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Economic Evaluation

Cost-Effectiveness of Proton Versus Photon Therapy in Pediatric Medulloblastoma Treatment: A Patient Volume–Based Analysis

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ABSTRACT

Background: Proton radiation therapy offers advantages over photon therapy, assisting with severe side effect avoidance. Pediatric patients with medulloblastoma have demonstrated benefit from this technology in recently published cohort studies. **Objectives:** To compare the costs and benefits between proton and photon therapy in treating pediatric medulloblastoma. **Methods:** The model was built with a lifetime horizon from the Brazilian health system perspective using a 3% discount rate. A microsimulation model was developed after a literature search, comparing scenarios of equipment life span and number of patients treated per year (50, 100, and 150 patients with 10, 25, and 20 years of equipment life span). The baseline parameters were 50 patients treated annually and 20 years of equipment life span. **Results:** The quality-adjusted life-year gain was 2.71, and the average incremental cost-effectiveness ratio was $34 590.54 per quality-adjusted life-year. For the willingness-to-pay threshold of 1 gross domestic product per capita, it was observed that the incorporation of the technology would be cost-effective if more than 150 patients were treated per year. The weight of the equipment life span and other variables was limited when it varied in the sensitivity analysis, without significant changes to the model results. **Conclusions:** Proton therapy is not cost-effective for pediatric medulloblastoma treatment from the Brazilian health system perspective. The investment is not worth when considering the number of potential patients and the country dimensions.

Keywords: cost-effectiveness, health technology assessment, pediatric medulloblastoma, proton therapy, treatment demand

Introduction

Medulloblastoma is the most common histological type of central nervous system tumor in children,[1] and its extensive irradiation area with this high dose volume tends to produce a range of effects that makes it a potentially eligible malignancy for proton beam therapy use.[2] Improved dose distribution and less irradiation of healthy tissues make proton beam therapy more advantageous when compared with photon therapy. The results are fewer side effects related to unnecessary tissue irradiation, allowing the use of higher doses and improving clinical results.[3-5] Furthermore, photon therapy delivers a high radiation dose in healthy tissues, generating many lifelong sequelae and compromising patient quality of life, especially for children.[3]

A recent report[6] with 77 patients and a 7-year follow-up demonstrated a lower incidence of neuroendocrine side effects with the use of proton beam therapy compared with photon therapy. Other reports[7] have shown no difference in mortality and tumor recurrence between those technologies. Clinical evidence of other side effects through a direct comparison of both

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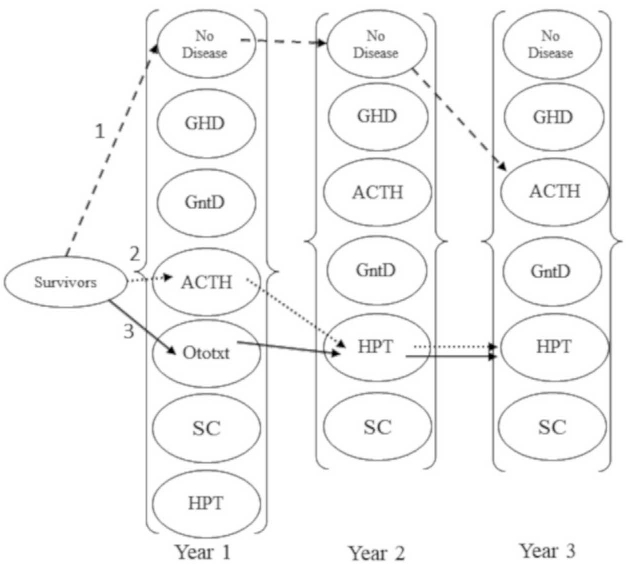

Fig. 1 – Microsimulation scheme representing patient side effect possibilities. The scheme illustrates all possible side effects (health states) that the patient who survived medulloblastoma can have throughout the model. The patient may develop 1 health state change each year. For example, the patient can develop ACTH deficiency in year 1, may develop HPT combined with the first in year 2, and may continue to have these 2 conditions in year 3. The 3 arrow types are examples of 3 possible patient possibilities. Death is a possibility in all states. ACTH indicates adrenocorticotrophic hormone; GHD, growth hormone deficiency; GntD, gonadotropin deficiency; HPT, hypothyroidism; Ototxt, ototoxicity; SC, secondary cancer. Adapted from Vega et al.[31]

Table 1 – Model parameters.

Variable	Values	Source
Photon therapy costs	$12 450 121.63	Brazilian National Cancer Institute[42-45]
Proton therapy costs	$126 738.011	Emergency Care Research Institute[23]
Diagnostic and medical visits ($/y)		
Neuroendocrine effects	16.09	Ministerio da Saúde[46]
Hearing loss	212.03 (1 y); 32f47.10 (further)	Ministerio da Saúde[46]
Medications ($/y)		
Growth hormone (0.05 mg/kg)	20.76/mg	Ministerio da Saúde[46,47]
Hypothyroidism	9.04 (to 12 y old); 59.09 (<12 y old)	Ministerio da Saúde[46,47]
Osteoporosis	650.22	Kowalski et al[24]
Gonadotropins		
Male	66.81	Banco de Preços em Saúde[47]
Female	167.9 (to age 14 y); 98.49 (<14 y)	Banco de Preços em Saúde[47]
Secondary cancer, mean ± SD		
Chemotherapy	1290 ± 2009	DATASUS[19]
Radiotherapy	1157 ± 1222	DATASUS[19]
Hospitalization	738 ± 1128	DATASUS[19]
Hearing loss (prosthesis), mean ± SD	213 ± 62	Ministerio da Saúde[46]

SD indicates standard deviation.

technologies is scarce, and dosimetric models have been used to inform economic evaluations.[8] A systematic review of cost-effectiveness studies showed positive results in proton beam therapy use to treat medulloblastoma.[9]

The high investment in a proton beam therapy system is a concern for decision makers in upper middle-income countries. A universal health system in a highly populated country such as Brazil could produce the necessary patient volume for using this technology to treat medulloblastoma, whose incidence is estimated to be 150 patients/year.[1] Nevertheless, only a cost-effectiveness analysis based on the demand for proton beam therapy can evaluate this decision clearly. The objective of the present study was to evaluate the cost-effectiveness of proton beam therapy compared with photon therapy to treat pediatric medulloblastoma from the health system perspective.

Methods

Model Assumptions

After a literature review to elucidate the best model structure,[9,10] a first-order Monte-Carlo simulation model was built to evaluate the costs and benefits of treating medulloblastoma with proton beam therapy versus photon therapy. The model simulated 7 side effects attributable to radiotherapy in pediatric oncology patients (Fig. 1): (1) growth hormone deficiency, (2) adrenocorticotrophic hormone (ACTH) deficiency, (3) gonadotropin deficiency, (4) hearing loss, (5) hypothyroidism, (6) secondary tumor, and (7) osteoporosis.[10-13] Relapse was also considered in the model until patients turned 8 years old,[14] and there was no difference between alternatives.[7] Possible acute events of treatment were not considered. The cohort was followed just after treatment for a lifetime horizon, and we began the simulation when patients were 5 years old. The model cycle was counted yearly. All patients were assumed to have standard risk medulloblastoma and were treated with cerebrospinal irradiation of 18 to 27 Gy.[6,8,15-18] The model measured the benefits in quality-adjusted life-years (QALYs). TreeAge Pro® 2016 software (TreeAge Software, Inc, Williamstown, MA) was used for the analysis. Effects and costs were discounted at 3%. The simulation parameters are presented in Tables 1, 2, and 3. The management of collateral effects is presented in Table 4.

The base-case analysis considered treating 50 patients/year with an equipment life span of 20 years. National databases showed that 54 pediatric patients with medulloblastoma[19] were treated in the national system in 2014. A proton beam therapy manufacturer (Varian Medical Systems, Palo Alto, CA) and clinical engineers of the Brazilian National Cancer Institute were contacted to estimate equipment costs and life span.

Risk Estimates

Neuroendocrine effect probabilities were extracted from a 7-year follow-up cohort study and were inserted as beta distributions.[6] This study was the only one found, which analyzed endocrine effects with real-world data in a follow-up longer than 5 years. A

Table 2 – Disutility values.

Disutility	Values	Source
ACTH deficiency	0.10	Vega et al[31]
Hypothyroidism	0.10	Verma et al,[9] Bona et al[32]
Growth hormone deficiency	0.20	Verma et al,[9] Burman et al,[33] Lagrou et al,[34] Rosén et al[35]
Osteoporosis	0.02	Verma et al,[9] Borgström et al[36]
Gonadotropins deficiency	0.20	Vega et al[31]
Hearing loss	0.18	Verma et al,[9] Bichey et al[37]
Secondary cancer	0.20	Vega et al[31]

ACTH indicates adrenocorticotrophic hormone.

dosimetric model informed secondary cancer incidence, which varied across patient age.[8] The values were extracted with freeware software WebPlotDigitizer® version 4.1 (Ankit Rohatgi, Austin, TX) from published graphs. Two cohort studies informed the hearing loss probabilities, and a third one showed that this event occurs mostly in the first year after treatment. Osteoporosis risk was based on an observational study.[16,17] No difference was found in cancer recurrence.[7] The model did not consider cardiac effects, because the only study based on a dosimetric model that was found as a possible data source[8] did not include pediatric medulloblastoma.[20]

World Health Organization data on the cancer lethality rate informed the secondary cancer death probability.[21] A cohort study informed the medulloblastoma death rate,[7] and national databases informed all-cause mortality.[22] The annual mortality rate attributable to medulloblastoma was 8% in the first 10 years after treatment. The rate was 0.6% between 10 and 20 years, and all-cause mortality was applied for the rest of the time horizon.[9]

Costs

Photon therapy annual maintenance and spare parts costs were summed and calibrated throughout the life span, with yearly price

Table 3 – Risk values.

Variable	Values		Source
	Proton	Photon	
Beta distributions			
Hypothyroidism	$\alpha = 9$ $\beta = 31$	$\alpha = 24$ $\beta = 13$	Eaton et al[6]
Gonadotropin deficiency	$\alpha = 1$ $\beta = 39$	$\alpha = 7$ $\beta = 30$	Eaton et al[6]
Growth hormone deficiency	$\alpha = 21$ $\beta = 19$	$\alpha = 21$ $\beta = 16$	Eaton et al[6]
ACTH deficiency	$\alpha = 2$ $\beta = 38$	$\alpha = 3$ $\beta = 34$	Eaton et al[6]
Annual risks			
Ototoxicity	0.13	0.173	Jimenez et al,[16] Vieira et al[17]
Osteoporosis	RR = 0.12	0.024	Verma et al[9]

ACTH indicates adrenocorticotrophic hormone; RR, relative risk.

Table 4 – Management strategies.

State	Management strategy
Hypothyroidism	Levothyroxine daily
Ototoxicity	Hearing aid 5 y life span, audiometric evaluation (semesterly), speech therapist (first year)
Gonadotropin deficiency	Men: testosterone monthly Women: estradiol + progesterone and hormone check (semesterly)
ACTH deficiency	Prednisone daily
Growth hormone deficiency	Somatropin pen and IGF 1 checks (annual)

ACTH indicates adrenocorticotrophic hormone; IGF, insulin-like growth factor 1.

readjustment rates based on historical data values of the photon therapy system installed in the National Cancer Institute in Brazil. These rates were 10% for maintenance costs and 32.5% for spare parts. Acquisition and infrastructure costs were added to the sum, brought to present value, and then divided for the number of patients treated throughout all equipment life spans in each scenario. Annual operational costs such as human resources and electric power were summed and divided by the number of patients treated in 1 year. This approach to calculating the capital costs incorporated the demand for the technology and transformed it to a unitary cost attributable to each patient. The Emergency Care Research Institute database informed the global estimates for acquisition, implantation, and maintenance costs of a proton beam therapy in a single-room configuration.[23] These costs were also transformed to unitary costs by the process described earlier.

Direct medical costs such as patient care, professional visits, laboratory and image examinations, side effects and sequelae management, emergency room, and inpatient costs were informed by national databases.[19] Cost studies performed in national hospitals were also consulted, especially for osteoporosis.[24] Outdated values were updated using an inflation rate for health services and goods. National guidelines informed resource utilization[14,25-30]; radiotherapists, oncologists, and a pediatric endocrinologist were consulted to confirm the information. The epidemiological estimate for the annual incidence of pediatric medulloblastoma is approximately 150 patients/year.[1] Therefore, the alternative scenarios were 100 and 150 for the number of patients treated and 10 and 15 years for the equipment life span.

Utilities

Several studies provided utility measures that estimated a decrease in patient quality of life if they were affected by some treatment side effects.[9,31-37] Patients with no side effects had a utility value of 1, and they had a utility value of 0 in the death state. Individuals could be affected by any side effect at any cycle in the model, with the exception of hearing loss (just in the first cycle) and osteoporosis (just after 20 years of treatment). The patients, tracked to detect the incidence and prevalence of side effects, had their utility values discounted, and annual costs were related to the morbidities summed. At the end of the simulation, each patient had a final value of utility and cost, summed for all the cycles. The utility was discounted only in the cycle of the respective morbidity incidence for ACTH deficiency and hypothyroidism. After consulting specialists, it was assumed that patients returned to a normal quality of life in the second year of hormone replacement therapy. Utility values were discounted for

Table 5 – Base-case results (50 patients; 20-y equipment life span).

Strategy	Cost ($)	Incremental cost ($)	Effectiveness (QALY)	Incremental effectiveness (QALY)	ICER ($)
Photon therapy	112 135.52		22.14		
Proton therapy	206 299.36	94 163.84	24.86	2.72	34 590.54

the time the patient stayed with them until death for all other sequelae.[9,38,39] Costs for each side effect were summed through all their durations.

Finally, mean estimates of utility and costs were provided for each technology. The incremental cost divided by the incremental effectiveness provided an incremental cost-effectiveness ratio (ICER), which was compared with a willingness-to-pay threshold. A study based on per-capita healthcare expenditure and life expectancy increases showed that 1 GDP per capita/QALY was a societal threshold for Brazil. The simulation results were compared with the $8649.95/QALY threshold.[40,41]

Sensitivity Analyses

A deterministic sensitivity analysis was built to demonstrate the influence of the parameters that produce the most uncertainty in the results. A probabilistic sensitivity analysis with an acceptability curve demonstrated the results for each scenario, simulating 50, 100, and 150 patients and 10, 15, and 20 years of life span for each patient scenario. The adopted threshold range was $8649 to $31 746 (1-3 times the GDP per capita).

Results

The base-case cost and benefit results are presented in Table 5. The most frequent side effects were growth hormone deficiency and hypothyroidism in both scenarios. Proton beam therapy proved to be the most effective strategy, although with higher costs. The mean ICER was $34 590.54/QALY for the base case. According to the deterministic sensitivity analysis, the number of patients was the most influential variable followed by the proton-to-photon cost ratio (Table 6). Variations in equipment life span, secondary cancer cost, disutility incidence (only in adulthood or lifetime), and model starting age had a minor impact on the results when compared with the number of patients.

Table 6 – Deterministic sensitivity analysis results.

Parameters	Δ QALY	Δ Cost ($)	ICER ($/QALY)
Base case (50 patients/20 y)	2.72	94 163.84	34 590.54
100 patients	2.78	42 019.2	15 098.3
150 patients	2.71	24 776.74	9135.06
15-y life span	2.71	91 439.04	33 768.75
10 y life span	2.61	99 014.02	37 961.11
100 patients/15 y	2.67	40 706.06	15 238.55
100 patients/10 y	2.72	44 617.42	16 376.98
150 patients/15 y	2.72	24 062.04	8837.32
150 patients/10 y	2.74	26 458.96	9664.69
Secondary cancer cost (10×)	2.71	85 723.87	31 623.18
Disutility after 18 y old	2.51	93 714.15	37 325.83
Proton vs photon cost ratio (2.4×)	2.72	46 121.11	16 932.18

ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Acceptability curves for each scenario were plotted (Fig. 2) to show the influence of life span and number of patient variations. The graphic suggests that the cost-effectiveness results are better when a greater number of patients are treated. Variation in life span did not change the results significantly.

In the 50-patient scenario, the probability of cost-effective iterations was greater than 50% only above the $31 746/QALY threshold. Treating 100 and 150 patients per year (independent of life span) results in a probability of approximately 50% at $15 238/QALY and $8649/QALY, respectively (Fig. 2). The probabilities of each scenario are presented in Table 7.

Discussion

This study contributes to estimating the cost-effectiveness of proton beam therapy, considering the demand for treatment of pediatric medulloblastoma. The simulation results showed that proton beam therapy cost-effectiveness is highly dependent on the number of patients using the technology per year. This finding is clearly demonstrated by the 1-way sensitivity analysis and the acceptability curves. In the base case and the simulated scenario, the number of eligible patients was closer to the Brazilian reality. Proton beam therapy was demonstrated not to be a cost-effective technology, even when presenting better effectiveness and less clinical costs because of side effect avoidance.

The acceptability curves showed that proton beam therapy could only have more than 50% cost-effective iterations under $8649/QALY thresholds if more than 150 patients were treated per year. The variation in the ICER between the lower and the highest patient scenarios for a 20-year life span was 3.78 times. To our knowledge, this study was the first to show the influence of the annual number of patients treated in the decision process.

In addition to considering the treatment demand, another strength of the study is the use of recently published data of an observational study that directly compared both technologies. This study measured the neuroendocrine effects in a follow-up of 7 years for photon therapy and 5.8 years for proton beam therapy.[6] Neuroendocrine effects represent more than half of the side effects of the present simulation. To our knowledge, this is the first proton beam therapy cost-effectiveness study to consider real-world data from a direct comparison study. Specialists were also consulted to validate patient quality-of-life behavior through the follow-up, and these conditions were simulated in the model.

A systematic review of cost-effectiveness analysis of proton beam therapy found 2 studies regarding pediatric medulloblastoma that considered capital costs and multiple side effects and therefore are comparable to this study.[9,10,31] Proton beam therapy was considered cost-saving in both studies. Neither study considered the demand for treatment in the analysis. The 2005 study considered multiple side effects and a societal perspective, including costs related to productivity loss in the analysis.[9] Although the number of patients to be treated was not analyzed, the author describes in the discussion that "… approximately 110 patients per year would have to be treated to make the proton facility cost neutral compared with conventional radiation."[9] These data are close to what was found in this study; treating

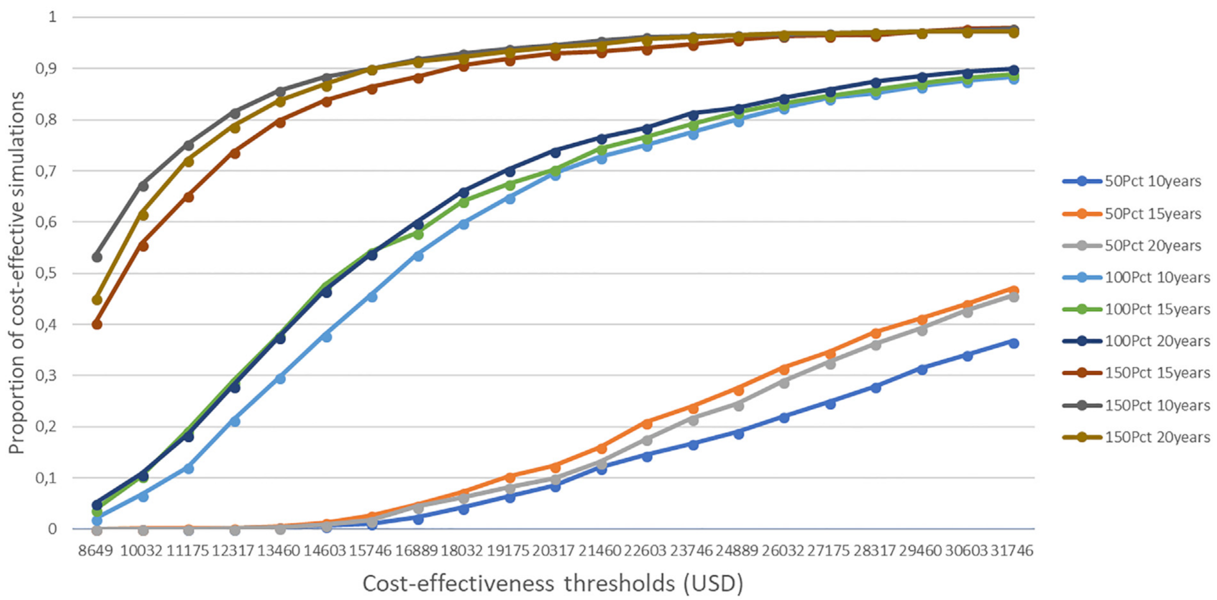

Fig. 2 – Acceptability curves of all simulated scenarios. The graph describes the probability of the simulations of being cost-effective in different thresholds. pct indicates patients.

more than 150 patients would make the technology a cost-effective strategy, considering the proposed threshold.

A study from 2013[31] also analyzed multiple side effects but disregarded patient volume. Although the study resulted in proton beam therapy being deemed cost-saving, it notes that "... the prevalence of the disease is low and may not provide sufficient patient volume for the cost-effective use of many facilities." This assumption points to the importance of considering patient volume for treatment in the analysis, and this knowledge gap is filled in this study. This consideration is important because a cost-effectiveness analysis has inputs related to 1 patient/year. Only the conversion of capital costs to this unit of analysis can properly bring a wide perspective of how the model results behave with a variation in the number of patients, which can be crucial for decision makers.

The same report considered the proton-to-photon cost ratio to be 2.4 times.[31] In the present study, this ratio was 10 times, and, if decreased to 2.4 times, the ICER decreased to half of the base-case value ($16 932.18). This reduction in cost ratio is too large and probably does not reflect the reality; nevertheless, even after considering the same proton-to-photon cost ratio found in the literature,[31] the result was still not cost-effective at the proposed threshold. This result reinforces the profound impact of demand on the analysis.

Table 7 – Probabilities of iteration being cost-effective at different thresholds.

No. of patients	1 GDP/QALY	2 GDP/QALY	3 GDP /QALY
50 patients	0%	5.7%	30.6%
100 patients	5.1%	64.6%	85%
150 patients	45.1%	92.2%	96.8%

GDP indicates gross domestic product; QALY, quality-adjusted life-year.

The use of dosimetric model data to estimate secondary cancer incidence is an important limitation of this study.[8] Secondary tumors used to arise later in a patient's life, and this outcome was not reported in the studies because of insufficient follow-up time. Furthermore, the costs of this morbidity were underestimated, because the cost of high-priced drugs as biological therapies was disregarded. This limitation penalizes the proton beam therapy strategy, where fewer patients developed the disease. The deterministic sensitivity analysis showed that the range of values tested had a minimum impact on the results.

With the lack of reliable data from cohort studies on other side effects, important consequences such as cardiovascular and cognitive deficits were excluded from the analysis. The cohort study that included cardiovascular consequences and used the dosimetric model did not mention patients with medulloblastoma.[18] Cognitive loss data were scarce and thus were not considered. Moreover, the main costs related to this event came from productivity loss, which is disregarded in a health system perspective study. The only health state that affected death, with the exception of medulloblastoma and all-cause mortality, was secondary tumor. This assumption can underestimate the number of patient deaths at the end of the simulation, and it penalizes the proton strategy, which is supposed to avoid this lethal side effect. Findings[31] from the literature showed a very low variation in the ICER when the incidence of cardiac effects changed.

The present study used the same utility values to reflect the preferences in pediatric and adult years of life. The use of adult utility values to deduce pediatric preferences is criticized frequently. The solution applied by a similar study[31] was to start considering the utility discounts of health states only when the patient reached adulthood. This scenario was simulated, and the differences in the results were low (7.9%) compared with those obtained by various other parameters. All the assumptions likely to limit the study conclusion were tested in a 1-way sensitivity analysis or were investigated by other similar studies and compared with the present results. The variables that presented any kind of limitation did not change the results significantly when tested.

Conclusions

The objective of this cost-effectiveness analysis was to compare the use of proton beam therapy with photon therapy in pediatric medulloblastoma. The results changed widely with the variation in the number of patients treated per year. Proton beam therapy was not a cost-effective technology in the base case, but the results differed if more than 150 patients were treated. Considering that Brazil is a continental country and that the installation of a treatment center would have a limited range of action over a given population, treating more than 150 patients (population-based estimate) at the national level overestimates the occupancy rate of only one piece of equipment in a given geographic area. The number of patients treated with the equipment in a limited geographic area would be insufficient for making the investment cost-effective. Even if the demand approaches population-based estimates, the number of patients covered in a given region would be closer to the 50-patient scenario, for which the proton beam therapy was not cost-effective. Therefore, proton beam therapy was not cost-effective for the treatment of pediatric medulloblastoma from the Brazilian health system perspective. If further studies show robust effectiveness evidence of proton beam therapy in other disease treatments, it would be possible to study more indications and increase the volume of patients using the technology.

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