of the factors associated with overall survival between standard-dose and high-dose radiation have demonstrated that lower heart V5 is associated with improved overall survival. More recent prospective data have demonstrated that heart doses with PBT are substantially lower compared with IMRT doses. The heart V5 value for 103 patients on an ongoing prospective trial revealed mean ± standard deviation values for heart V5 of 14.6% ± 13.6% with PBT versus 44.3% ± 33.3% with IMRT (P < .0001).\textsuperscript{73} Liao and colleagues previously investigated whether the heart dose affected overall survival in patients with NSCLC by evaluating the relationship between mean heart dose and overall survival in a 532-patient retrospective cohort.\textsuperscript{74} Mean heart doses ranged from 0 to 55.4 Gy, and the median was 22.3 Gy for 3DCRT, 15.1 Gy for IMRT, and 6.5 Gy for PBT. On multivariate analysis, mean heart doses above the 25th percentile were significantly associated with an increased risk of death. To further evaluate the impact of PBT, these investigators also analyzed the mean heart dose in 103 patients who were randomized to a 2-institution PBT versus RT trial and observed that mean heart doses were consistently lower for PBT.\textsuperscript{75} These important data have now been used to develop the randomized RTOG 1308 trial testing RT versus PBT, and the clear dosimetric advantages with putative cardiopulmonary toxicity reductions will likely have a major impact on future CE analyses for NSCLC.

Dramatic technological innovations to optimize PBT are occurring at this point, including pencil-beam scanning, intensity-modulated proton therapy, image guidance, hypofractionation,\textsuperscript{76} and compact units; these will likely further decrease treatment costs.\textsuperscript{77} The use of cyclotrons versus synchrotrons also has been related to cost-effectiveness\textsuperscript{78} along with postulation that, one day, 4-dimensional proton treatment may be the standard of care for some tumors.\textsuperscript{79} Recent advances in optimizing treatment times,\textsuperscript{80} proton units,\textsuperscript{81} beam energies,\textsuperscript{82} and field design\textsuperscript{83} can improve cost-effectiveness, as can achieving a balance of PBT-indicated cases and "nonessential" cases.\textsuperscript{84} None of these factors were taken into account by any study in this review. However, partially because of these innovations, data indicate that over the next decade, treatment costs could drop by a very substantial 20\%.\textsuperscript{85} Moreover, PBT reimbursements already have decreased compared with past levels.\textsuperscript{86} Finally, because clinical and toxicity data are currently accruing and maturing for PBT, a clearer picture of efficacy, and thus economic balance, will likely be available in the future, indicating that the current review is likely to require revision once further data become available.

In summary, it is highly unlikely that PBT will be the most economic option for all cancers or even for all patients with a given type of cancer. Rather, the major goal for ongoing and future research will be to identify the subpopulation(s) of each cancer type for whom PBT is most cost effective. It is also very important to consider that CE analyses are inherently depend greatly on existing (largely retrospective) literature, study methodology, and a multitude of variables that cannot all be adequately captured on analysis. Hence, we encourage reporting of CE
data from a variety of sources to be able to corroborate the findings in this review.

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