Cost-comparativeness of proton versus photon therapy

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Abstract: Proton beam radiotherapy (PBT) offers great promise in the treatment of a wide variety of cancers owing to the sharp drop-off in radiation dose at a defined point, known as the Bragg peak, beyond which there is no appreciable dose. However, it is also well-understood that PBT is associated with large economic costs, including both capital investment and operating costs. From a medical as well as societal perspective, therefore, it is important to be aware of the economic implications of new technologies such as PBT, and to evaluate the cost effectiveness based on different clinical and treatment scenarios. This review examines PBT from a health economics perspective, evaluating both the design and results of cost-effectiveness (CE) studies that have been performed previously. We further examine several salient variables that can affect CE of PBT, including patient, tumor, treatment, and logistical factors. We discuss the implication of technological advances on PBT delivery, and its impact on overall healthcare delivery costs. Additionally, we evaluate the status of economic analyses for PBT and discuss the role of ongoing and future CE studies in better defining the economic role of PBT as part of modern cancer therapy.

Keywords: Cost-effectiveness (CE); economics; proton therapy; radiotherapy (RT)

Background and importance

The clinical application of proton beam radiotherapy (PBT) in the treatment of various cancers is growing rapidly. Ten years ago, there were only four operational PBT facilities in the United States; as of the writing of this article, 16 centers are operational and several dozen additional facilities are in development. There will be an estimated 91 operational facilities worldwide by 2020 (1). Though PBT is not a new technology, having been used clinically for selected tumor types for approximately six decades, there has been increasing clinical interest and investigation for using proton therapy for a number of tumor types based on early

successes demonstrating favorable toxicity profiles (2).

The physical interactions of heavy charged particles such as protons dictate that the maximal radiation dose deposition (termed the Bragg peak) occurs near the end of the beam path. This leads to minimal to no dose absorbed by normal tissues distal to the target of interest. Other consequences also include utilization of a limited number of treatment fields, which further reduces the whole-body integral radiation dose. Additionally, this offers potential to escalate tumor dose that could improve local control and clinical outcomes while maintaining safe doses to dose-limiting organs compared with photon therapy. As a result, dosimetric benefits of PBT have consistently been established (3). Although such

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data provide convincing rationale for PBT utilization, the clinical significance of these findings has not been clearly demonstrated for most cancers. Currently, PBT has been studied for a variety of cancers including pediatric (4), skull base (5), hepatocellular (6), head/neck (7,8), central nervous system (9), breast (10), lung (11), prostate (12), testicular (13), and ocular tumors (14).

Due to issues regarding continued rising costs of cancer care, there is growing concern that conventional PBT centers may not be sustainable in the future. This is currently associated with relatively high reimbursements to offset high capital investment, quality assurance, and operational costs (15,16). Others have argued that due to incomplete clinical and toxicity data for PBT versus photon-based radiotherapy (RT), current justifications for using PBT in light of its increased relative costs over photon RT and PBT's cost-effectiveness (CE) are presently difficult to truly assess (17,18). Furthermore, because PBT technology and delivery have undergone a significant revolution over the past several years, existing presumed cost-variables (mostly based on passively scattered therapy and other older proton technologies) may be dated and inaccurate, rendering previous cost comparisons obsolete (19,20).

In this controversial environment, evidence-based rationale for using new treatment modalities is essential, especially in order to balance absolute costs with the potential to reduce radiation-induced morbidities and/or mortalities. In this review, we will examine economic CE analyses of PBT and discuss several factors that could shape further analyses.

Methodology of CE studies

Prior to the use of modern CE and simulation models, cost estimates for proton therapy were performed based on epidemiologic studies of cancer incidence and other factors, often as part of a joint committee analysis as were performed for several tumor types by Swedish investigators in 2005 (21). Though these initial estimates were based on only a limited number of clinical factors, multiple similar assessments corroborated that in various European countries, 10–15% of all irradiated patients could potentially be eligible for PBT (22,23). These early studies have served as the basis for modeling studies testing patient recruitment for PBT (24).

The goal of CE studies is to tabulate all known costs associated with an intervention (e.g., PBT vs. photons) and compare them with all known benefits associated with that

intervention (25). It follows, then, that the accuracy of a CE study in estimating cost and CE estimates relates to (I) the breadth of potential costs that can be encompassed; and (II) the breadth of published data describing toxicities of both interventions. Logically, it is very difficult from a methodological perspective to account for and assess every single cost associated with an intervention, as there are myriad direct and indirect costs of both PBT and photon RT, associated not only with construction of RT facilities, but also all aspects of operation (e.g., personnel costs, electricity and maintenance, beam delivery time, number of patients treated, etc.). Similarly, it is potentially even more difficult to ascertain and quantify all potential treatment toxicities and the associated costs of those toxicities, especially in light of the relatively sparse high-quality clinical data currently available for PBT. Taken together, a critical caveat to firstly note is that CE analyses cannot perfectly encompass all potential variables, and hence all contain inaccuracies to some degree. Furthermore, a significant number of CE analyses have been performed in Europe, where healthcare systems and cost estimates may be vastly different from those in the United States and elsewhere. As a result, the reader is advised to interpret any study with caution.

Many CE studies use two or more hypothetical groups of patients receiving the treatment modalities of interest (e.g., PBT and conventional RT) and simulate lifetime events in individual patients (based on published probabilities) until death or an appropriate time period. First, costs of administering various RT modalities are tabulated (e.g., capital investment and operational costs). Next, relevant clinical parameters are incorporated (rates of which are based on literature estimates), including the chance of adverse events from RT modalities, chance and cause of death, and various outcome measures; the costs of these variables are then calculated. Common examples include the cost of a procedure, supportive medication, and/or hospital stay related to RT-induced toxicities. Outcomes for the cohorts can be assessed using overall cost (all possible costs saved from morbidity and/or mortality reduction vs. all possible expenses), or the total life-years gained or lost, scaled for quality of life, also known as quality-adjusted life years (QALYs) (26). All modeling studies have limitations, including probabilistic assumptions on several of the aforementioned parameters, although usually they are (and should be) cross-checked against existing literature; results therefore must always be interpreted with caution.

Markov modeling, a method to execute cost tabulations

and comparisons, appears most frequently in the CE literature (27). There are also other methods, such as Monte Carlo modeling, which use individual patient simulations (based on known probability distributions) rather than modeling at the cohort level as in Markov models. Other common sources of economic investigations include retrospective analyses of Medicare reimbursements or Surveillance, Epidemiology, and End Results (SEER) data, which represent large population-based datasets but are also prone to limitations, such as their retrospective nature, the time period of cost data, geographic variations in reimbursements, and a relative lack of accountability of adverse effects.

Factors affecting CE

To better understand the theoretical basis of CE, we categorize the associative and/or causative factors, and independently examine CE from the patient, tumor, treatment, and economic/logistical perspectives.

Patients that are most likely to be associated with greater CE for PBT are the patients that (I) experience relatively high toxicity, potentially caused by (II) close anatomical relationships with various dose-limiting organs; and (III) those patients that live long enough after RT to be able to manifest effects of RT toxicity. Though PBT can be useful for reirradiation cases, this group can possibly be a fourth category depending on anatomical location and life expectancy. Additionally, an understudied aspect of patient characteristics includes existing comorbidities (e.g., preexisting diseases influencing toxicity risks and events). If subgroups of patients can be selected that are most likely to benefit from normal tissue dose-sparing with PBT to organs in which substantial pathology already exists, then there may be a greater likelihood of "actualizing the dosimetric potential" of PBT and swinging CE closer towards PBT.

Similarly, tumor characteristics may also predict which patients are most likely to benefit from PBT treatment in the economic realm. Tumors with poor prognosis in general may have more limited CE with PBT as patients may not live long enough to enjoy potentially improved QALYs. This must be considered in the context of the severity of potential side effects for a given disease. For instance, PBT in a poor prognostic setting such as locally advanced lung cancer could still prove to be cost-effective, since there is an expected mortality rate from treatment-induced pneumonitis and hospitalization rate from esophagitis that happens within 6 months of therapy, which may still impact patient quality-of-life or survival despite the overall poor prognosis of the cancer. Tumor size, location, and histopathology also play a role. Tumors that are very close to dose-limiting organs-at-risk may be economically more favorable for PBT, depending on whether or not dosimetric gains can translate into clinical toxicity reductions. Tumors that are biologically thought to be relatively radioresistant [e.g., melanoma (28)] may or may not be similarly difficult to control with PBT (dose-escalation for these tumors needs further characterization). Lastly, tumor size can be associated with worse prognosis (e.g., T-stage) or closer to potential dose-limiting structures, which may make PBT less or more cost-effective, respectively.

Treatment volumes and fields are also important for PBT. Other potential areas of clinical disease in addition to the gross tumor, whether prophylactic/elective or therapeutic, can also influence potential toxicities. For example, increasing use of regional nodal irradiation in breast cancer may be associated with increased cardiac toxicity due to treatment of internal mammary nodes, which can increase incidence of cardiac events (29-32). Quantification of such adverse events is important for future PBT studies and hence CE. Utilization of hypofractionated treatments is efficacious and cost-effective for many cancers, and the corresponding decrease in cost can be applied to, and are potentially more significant for, PBT as well; technical challenges and existing lack of data for PBT-based hypofractionation in various cancers, however, will continue to hamper CE analyses in the short-term. RT dose will also impact treatment cost and CE analyses, and current research in photons examining de-escalated RT regimens—for instance in p16-positive head and neck cancers—will be particularly interesting to monitor from the proton perspective as well.

Lastly, the nature of insurance company and hospital interactions greatly influences economic cost. Type of insurance, type of treatment center (hospital-based versus free-standing), referral patterns, as well as location (geographic region of the proton center & geographical clustering of proton centers), undoubtedly play a role in reimbursement for PBT treatments and should not be overlooked. For instance, various insurance companies are willing to reimburse for emerging technologies to differing amounts, based on the quality and quantity of existing data. Additionally, if PBT is covered by a particular insurance, the presence of "competing" PBT facilities in proximity could result in potential decrease in costs, per fundamental economics. Availability of treatment machines, proportion

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of each type of cancer treated, operational costs, and treatment duration (e.g., number of fields) also can play large roles in reimbursements. The Centers for Medicare and Medicaid Services have also previously decreased reimbursements for PBT (33), so CE analyses will need to be constantly revised in accordance with newer economic times and with greater clinical data available.

Summation of current data—pediatric cancers

Although pediatric cancers represent a small fraction (10–13%) of patients treated with PBT in the US (34), the greatest number of reports documenting clinical reductions in toxicities (e.g., growth disturbances, hearing loss, intelligence quotient and learning disabilities) exists for these cancers. An early report from Sweden paved the way for current thought on CE for PBT in pediatric cancers (35). Using Markov modeling, 5-year-old children with medulloblastoma were simulated to receive PBT or intensity-modulated radiotherapy (IMRT). Initial costs of PBT were estimated as €10,218 ($12,364) versus €4,239 ($5,129) for conventional radiation (2.4-fold increase); however, total costs of all 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 difference in favor of PBT). The greatest factors contributing to adverse event costs were IQ decline, hearing loss, and growth hormone deficiency. This group performed another Markov analysis in medulloblastoma (36) that demonstrated PBT was fully cost-effective compared with photon therapy [€23,647 ($28,613)/patient saved; 0.683 QALYs gained from PBT].

Similar results in medulloblastoma have been reported using Monte Carlo modeling (37). While lifetime (including morbidity management) IMRT cost was estimated at $112,790, PBT costs at $80,211 were significantly lower. This report also corroborated that a decrease in adverse effects drove the cost benefits of PBT.

Another study, using Markov simulation, specifically examined growth hormone deficiency in post-PBT or IMRT treated pediatric brain tumor patients (38). The authors concluded that PBT's advantages are maintained across an entire dose-range; greater differences in hypothalamic dose between photons and protons created larger CE spreads. Similar results were obtained by Hirano and colleagues when specifically examining hearing loss due to cochlear dose reduction with PBT versus IMRT (39).

Taken together, utilizing a variety of economic factors and simulation methodologies, data suggest that PBT is comparable, if not more, cost-effective for pediatric cancers, owing to substantial decreases in long-term toxicities for pediatric patients who have relatively high life expectancies. However, there remain several caveats for these studies: the data are limited to just a few cancers, and long-term follow-up for PBT in pediatric cancers to date is limited in the literature.

Estimating CE in the pediatric population is not without challenges. Despite the lack of PBT data with long-term follow-up, many pediatric CE studies follow patients for a large portion of adult life, and estimating costs of lost future wages (in adulthood) in the post-RT population is associated with large uncertainties. Similar challenges exist in estimating parents' lost wages during and after treatment. These issues are largely unique to pediatric patients, and the extent to which existing studies account for many of these factors can vary substantially. Unfortunately, however, there is no fixed modeling factor that can take potential lost wages into account uniformly; current studies use a wide variety of estimates, and it may be safe to perform a mathematical average of estimates utilized by these studies.

Summation of current data—adult cancers

PBT for the routine treatment of breast cancer, across all patient groups, has not been shown to be cost-effective, with increases in total costs of approximately €6,000 with minimal corresponding increase in QALYs (36,40). Specific populations may benefit, however, such as patients with left-sided tumors or those with internal mammary nodal metastases who may be more susceptible to developing late cardiac toxicities from therapy. Such benefits, however, may be difficult to precisely quantify and are subject to inherent uncertainties in modeling RT-induced cardiac toxicities. When examining a population estimated to have twice the risk of nonradiotherapy-related cardiac disease (owing to baseline hypertension, obesity, hypercholesterolemia, cardiac disease history, etc.), the average cost for PBT per additional QALY was nearly halved from €66,608 ($80,596) to €34,290 ($41,491), largely due to a reduction in anticipated cardiac morbidity (40). A more recent cost analysis (41) for accelerated partial breast irradiation (APBI) showed that IMRT was the most expensive, whereas linac-based three-dimensional conformal radiotherapy (3DCRT) APBI was the least. Furthermore, Medicare charges for PBT APBI were $13,883, only marginally greater than

conventional WBI ($13,149). APBI using PBT was also less expensive than strut-adjusted volume implant applicators ($14,859) and only slightly more than balloon-based high dose rate brachytherapy ($12,245). Ongoing research examining APBI versus WBI could have implications for incorporation of PBT. A major limitation of this study (41), however, was that it was a primary "cost" analysis and not a "CE" analysis, and hence it did not take toxicities into account.

PBT CE data in non-small cell lung cancer (NSCLC) is limited. Whereas stereotactic body radiotherapy (SBRT) is most cost-effective for early-stage (inoperable) stage I NSCLC (42), Markov analysis of advanced NSCLC requiring concurrent chemoradiotherapy showed that PBT increases QALYs by 0.549 and 0.452 compared to 3DCRT and IMRT, respectively (43). Though data are limited, they suggest that advanced-stage lung cancers may be more cost-effectively treated with PBT as compared to early-stage cancers, but whether PBT is the most cost-effective option requires additional research. A national clinical trial of PBT for locally advanced NSCLC (RTOG 1308) is underway and will address the CE question as a secondary analysis.

Markov simulation in a study (36) for head and neck cancers illustrated the cost of PBT to be marginally higher [€3,811 ($4,141)/QALY], with a considerably large 1.02 QALYs gained from PBT. Another report from the Netherlands (44) specifically examined patients with stage III–IV head and neck cancers. In addition to comparing IMRT against intensity-modulated proton therapy (IMPT), a third population consisted of mixed IMPT/IMRT—for which IMPT was used only if it was "expected to be cost-effective" (calculated based on estimated 6-month-risk of xerostomia). At 12 months, xerostomia and dysphagia rates were 22% and 18%, respectively, with IMPT; 36% and 21% with mixed IMPT/IMRT; and 44% and 23% with IMRT. Though all three groups had similar QALYs, costs were as follows: €50,989 ($61,697) for IMPT, €41,038 ($49,656) for IMRT, and €43,650 ($52,816) for mixed. Therefore, further characterizing the population of head and neck cancer patients receiving greatest benefit from PBT is of great interest not only for future toxicity analyses, but also for CE analyses.

CE of PBT over IMRT for prostate cancer has not been proven to date. The previously discussed Swedish study (36) showed an increase in costs for PBT without corresponding increases in QALYs. Konski *et al.* (45) modeled intermediate-risk prostate cancer from a CE perspective, and when accounting for a 10 Gy dose-

escalation afforded by PBT (91.8 CGE) over IMRT (81 Gy), certainly a questionable assumption owing to a lack of concrete associated data, showed that PBT was not as cost-effective as IMRT. When comparing age groups, however, CE for treated 60-year-old men was superior to their 70-year-old counterparts, indicating that life expectancy is important in determining PBT's CE for tumors with relatively good prognosis. Given the conflicting reports to date, clinical improvements in toxicities and quality of life need to be demonstrated in ongoing clinical trials to determine whether PBT for prostate cancer is truly cost effective (46,47). With the increasing use of hypofractionated RT for prostate cancer, Parthan *et al.* reported that SBRT for prostate cancer was the most cost-effective modality (48). However, this report did not take into account that PBT can be used to deliver SBRT, and if proven efficacious, would signify a decrease in PBT costs owing to fewer delivered treatments.

As discussed earlier, PBT has been used to treat uveal melanomas since the late 1960s (14). A recently published CE study (49) showed similar costs for PBT, enucleation, and plaque brachytherapy with nearly identical QALYs. A criticism of the analysis was that tumors were not stratified for size. Moreover, the study did not use high-fidelity quality-of-life data, because enucleation is known to be associated with poorer quality of life, and the also study failed to take into account recent phase III trials showing improved outcomes with PBT versus brachytherapy (50,51). Overall, this highlights the great dependence of CE analyses on available prospective trials, and necessitates additional analyses in the future as additional data emerge.

Impact of technical advances

There are several technical factors that complicate comparison of proton and photon therapies. Protons often require larger margins, primarily to account for range uncertainties. This produces dose distributions that are less conformal, with larger high- and intermediate-dose volumes compared with the same plans generated for photons (52). In turn, this can result increased toxicity in organs-at-risk adjacent to the tumor. This can be ameliorated through the use of beam-specific planning target volumes (PTV) and robust planning (53-58). Additionally, several groups are investigating technologies for *in-vivo* range verification (59-64). While this may facilitate margin reduction in PBT, it will also likely increase capital costs associated with additional instrumentation. PBT is further challenged

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by the lack of modern image guidance. While cone beam CT has been available on conventional linear accelerators for over a decade, only two proton treatment rooms in the world to date have equivalent volumetric imaging capabilities. Without volumetric imaging, larger margins are needed to account for setup uncertainties.

While the benefits of IMPT have been demonstrated in numerous planning studies (11,65-67), clinical implementation is limited by several factors. Because proton dose deposition is highly dependent on range, small setup differences or changes in anatomy can have a profound impact on target and OAR dose and thus tumor control and complications. Dosimetric errors are exacerbated with multifield optimization (MFO), in which each beam may deliver a highly heterogeneous dose (68,69). While these challenges can be mitigated in part through the use of regular verification imaging and adaptive replanning as needed, such an approach requires added resources in terms of imaging equipment and planning time. Similarly, motion management remains an impediment to the use of pencil beam scanning (PBS) in general, and IMPT specifically, in those sites subject to respiratory motion (58,70). Fortunately, the interplay effect, dose errors due to the potential synchronization of tumor motion with PBS delivery, is effectively mitigated through fractionation and/ or repainting (71).

To reach the full clinical potential of PBT, technology must be on an even footing and requires a comparison of the best-in-class proton technology with that of conventional RT. For PBT, this means decreasing PTV margins by reducing range uncertainties, daily use of volumetric imaging for patient setup and assessment of anatomical changes, regular adaptive replanning to account for such changes and robust methodologies for management of respiratory motion.

Proton technology is evolving at a rapid pace, with advances in accelerators—next generation compact synchrotrons, synchrocyclotrons and gantry-mounted superconducting cyclotrons—compact gantries, and volumetric image guidance. In addition, at least four vendors now offer single room solutions. The cost of 4- and 5-room centers will remain a significant disincentive to proton utilization. Indeed, financial challenges have emerged at several existing centers throughout the United States and recently resulted, in part, in the closure of one multi-room facility as well as a halt of construction at two others. Johnstone *et al.* have suggested that the workloads required to sustain multi-room proton centers is compatible

only with simple (i.e., one or two fields) treatments (72); that is, multi-room centers and complex treatments are mutually exclusive from a financial point of view. Until this paradox is resolved, it will be challenging to generate CE data that conclusively demonstrates the value of proton therapy. In contrast, less expensive single-room systems with next generation delivery and imaging capabilities, and which may have significantly lower operating costs, may radically change the cost effectiveness picture.

Conclusions and future outlook

Greater availability of PBT has caused the generation of a larger body of clinical data to support its utility and efficacy. In addition to clinical data and randomized trials, economic analyses are also crucial, because existing cost effective analyses are largely based on currently-sparse outcomes research.

There are several key points to take from this discussion. First, CE analyses are heavily dependent on published literature of clinical efficacy and toxicity; the lack thereof for PBT (especially prospective data) should rightfully lead to caution when interpreting CE data. Secondly, it is important to recognize that PBT likely will not be the most economical option uniformly for all cancers of a certain type/subsite; rather, subgroups of patients (as stratified for patient, treatment, and tumor characteristics, among others) for various cancers will need to be delineated as those most likely to "economically benefit" from PBT. Key goals of future CE studies should be to identify those subgroups [e.g., as done by Ramaekers *et al.* (44) and Ovalle *et al.* (41)] that gain the most QALYs with PBT treatment. Because this term encompasses both quality-of-life and life expectancy, both will be important for assessment in future trials. Currently, secondary analyses of cost/CE are planned for several national and cooperative group clinical trials for cancers in the brain (73), head/neck (74), breast (75), and lung (76). Like the clinical outcomes, the results of these CE analyses are highly anticipated. Lastly, it cannot be understated that time is a large factor in CE. Indeed, owing to greater preliminary data and both retrospective/ prospective experience, technological innovations, and even newer methods to model CE, some have opined that over the next decade, treatment costs could drop by a very substantial 20% (77).

Economic analyses for oncology and medical economics in general, are quite dynamic (78). Medical economics seeks to provide evidence for the utilization of up-and-

coming technologies so as to provide economic sustainability. In a time of healthcare reform in the United States, it is imperative to provide evidence-based justification of relatively untested and new technologies such as PBT (79,80). In the presence of relatively low levels of CE evidence to support PBT for the vast majority of cancers, corresponding caveats must be understood in the context of relatively poor quality CE data that exists. Because there is no single accepted RT modality to treat all cancers, clinicians must be cognizant to balance treatment costs with potential for improvements in morbidities and adverse events.

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Footnote

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