



# Proton Therapy - An Overview

Current practice,  
opportunities and challenges

Published in May 2022

Life.  
Science.



# Foreword

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Since IBA first started to develop proton therapy solutions, we have focused on collaboration and the sharing of information. This culture of cooperation allows us to work collectively with clinical partners to make proton therapy available to anyone who needs it.

Our purpose is simply to offer more cancer patients effective treatments, decreased late effects, and a better quality of life.

The amount of clinical data on proton therapy is increasing rapidly, making it a challenge to keep up with new findings and advancements. We decided to take advantage of our day-to-day involvement with experienced clinical teams from proton therapy centers worldwide, and gather and share information on the use of proton therapy in oncology.

We've compiled this information in a series of white papers on the latest scientific and clinical advances in proton therapy. The information that follows is the result of our in-depth review of the latest articles published in key scientific journals.

We have undertaken this information-gathering exercise with honesty and ethics. While all care has been taken to ensure that the information contained in this publication is correct, unbiased and complete, the reader must be aware

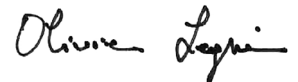
that articles have been selected and data interpreted. We invite you to treat this data with care, exercising your own critical and scientific judgment.

The IBA team believes in the benefits of proton therapy for patients and society. We hope that this information will help you and your team learn more about the extraordinary promises of proton therapy, so that we can continue to make it accessible to more patients.

We wish you a good reading,

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In 2021, the International Agency for Research on Cancer published the GLOBOCAN 2020 estimates of cancer incidence and mortality<sup>1</sup>. According to these estimates, 19.3 million new cancer cases (18.1 million excluding nonmelanoma skin cancer) and almost 10.0 million cancer related deaths (9.9 million excluding nonmelanoma skin cancer) were recorded in 2020. Female breast cancer was the most common type of cancer, with an estimated 2.3 million (11.7%) new cases, surpassing lung cancer that followed (11.4%) along with colorectal (10.0%), prostate (7.3%), and stomach (5.6%) cancers. Nevertheless, lung cancer remained the leading cause of cancer related deaths, with an estimated 1.8 million deaths (18%), followed by colorectal (9.4%), liver (8.3%), stomach (7.7%), and female breast (6.9%) cancers. The global cancer burden is expected to rise by 2040 to 28.4 million cases, a 47% increase from 2020, and to 16.2 million cancer related deaths, solely due to the growth and aging of the population. Thus, the need for a global escalation of efforts in both preventative measures and cancer care to control the disease is inevitable.

## Introduction

Fighting cancer by treating the rising number of patients with the latest medical advances, is a prominent goal among medical professionals and healthcare policy makers. Multi-disciplinary approaches for cancer care often include surgery, chemotherapy and radiotherapy. As an essential part of cancer management, radiotherapy can be used alone or in combination with surgery and/or systemic therapy in the curative setting. Approximately 52% of new cancer patients can benefit from radiation therapy as part of their treatment, with almost a quarter of them (23%) requiring re-treatment<sup>2</sup>.

Radiotherapy works by delivering ionizing radiation that damages the DNA of target cells, leading to cell death. Consequently, the therapeutic window of radiotherapy is achieved by managing the tumor whilst minimizing the development of complications to the surrounding healthy tissue. Optimized treatment plans allow to maximize the radiation dose delivered to cancer cells, while minimizing the exposure of adjacent healthy cells, enhancing the probability of local tumor control, and minimizing the risk of healthy tissue complications. Most of the radiotherapy approaches for cancer treatment are performed by external beam radiotherapy (EBRT) that delivers high energy (6-25MV) photon radiation. Over the past few decades, radiotherapy technologies have evolved from the two-dimensional simple treatment field technology to three-dimensional conformal radiotherapy (3DCRT) or to even more dynamic techniques such as intensity-modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT). These technological

advancements have accomplished greater radiation dose conformity to the target lesions and reduced exposure of the surrounding healthy tissues, which improves the therapeutic ratio of radiotherapy in terms of better tumor control and reduced treatment related toxicity<sup>3</sup>.

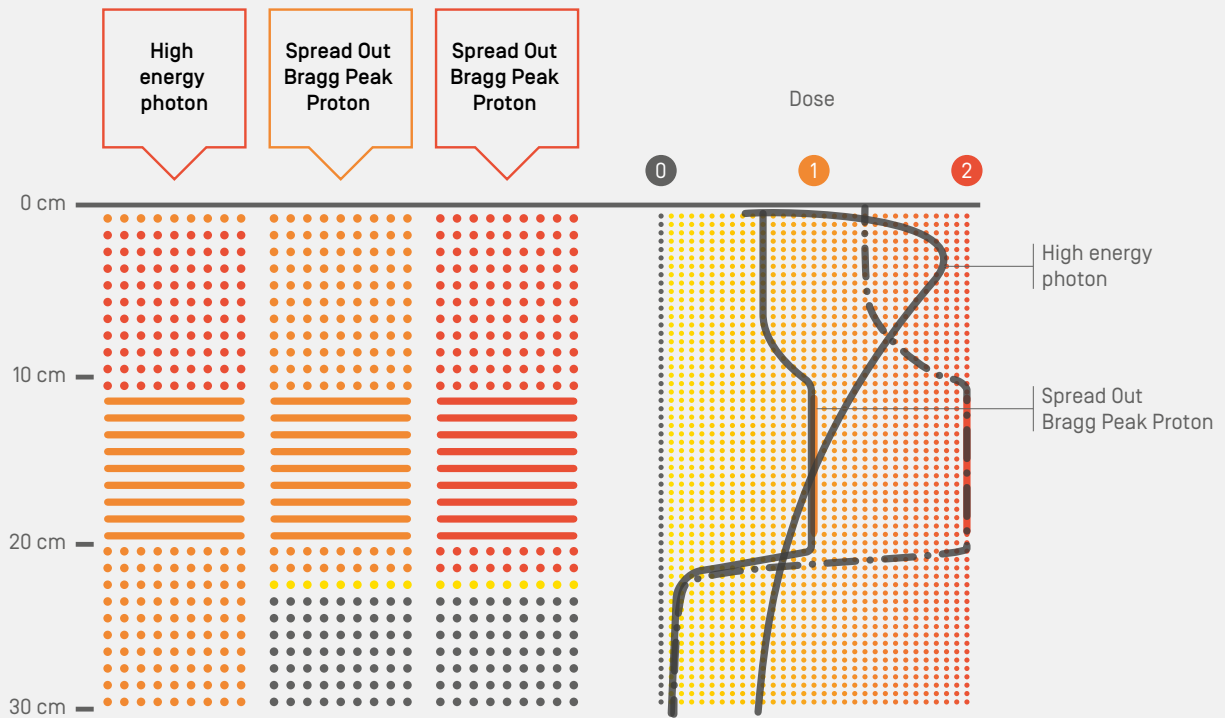
Even though photon radiation is the most common form of ionizing radiation used for cancer treatment, ionizing radiation can be delivered from several other particles such as electrons, protons, neutrons and carbon ions. Unlike ionizing radiation from photons that deposit the maximum energy of the radiation near the surface followed by a gradual depth associated reduction, ionizing radiation from protons is advantageous because almost all the energy of the radiation is deposited in a sharply defined energy peak (the so called Bragg Peak) that is at the end of the penetration range. Proton beams with defined energy peaks targeting the depth of the tumor, deposit the maximum energy of the radiation to the tumor with little energy deposited beyond the target. This physical advantage of protons over photons that translates into lower dose to healthy tissues and higher dose to the tumor, can potentially reduce radiation-induced side effects and provide better tumor control.

Clinical applications of proton therapy continue to expand, with increasing numbers of proton therapy facilities in operation worldwide. This white paper provides an overview on the clinical utilization and the evaluation on health economics of proton therapy today.

## Physical advantage and potential clinical benefits

The physical properties of protons are advantageous over photons, as shown in **FIGURE 1**, when the relative dose deposition in depth of high energy photons is compared with the single Bragg Peak of protons and the Spread Out Bragg Peak Protons (SOBP)<sup>4</sup>. The illustration below shows

that compared to the standard dose delivery from a photon beam, the proton beam delivers the requested dose to the target at a given depth through a single field, with deposition of a small dose beyond the SOBP, and with delivery of a lower dose in front of it.



**FIGURE 1** Schematic representation of the physical properties of photon and proton radiation beams. Comparison of the in depth relative deposition of the radiation dose for high energy photons with the pristine Bragg Peak and the spread out Bragg Peak. Source: <sup>4</sup>

The depth-dose distributions of protons enable a high degree of conformality to the tumor target and greater sparing of surrounding healthy tissues compared to photon therapy. This can potentially translate into clinical benefits using different strategies <sup>5,6</sup>, such as:

- By escalating the dose to the target improving tumor control, while keeping the side effects to a level similar to photon-based techniques.
- By reducing the dose to the surrounding healthy tissues in order to minimize radiation-induced side effects, while keeping the target dose the same.
- By reducing the integral dose to reduce the risk of secondary malignancies.

In *in vitro* studies, at the same level of physical radiation dose, proton radiation was shown to be approximately 10% more effective in killing cancer cells than photon radiation, due to the proton's denser linear energy deposition at the microscopic scale <sup>7</sup>. Taking the available data into consideration, the International Commission of Radiation Units and Measurements has specified a single generic value of proton Relative Biological Effectiveness (RBE) of 1.1 [relative to photon radiation] to be recommended for both cancer cells and healthy tissue cells.

## Increasing number of facilities and patients treated

In 1946, Robert Wilson was the first to propose the use of accelerated protons and heavier ions for radiation treatment. The first patient was treated eight years later, in 1954, at Berkeley University of California. Three years later, at the Gustav Werner Institute in Uppsala, Sweden, the same achievement was accomplished for the first time in Europe. Proton therapy was initially confined to very few centers around the world and typically practiced in a research environment. The first hospital-based proton therapy system was installed in 1990 at the Loma Linda University Medical Center in California<sup>8</sup>.

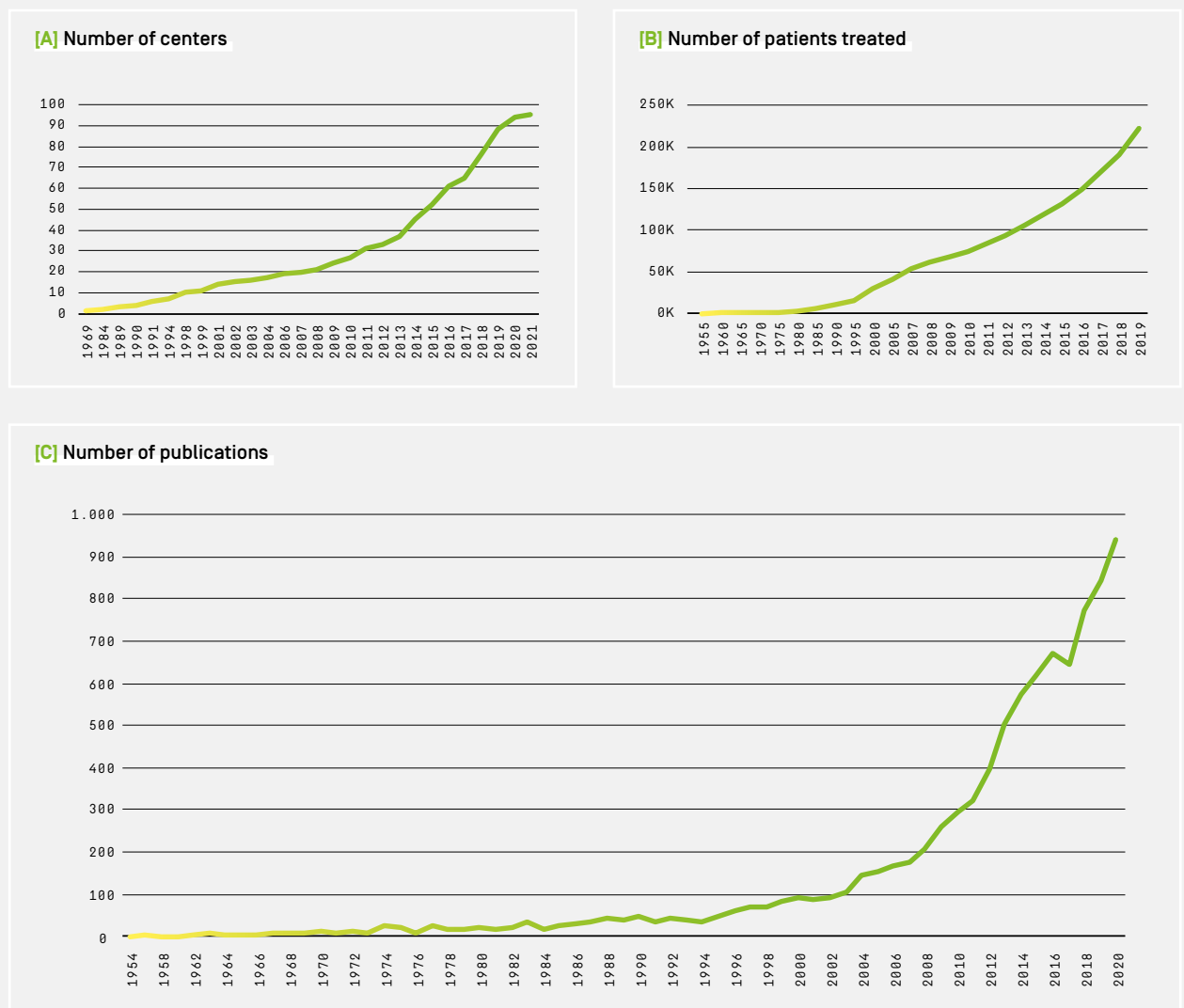
Today, there are 95 proton therapy centers in operation worldwide, and another 32 centers under construction which will be in service in one to two years. Over the past two

decades, proton therapy has undergone a rapid growth both in numbers of facilities and patients treated (**FIGURE 2 A** and **B**). According to the statistics of Particle Therapy Co-Operative Group (PTCOG), 222,425 patients were treated by proton therapy at the end of 2019<sup>9-11</sup>.

The increasing number of proton centers and treated patients has facilitated an increase in clinical research and cooperative trials to be performed, providing a significant improvement in our knowledge and the utilization of this therapeutic modality in the clinical setting. The upsurge of scientific literature and clinical outcome publications (searched for in PubMed), reflects the growing interest and the expanded clinical activities on proton therapy (**FIGURE 2 C**).

**FIGURE 2**

Evolution of the number of centers delivering proton therapy **[A]**, the number of treated patients **[B]** and the number of publications **[C]**.



## Clinical indications and patient selection

The American Society for Therapeutic Radiology and Oncology (ASTRO) has given clear guidance about indications or medical necessity for proton therapy. It recommends proton therapy to be considered “reasonable” in instances where sparing the surrounding normal tissue cannot be adequately achieved with photon-based radiotherapy and is of added clinical benefit to the patient <sup>12</sup>.

### Examples of such advantages might be:

1. The target volume is in close proximity to one or more critical structures and a steep dose gradient outside the target must be achieved to avoid exceeding the tolerance dose to the critical structure(s).
2. A decrease in the amount of dose inhomogeneity in a large treatment volume is required to avoid an excessive dose “hotspot” within the treated volume to lessen the risk of excessive early or late normal tissue toxicity.
3. A photon-based technique would increase the probability of clinically meaningful normal tissue toxicity by exceeding an integral dose-based metric associated with toxicity.
4. The same or an immediately adjacent area has been previously irradiated, and the dose distribution within the patient must be sculpted to avoid exceeding the cumulative tolerance dose of nearby normal tissue.

The policy recognizes the advantages of proton therapy and requests an informed assessment of the benefits and risks. It also recognizes two groups of patients to be considered for proton therapy: Group 1 in which patients fulfill the above mentioned medical necessities and with confirmed disease sites that frequently support the use of proton therapy, and

Group 2 which covers all other indications not listed in Group 1 and are suitable for Coverage with Evidence Development that requires the development of clinical evidence and comparative effectiveness analysis for the appropriate use of proton therapy on various disease sites.

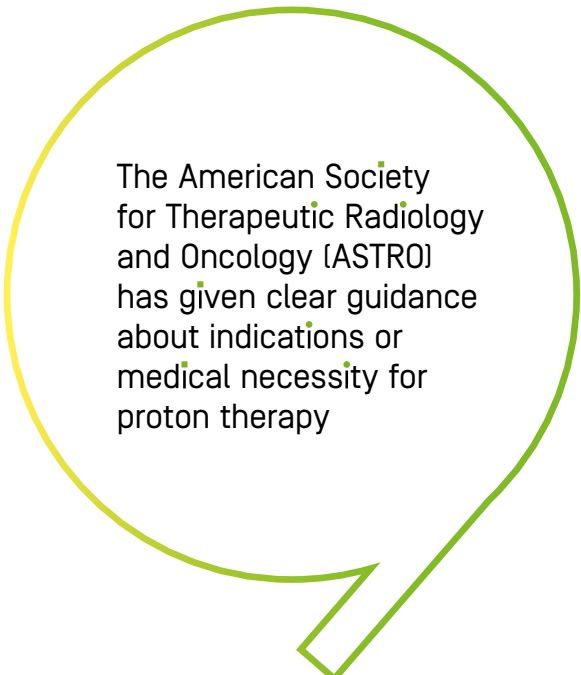
### Indications considered for Group 1 include:

- Ocular tumors, including intraocular melanomas
- Tumors that approach or are located at the base of the skull, including but not limited to: Chordoma and Chondrosarcomas
- Primary or metastatic tumors of the spine where the spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated
- Hepatocellular cancer
- Primary or benign solid tumors in children treated with curative intent and occasional palliative treatment of childhood tumors when at least one of the four criteria noted above apply
- Patients with genetic syndromes making total volume of radiation minimization crucial such as, but not limited to, NF-1 patients and retinoblastoma patients
- Malignant and benign primary CNS tumors
- Advanced (e.g. T4) and/or unresectable head and neck cancers
- Cancers of the paranasal sinuses and other accessory sinuses
- Non-metastatic retroperitoneal sarcomas
- Re-irradiation cases (where cumulative critical structure dose would exceed tolerance dose)

### Indications considered for Group 2 include:

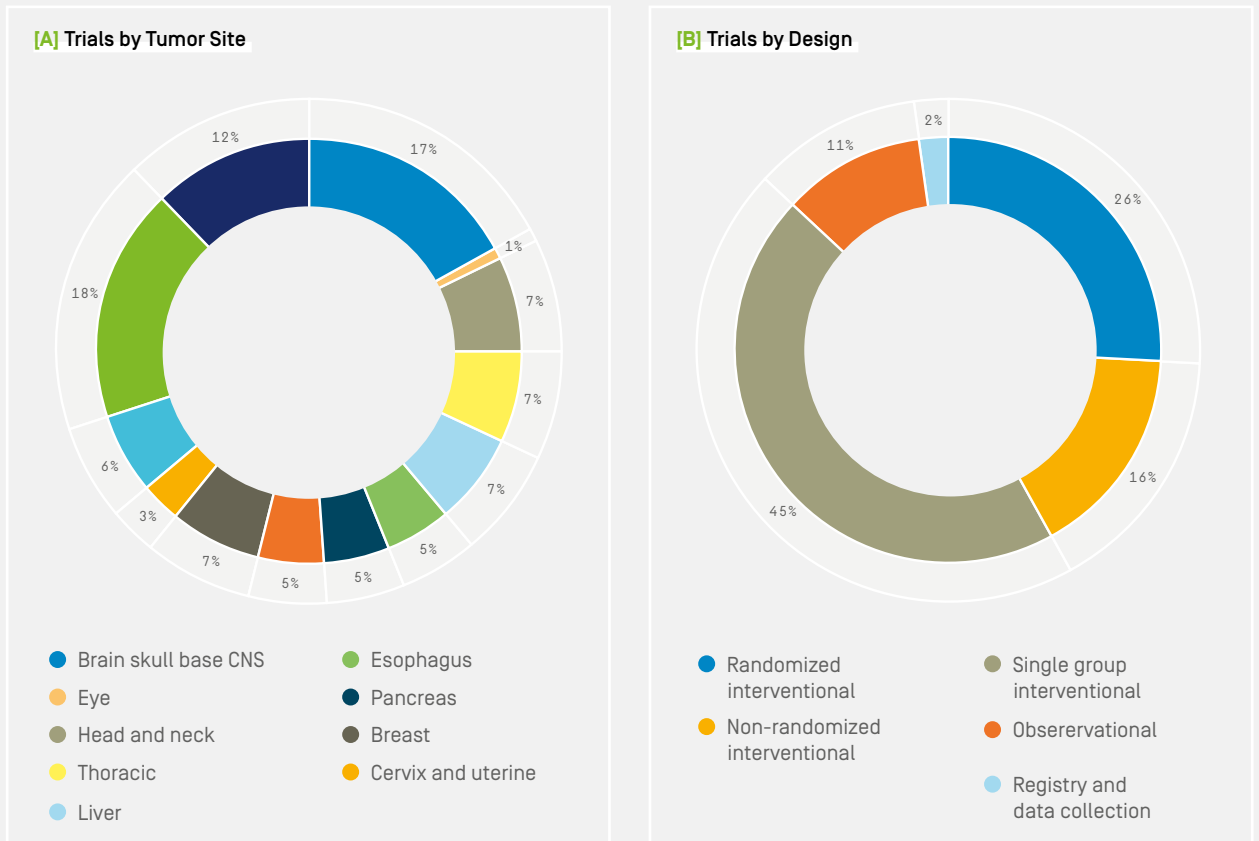
- Non-T4 and resectable head and neck cancers
- Thoracic malignancies, including non-metastatic primary lung and esophageal cancers, and mediastinal lymphomas
- Abdominal malignancies, including non-metastatic primary pancreatic, biliary and adrenal cancers
- Pelvic malignancies, including non-metastatic rectal, anal, bladder and cervical cancers
- Non-metastatic prostate cancer
- Breast cancer
- Prostate cancer

In addition, the latest National Comprehensive Cancer Network guidelines in 2021 <sup>13</sup> also support the use of proton therapy as a treatment option for various cancer types including bone cancer, cancers of the central nervous system (CNS), chondrosarcoma and chordoma, esophageal and esophagogastric junction cancers, head and neck cancers, hepatobiliary cancers, Hodgkin and non-Hodgkin lymphoma, malignant pleural mesothelioma, non-small cell lung cancer, soft tissue sarcoma, thymomas and thymic carcinomas, prostate cancer and uveal melanoma.



The American Society for Therapeutic Radiology and Oncology (ASTRO) has given clear guidance about indications or medical necessity for proton therapy

## Clinical trials and NTCP model-based approach



**FIGURE 3** Illustration of the distribution of clinical trials assessing the effectiveness and safety of proton therapy by type of cancer **[A]** and by trial design **[B]**.

Proton therapy treatment options established by evidence-based medicine, require clinical outcome data of proton therapy. In recent years, the increase in the number of relevant clinical trials that generate clinical evidence is noticeable. At present, results have been reported from 31 completed trials, and further data are expected from 83 additional active trials that are registered on clinicaltrials.gov. (as of August 2021). These ongoing clinical trials cover various tumor conditions such as in the CNS, head and neck, thorax, gastrointestinal track, breast, prostate and gynecologic sites. Furthermore, a significant number of trials focuses on children and young adult patients (**FIGURE 3**). Even though the majority are single group intervention trials, the proportion of randomized interventional trials is more than a quarter [26%] of the ongoing trials. (**FIGURE 3**).

Despite the convincing advantages of proton therapy in dose distribution, prospective and comparative data from clinical trials that is critical to show clinical benefits of proton therapy are lacking <sup>14</sup>. Further to improving the quantity and quality of clinical trials, an alternative ap-

proach is a data-based treatment strategy that involves prediction of individual patient benefits, using normal tissue complication probability (NTCP) models. Compared to the randomized controlled trials (RCTs), the NTCP model-based approach can be more effective and practical in identifying the patient population that benefit from proton therapy <sup>15</sup>. Numerous studies have established and validated NTCP models in selecting patients of head and neck cancer for proton radiation treatment <sup>16,17</sup>. This approach has been proven in actual clinical practice to be a cost-effective selection method of head and neck cancer patients for proton therapy and in the Netherlands, patients selected with this method receive full reimbursement for proton therapy<sup>18</sup>. Studies on NTCP models have expanded to several indications such as lung cancer <sup>19</sup>, brain tumors <sup>20</sup> and prostate cancer <sup>21</sup>. Applying NTCP models, can select the patient groups that benefit from proton therapy and provide supportive evidence regarding the value of proton therapy, however NTCP models based on photon outcome data are inherently limited in their prediction accuracy.

## Developments in proton technology

Technological developments in proton technology have been accelerating over the past decade, creating more facilities in service and expanding their utilization, that further support technological developments. These significant improvements in both delivery techniques and workflow, help unlock the full clinical potential of proton therapy.

### Pencil Beam Scanning

Pencil Beam Scanning (PBS) is the latest delivery technique, achieved through magnetic scanning of proton beamlets. With PBS, the position and depth of a beam that is just a few millimeters wide, can be controlled, allowing for a precise delivery of radiation in all three dimensions of the tumor. The positions and intensities of a proton beam spot are determined by the treatment planning system, to achieve the best possible approximation of the desired dose distribution. PBS provides greater flexibility and control for creating the optimum dose distribution that enables Intensity Modulated Proton Therapy (IMPT). The use of multiple (up to five) scanning beam fields in IMPT achieves even higher levels of conformality to the target, while further decreasing radiation exposure to the surrounding tissues compared to the broad beam technique <sup>22</sup>.

### Single-Room System

The high cost associated with building and maintaining large multiroom proton facilities and the lack of adequate space available at some cancer centers have been major factors in limiting the availability of proton therapy. Single-room proton systems have been introduced as a solution. The compact single-room system is fully integrated with the latest technologies such rotational gantry and PBS, similar to those of multiple-room systems, but requires reduced overall space, upfront overhead, and continued maintenance. Single-room systems provide a viable option for institutions preparing to invest in particle therapy. Single-room systems that are in service, have reported satisfying capacity similar to multi-room systems in treating diverse cancer types and various patient population <sup>23</sup>.

### Motion Management

PBS is a dynamic delivery technique that interferes with target motion, namely the interplay effects, when pencil beam motion occurs on a similar time scale as the intra-fractional tumor motion. This interplay leads to deterioration of the dose distribution. Treatment of moving targets with scanned proton beams requires motion mitigation techniques such as rescanning, breath hold, gating, or tracking <sup>24</sup>. Repeated delivery or 'repainting' of each field several times within a fraction has been suggested based on the tumor motion amplitude, breathing period, asymmetry in the motion trajectory for the target and time required to change the beam energy for the delivery system <sup>25</sup>. A recommended motion management strategy includes personalized (patient-specific) motion analysis, estimation of the dosimetric impact through 4D dynamic accumulated dose based on 4D CT images, robust optimization

of the treatment plan, and employing motion mitigation delivery techniques <sup>26</sup>.

### Adaptive Proton Therapy

Proton therapy is now armed with image guidance. CT and MRI are routinely used in proton centers. Gantry-mounted kV cone beam CT (CBCT) has been commercially available since 2014. Some centers are equipped with in-room CT. In an adaptive planning workflow, new and reference images are registered through a rigid deformation, followed by contours propagated on the new image and validated by the physician. If the dose distribution recalculated on the new data is out of the defined tolerances and the dose volume histogram [DVH] constraints for the organs at risk [OAR] that are not met, the reference plan will be adapted and re-optimized. Once the adapted plan is validated by the physician and the physicist, it will go under patient QA measurement, and the dose accumulation is performed on the reference CT for legal dose record. Adaptive proton therapy can be set up in any center using diagnostic CT and off-line workflow. In-room image solution and the CBCT image correction methods and dose computation speed improvement allow on-line adaptive process <sup>27</sup>.

### Proton Arc Therapy

Instead of using a traditional series of beams that intersect a tumor and require the gantry or patient to be rotated for each beam, spot-scanning proton arc therapy (SPArc) is an emerging technique that can deliver the proton beam through a dynamic rotational gantry. Because SPArc plans are delivered from hundreds of beam angles selected from a smart energy and spot selection algorithm, SPArc has significant advantages over the multi-beam IMPT in improving dose distributions and delivery <sup>28</sup>. Preliminary results demonstrated the potential clinical benefits from a reduction in radiation delivered to OARs, shortening the treatment delivery time and simplifying the clinical workflow for various disease sites, including prostate, head and neck, lung, brain cancers and breast cancer <sup>29</sup>.

### Flash Irradiation

Flash irradiation is a potential modality that can dramatically change the landscape of radiotherapy and patient cancer care. With FLASH irradiation the delivery of a pre-defined dose at single ultra-high dose rates (>40 Gy/s) that are several orders of magnitude higher than the conventional dose rates (~5 Gy/min) that are used clinically. FLASH irradiation seems to reduce radiation-induced toxicities in healthy tissues, while maintaining tumor cytotoxicity. Regarding its clinical application, FLASH radiotherapy from electron beams is limited due to low tissue penetration. Thus, proton FLASH is a promising therapeutic approach as the radiation dose can be deposited deeper within the tissue. Both in vivo and animal model studies have shown the feasibility of FLASH proton therapy. Several high-energy clinical proton facilities already in place can be modified to generate FLASH dose rates for further research into proton FLASH irradiation <sup>30</sup>.



## Cost-effectiveness of proton therapy

The clinical application of proton therapy for the treatment of various cancers is growing rapidly. The dosimetric benefits in the reduction of radiation exposure to OARs and the whole-body integral dose are well established, however the clinical benefits have not been clearly demonstrated yet. In addition, with the rising costs of cancer care, there have been studies investigating the health-economics of proton therapy, especially in comparison to the current standard treatment delivered by photon-based radiotherapy.

The population-based Markov modeling is commonly used for studying the cost-effectiveness of radiotherapy modality including proton therapy. The overall cost estimates are taking into consideration not only the actual treatment costs but also the cost of the aftereffects including the quality and quantity of survival [quality-adjusted life-years (QALYS)] and the costs associated with each QALY gained from each radiotherapy modality [incremental cost-effectiveness ratio (ICER)].

### Pediatric malignancies

Numerous cost-effectiveness studies have established that proton therapy is the most cost-effective option for several pediatric brain tumors especially medulloblastoma

given the radiation-induced side effects such as hormone deficiency, cognitive and neurological deficiency, hearing loss and quality of life <sup>31</sup> (TABLE 1).

In 2021, Mailhot Vega et al. applied the Markov model to assess the cost-effectiveness of proton therapy in pediatric patients with mediastinal Hodgkin lymphoma <sup>32</sup>. They showed that a 5 Gy mean heart dose decrease was associated with a proton therapy incremental cost-effectiveness ratio <\$100K/QALY in 40% of scenarios, suggesting therefore that proton therapy can be cost-effective at least in a select minority of patients with mediastinal Hodgkin lymphoma based on age, sex, and mean heart dose reduction. Spiotto et al. <sup>33</sup> published a review in 2021 evaluating the impact of proton therapy in childhood head and neck cancers in reducing acute and late radiation toxicities, including risks for secondary cancers, craniofacial development, vision, and cognition impairment. Based on the available clinical data and modeling results of proton radiotherapy, the authors suggested that the downstream costs of treating secondary cancers, craniofacial abnormalities, and other late complications, including dental hypoplasia, likely outweigh the upfront financial cost of PBT, as long-term survival rates of children with cancer increased.

**TABLE 1:** Summaries of studies (up to 2016) examining the cost effectiveness for pediatric tumors.

Reference, Country, Year of Cost Analysis	Methodology	Key Assumptions of Model	Cancer Details	Therapy Comparisons	Total Costs	QALYs	ICER	Conclusions and Criticisms
Lundkvist 2005 <sup>16</sup> ; Sweden, 2002	Markov	<ul style="list-style-type: none"> <li>25% of IQ loss attributable to RT</li> <li>75% of patients with hearing loss incur only 1-time cost of hearing aid</li> <li>Capital investment costs distributed evenly among all patients treated at facility</li> <li>Operational/labor costs not included</li> </ul>	Children aged 5 y with Medulloblastoma	PBT vs IMRT	PBT, €14,450 (\$17,484); IMRT, €38,096 (\$46,096)	PBT, 12.778; IMRT, 12.095	—	<ul style="list-style-type: none"> <li>PBT superior because of less IQ loss, hearing loss, GH deficiency</li> <li>Used same utility values for pediatric and adult life</li> <li>Did not account for QOL secondary to IQ and hearing loss</li> <li>Little mention of RT doses, was performed before dose de-escalation to neuraxis</li> <li>Sensitivity analysis: appropriate variability in costs</li> </ul>
Lundkvist 2005 <sup>39</sup> ; Sweden, 2002	Markov	<ul style="list-style-type: none"> <li>IQ loss of 25% attributable to RT</li> <li>Average IQ loss, 17 points</li> <li>Risk of hearing loss, around 13%</li> <li>No capital investment, labor, or operational costs included</li> </ul>	Children aged 5 y with medulloblastoma who received PBT or 25 fractions CRT	PBT vs CRT	€23,647 [\$28,613] lower for PBT	Gained 0.683 from PBT	−23,600 [−\$26,419]/QALY	<ul style="list-style-type: none"> <li>PBT superior</li> <li>Costs per fraction of RT used for all types of cancers (including palliation)</li> <li>Accounted for travel/lodging costs for some but not all cancer types</li> <li>Did not account for QOL secondary to IQ and hearing loss</li> <li>Little mention of RT doses, was performed before dose de-escalation to neuraxis</li> <li>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</li> </ul>

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Reference, Country, Year of Cost Analysis	Methodology	Key Assumptions of Model	Cancer Details	Therapy Comparisons	Total Costs	QALYs	ICER	Conclusions and Criticisms
Mailhot-Vega 2013 <sup>40</sup> ; USA, 2012	Monte Carlo	<ul style="list-style-type: none"> <li>Linear correlation between IQ reduction (average 10 points) and wage decrease (productivity)</li> <li>No other diseases impact death other than heart disease and second cancer</li> <li>No capital investment, labor, or operational costs included</li> </ul>	Children aged 5 y with medulloblastoma	PBT vs IMRT	PBT: \$80,211 (€71,652), IMRT, \$112,790 (€100,755)	PBT, 17.37; IMRT, 13.91	—	<ul style="list-style-type: none"> <li>PBT superior owing to decrease in adverse effects</li> <li>Started to track posttreatment health benefits/costs at age 18</li> <li>Did not take other endocrine disorders from neuraxial radiation into account</li> <li>No pediatric QOL data</li> <li>Sensitivity analysis: appropriate variability in costs</li> </ul>
Hirano 2014 <sup>41</sup> ; Japan, 2012	Markov	<ul style="list-style-type: none"> <li>Cochlear RT doses calculated Based on institutional data</li> <li>QOL data used for hearing loss</li> <li>Used general death rates to account for other mortality</li> <li>Operational costs included, but no capital investment or labor costs</li> </ul>	Children aged 6 y with medulloblastoma	PBT vs IMRT	—	PBT, 23.44; IMRT, 22.46	\$11,773 (€10,517)/QALY, \$20,150 (€18,000)/QALY, or \$21,716 (€19,399)/QALY, depending on QOL scale used	<ul style="list-style-type: none"> <li>Specifically assessed cochlear dose-related hearing loss</li> <li>Did not include IQ, productivity/wage loss</li> <li>Operational costs were simply median costs in Japanese facilities regardless of type/area of treatment</li> <li>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%)</li> </ul>
Mailhot Vega 2015 <sup>42</sup> ; USA, 2012	Markov	<ul style="list-style-type: none"> <li>Linear correlation between hypothalamic RT dose and risk of GH deficiency</li> <li>GH costs included those for medications and office visits</li> <li>PBT costs were \$160,000 out-of-pocket more than photons</li> <li>GH deficiency does not impact death whatsoever</li> <li>No capital investment, labor, or operational costs included</li> </ul>	Children ages 4 and 12 y with brain tumors requiring hypothalamus RT dose	PBT vs IMRT	Various costs, depending on age and hypothalamic dose/GH deficiency	Various QALYs, depending on age and hypothalamic dose/GH deficiency	Various ICERs, depending on age and hypothalamic dose/GH deficiency	<ul style="list-style-type: none"> <li>PBT more superior if hypothalamic dose difference greater between IMRT and PBT</li> <li>PBT is more cost-effective unless its costs are \$580,000/€546,731 (for a child aged 12 y) or \$725,000/€683,414 (for a child aged 4 y) higher than IMRT</li> <li>Assumed same costs for GH in adulthood and childhood</li> <li>Did not include IQ or productivity/ wage loss</li> <li>Analysis limited to GH deficiency only without accounting for survival outcomes (toxicity only)</li> <li>Sensitivity analysis: appropriate variability in costs</li> </ul>

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.  
Source: Verma V, et al. <sup>31</sup>

## Head and neck cancer

Several studies are available supporting that PBT offers superior cost-effectiveness in selected head/neck cancer patients at higher risk of acute mucosal toxicities <sup>31</sup>.

Sher et al. applied the Markov model for stage III-IVB oropharynx cancer patients in the United States and found that IMPT was only cost-effective if assumed to achieve profound reductions in long-term morbidity for younger patients <sup>34</sup>. Similarly, application of the Markov model for paranasal sinus and nasal cavity cancers in China by Li et al. <sup>35</sup> showed that IMPT could be cost-effective, compared to IMRT, if the probability of IMPT eradicating cancer was  $\geq 0.867$  or if the probability of IMRT eradicating cancer was  $\leq 0.764$ .

In a more recent review by Huang et al. <sup>36</sup> in 2021, the methodology and quality of the cost-effective studies published up to date was assessed. The authors highlighted that the health-economics of proton therapy for head and neck cancer was comprehensive including the direct costs that are associated with the actual medical services delivered to patients by providers, and the indirect costs result from disability and productivity loss from disease-related [or treatment-related] morbidity. Future health-economic studies need to focus on optimizing toxicity endpoints that would enhance direct estimates by more accurately measuring the cost of treatment-related complications and incorporating the expenses incurred from treatment-related disability and productivity loss.

**TABLE 2:** Summaries of studies (up to 2016) examining the cost effectiveness for Head and Neck tumors.

Reference, Country, Year of Cost Analysis	Methodology	Key Assumptions of Model	Cancer Details	Therapy Comparisons	Total Costs	QALYs	ICER	Conclusions and Criticisms
Lundkvist 2005 <sup>38</sup> ; Sweden, 2002	Markov	<ul style="list-style-type: none"> <li>Mortality data for first 9 years from national registry</li> <li>Thereafter, assumed to have normal age-specific mortality</li> <li>Used constant utility score from quality-of-life studies</li> <li>No capital investment, labor, or operational costs included"</li> </ul>	Patients aged 65 y with head and neck cancers treated with PBT vs 35 fractions CRT (including hyperfractionation)	PBT vs CRT	€3,887 [\$4,703] higher for PBT	Gained 1.02 from PBT	€3,800 [\$4,254]/QALY	<ul style="list-style-type: none"> <li>PBT potentially can be cost-effective, especially in light of side effects</li> <li>Questionable use of hyperfractionation</li> <li>Data used but not incorporated into costs</li> <li>Calculated constant dentistry costs, unclear on relation to dose/fractionation/modality</li> <li>No data on toxicities/quality of life after PBT in existence for use at the time, thus inherently inaccurate comparison</li> <li>IMRT largely not used for these cancers at time of publication, limiting toxicity data</li> <li>Sensitivity analysis: appropriate variability in costs</li> </ul>

**TABLE 2:** Summaries of studies (up to 2016) examining the cost effectiveness for Head and Neck tumors.

Reference, Country, Year of Cost Analysis	Methodology	Key Assumptions of Model	Cancer Details	Therapy Comparisons	Total Costs	QALYs	ICER	Conclusions and Criticisms
Peeters 2010 <sup>17</sup> ; Holland, 2007	Cost estimates from literature	<ul style="list-style-type: none"> <li>Assumed facilities of either 2- room photons, 3-room PBT, or PBT/carbon ion (3 rooms) with average lifetime 30 y</li> <li>Investment capital, operational, and labor costs from literature and existing business plans, including interest and replacing linacs every 10 y</li> </ul>	No stratification for type or stage of head and neck cancer	PBT vs IMRT	PBT, €39,610 (\$47,928); IMRT, €11,520 (\$13,939)	—	—	<ul style="list-style-type: none"> <li>PBT not cost-effective</li> <li>Compared with photon facility costs, PBT costs increased by 3.2 and particle facility costs increased by 4.8</li> <li>Assumed linear correlation between cost/ fraction and number of fractions</li> <li>Lack of clarity on types of tumors treated at certain frequencies (or lack thereof)</li> <li>Not a "cost-effectiveness" analysis, without assessment of outcomes or toxicities</li> <li>Sensitivity analysis: performed for operational costs and not cancer specifically; Appropriate variability in costs</li> <li>Treatment timings/capacity potentially most variable</li> </ul>
Raemakers 2013 <sup>34</sup> ; Holland, 2010	Markov	<ul style="list-style-type: none"> <li>Many diverse health states, depending on disease status and RTOG grade ≥2 dysphagia and/ or xerostomia</li> <li>IMPT "if efficient" (mixed) group calculated based on ICERs on case-by-case basis and probability of xerostomia (mean probability for this group was 37% vs 26% for IMPT and 45% for IMRT)</li> <li>Assumed that toxicities within first 6 mo were partly reversible but irreversible thereafter</li> <li>No capital investment, labor, or operational costs included</li> </ul>	Stage III/IV oral cavity, laryngeal, pharyngeal	IMPT vs IMRT vs mixed	IMPT: €50,989 (\$61,697); IMRT, €41,038 (\$49,656); Mixed, €43,650 (\$52,816)	IMPT, 6.62; MRT, 6.52; mixed, 6.56	Mixed vs IMRT, €60,278 (\$67,478)/ QALY: IMPT vs mixed, €127,946 (\$143,229)/ QALY	<ul style="list-style-type: none"> <li>IMPT-only had increased costs at all examined levels, but was only compared with IMRT-only (mixed group not analyzed)</li> <li>Xerostomia/dysphagia rates at 12 mo were 22%/18% IMPT, 36%/21% mixed, 44%/23% IMRT</li> <li>Individual calculation of cost-effectiveness and toxicity risk very important to determine optimal modality</li> <li>Disease progression statistics based on old study with CRT</li> <li>Utility scores for disease states based on relatively weak cross-sectional analysis</li> <li>Vague methodology on time course and frequency of time points used to assess toxicities</li> <li>Not all toxicities and costs assessed (eg, odynophagia requiring pain medications, gastrostomy tube, etc)</li> <li>Sensitivity analysis: appropriate variability in costs</li> </ul>

Abbreviations: 3DCRT, 3-dimensional conformal radiation therapy; CRT, conventional radiotherapy; ICER, incremental cost-effectiveness ratio; IMPT, 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.  
 Source: Verma V, et al. <sup>31</sup>

## Breast cancer

Proton therapy costs for breast cancer were favorable for appropriately selected patients with left-sided cancers at high risk of cardiac toxicity when compared to brachytherapy for accelerated partial breast irradiation <sup>31</sup>. In the latest study by Austin et al. <sup>37</sup> it was found that even though IMPT was not cost-effective for most patients, it was cost-effective for left-sided breast cancer patients where IMRT delivered a significantly greater dose to surround-

ing healthy tissue. The authors propose an evaluation of the cost-effectiveness of proton therapy on an individual patient basis. The consensus from the PTCOG breast cancer subcommittee <sup>38</sup> stated that proton therapy may be cost-effective for more than 95% of women with  $\geq 1$  cardiac risk factor undergoing regional nodal irradiation for left breast cancer. Integrating an NTCP model-based approach can help select patients who will benefit from proton therapy with favorable cost-effectiveness.

**TABLE 3:** Summaries of studies (up to 2016) examining the cost effectiveness for breast tumors.

Reference, Country, Year of Cost Analysis	Methodology	Key Assumptions of Model	Cancer Details	Therapy Comparisons	Total Costs	QALYs	ICER	Conclusions and Criticisms
Lundkvist 2005 <sup>24</sup> ; Sweden, 2002	Markov	<ul style="list-style-type: none"> <li>Patients at risk of all-cause death every year</li> <li>Tumor-related death in first 10 y</li> <li>Mortality rates per Swedish life tables</li> <li>Population risk for cardiac disease based on national registry based on age</li> <li>Did not count patients who received regional lymph node irradiation and hence assumed 10-y survival of 65%</li> <li>No capital investment, labor, or operational costs included</li> </ul>	Women aged 55 y with left-sided breast cancer, secondary analysis of subpopulation assumed to have double the cardiac disease risk	PBT vs WBI	PBT, €11,248 (\$13,610) IMRT, €5001 (\$6051)	PBT, 12.35 IMRT, 12.25	€66,608 (\$80,596)/ QALY for general patients; €34,290 (\$41,491)/ QALY for subpopulation	<ul style="list-style-type: none"> <li>PBT potentially economically beneficial in select patients at high risk of cardiac toxicity</li> <li>Arbitrary assumptions of 14% pneumonitis risk, and 75% of those patients taking indeterminate amount of sick leave from work (productivity loss)</li> <li>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</li> <li>Sensitivity analysis: appropriate variability in costs; variations in estimated risk of cardiac disease most related to changes in costs of PBT vs WBI</li> </ul>
Lundkvist 2005 <sup>19</sup> ; Sweden, 2002	Markov	<ul style="list-style-type: none"> <li>Patients at risk of all-cause death every year</li> <li>Tumor-related death in first 10 y</li> <li>Cardiac diseases categorized as fatal (death-inducing) or nonfatal</li> <li>Base incidences of cardiac disease were age/sex-matched</li> <li>No capital investment, labor, or operational costs included</li> </ul>	Women aged 55 year with left-sided breast cancer; PBT vs CRT in 25 fractions	PBT vs CRT	€5,920 (\$7,163) higher for PBT	0.17 gained from PBT	€34,200 (\$30,551)/ QALY	<ul style="list-style-type: none"> <li>PBT not cost-effective</li> <li>Used outdated RT schemas, including no breast boost and assumption of 14% risk of severe pneumonitis, no corresponding utility reductions</li> <li>Adverse events included only cardiopulmonary toxicities and no others, including second cancers</li> <li>Little data for risk of cardiac events after breast cancer RT</li> <li>Sensitivity analysis: wide variability in costs; cardiac risk reduction most related to variability in costs</li> </ul>

**TABLE 3:** Summaries of studies (up to 2016) examining the cost effectiveness for breast tumors.

Reference, Country, Year of Cost Analysis	Methodology	Key Assumptions of Model	Cancer Details	Therapy Comparisons	Total Costs	QALYs	ICER	Conclusions and Criticisms
Taghian 2006 <sup>25</sup> ; USA, 2003	Medicare estimates	<ul style="list-style-type: none"> <li>Costs (professional/technical) assumed to be for 25 fractions with 5-fraction boost without chemo/hormone therapy</li> <li>No capital investment, labor, or operational costs included</li> </ul>	Breast cancer in a general representative population, without further details	PBT vs WBI (50 Gy in 25 fractions 10 Gy in 5 fractions) vs mixed photon-electrons (opposed lateral photons, en face electrons)	PBT, \$13,200 (€11,792) WBI, \$10,600 (€9,469) Mixed, \$5,300 (€4,734)	—	—	<ul style="list-style-type: none"> <li>PBT only modestly more cost-effective than conventional WBI</li> <li>"Cost" analysis and not a "cost-effectiveness" analysis without comparison for outcomes, toxicities, etc</li> <li>Only applicable to USA Medicare patients because of the specific source of cost data</li> <li>Sensitivity analysis: none; technical components of treatment provide most sources of cost variations</li> </ul>
Ovalle 2014 <sup>26</sup> ; USA, 2015	Medicare estimates	<ul style="list-style-type: none"> <li>Costs strictly based on Medicare figures without other salient parameters</li> <li>No capital investment, labor, or operational costs included</li> </ul>	Early stage breast cancer patients suitable for APBI	APBI vs WBI: APBI using SAVI, MammoSite, linear accelerator-based 3DCRT WBI using 3DFIF, hypofractionation, IMRT, hypofractionated IMRT"	PBT APBI, \$13,883 (€12,402) SAVI APBI, \$14,859 (€13,265) MammoSite APBI, \$12,245 (€10,938) 3DCRT APBI, \$6,771 (€6,049) 3DFIF WBI, \$13,149 (€11,746) Hypofractionated WBI, \$10,070 (€8,995) IMRT WBI, \$19,599 (€17,508) Hypofractionated IMRT WBI, \$11,747 (€10,494)"	—	—	<ul style="list-style-type: none"> <li>Currently in abstract form without precise methodologies reported</li> <li>Also used Medicare estimates without data on several other parameters as above</li> <li>Sensitivity analysis: none</li> </ul>

Abbreviations: 3DCRT, 3-dimensional conformal radiotherapy; 3DFIF, 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, non-small cell lung cancer; PBT, proton-beam radiotherapy; QALYs, quality-adjusted life-years; RT, radiation therapy; SAVI, strut-adjusted volume implant; SBRT, stereotactic body radiation therapy; SRS, stereotactic radiosurgery; WBI, whole breast irradiation; y, years.  
Source: Verma V, et al. <sup>31</sup>

In a systematic review by Verma et al. <sup>31</sup> the authors found that similar cost-effectiveness was observed for proton therapy, enucleation, and plaque brachytherapy in patients with uveal melanoma. Proton therapy was shown to be cost-effective for locoregionally advanced, but not early stage tumors in non-small cancer lung cancer. However, the cost-effectiveness for prostate cancer seemed to be suboptimal.

Based on these reports, it can be concluded that proton therapy does not appear to be the most economic option for all cancers or even for all patients with a given type of cancer. However, the cost-effectiveness of proton therapy has been identified in subsets of patients with a certain type of cancer. It is also very important to highlight that cost-effectiveness analyses are inherently dependent on the clinical outcome data. Future cost-effectiveness studies with high-quality clinical evidence inputs will provide a clearer picture of the actual value of proton therapy.

## Reimbursement for proton therapy treatment

In Europe, proton therapy is currently considered standard therapy only in a limited number of cancer types that vary from country to country. Most European countries accept proton therapy as a standard for pediatric indications which are covered by the national health insurance and the patient's healthcare package. For all other indications, some countries reimburse proton therapy according to a binding list (e.g., France, Italy, Poland, Switzerland). Other countries (e.g., Sweden, Denmark, the Czech Republic) do not have a fixed list of approved indications; here, the administration of proton therapy is based on decisions from multidisciplinary tumor boards. One country (the Netherlands) applies the model-based approach for selected novel indications<sup>39</sup>.

In the United States, public and private insurers such as Medicare, Aetna and Blue Cross-Blue Shield etc. set the policies that define the diagnoses and circumstances governing reimbursement for proton therapy<sup>40</sup>. However, the insurance authorization process causes delays to timely patient care, due to the time required for insurance authorization, the incidences of denials and appeals, and the outcomes of appeals. Although ASTRO published a list of proton therapy

indications recommended by experts for insurers, third-party payers may overlook the guidelines in determining coverage. Despite these barriers, the insurance approval and appeal rates for proton therapy were quite high, with 87% ultimately achieving coverage including approval for 2 of every 3 patients entering the appeal process<sup>41</sup>.

The reimbursement system in Asia mainly consists of government assistance, out-of-pocket and prepaid private spending. For more developed countries with established health care systems and better government reimbursements, the reimbursement system aims to transition toward providing universal health coverage<sup>42</sup>. In Korea and Japan, healthcare service payment in radiotherapy is mainly based on a fee-for-service system. Both the Japanese health insurance system (JHIS) and the Korean health insurance system (KHIS) require copayment from the insured and dependents who receive healthcare services, that is a part of their total healthcare expenses. Copayment for radiotherapy is 5% in Korea and 30% (7–69 years old) in Japan, with a ceiling system. There are some differences in the indications for proton therapy covered by national health insurance system of both countries<sup>43</sup>.

## Closing remarks

Over the last two decades, proton therapy has been rapidly growing worldwide. Continuous developments in technology and the increasing evidence from clinical research aim to fully exploit the potential of this radiation treatment modality. The clinical utilization of proton therapy gradually expands following the positive outcome data reported. Proton therapy's lack of integral dose and the reduced radiation exposure of healthy tissue is translated to clinical

benefits in terms of reduction of radiation-induced side effects in a select groups of patients. With the life expectancy as well as the survival rates of cancer patients being extended, proton therapy has the potential to address the concern over the long-term toxicities of radiation treatment. Collective efforts are being made to bring proton therapy to more cancer patients who will benefit from this advanced radiation therapy.

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