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Proton Therapy

Current Status and Future Directions

Edited by Thomas J. FitzGerald and Maryann Bishop-Jodoin

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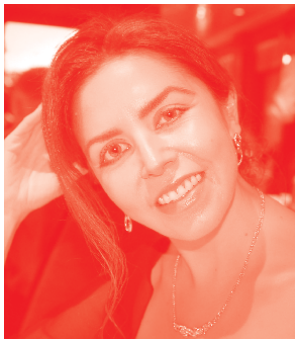

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Meet the editors

Dr. FitzGerald is the Professor and Chair of the Department of Radiation Oncology at the University of Massachusetts Medical School. The department has a strong academic mission and provides clinical care to multiple communities throughout central Massachusetts with several community centers providing advanced technology clinical care. Dr. FitzGerald has been Principal Investigator of the Quality Assurance Review Center (QARC) for more than 25 years. QARC provides imaging and radiation oncology data acquisition and data management service to the National Clinical Trials Network (NCTN) and industry partners. QARC is now part of the Imaging and Radiation Oncology Core (IROC), which centralizes data management and quality assurance service for NCTN clinical trials with offices in Rhode Island, Houston, TX, Columbus, OH, and Philadelphia, PA. In this capacity, proton institution applications are credentialed for clinical trial participation and data are reviewed for protocol compliance. Dr. FitzGerald serves in an advisory capacity for The Cancer Imaging Archive (TCIA).

Maryann Bishop-Jodoin, MEd, is an instructor and scientific writer in the Department of Radiation Oncology, University of Massachusetts Medical School. Ms. Bishop-Jodoin has worked with Dr. FitzGerald at the Quality Assurance Review Center (QARC) program for more than 25 years. She writes and edits manuscripts, books, and grants as well as the QARC quality management system documentation.

Contents

Preface

It is a privilege to have the opportunity to provide a comprehensive update on the status and future direction of proton therapy in radiation oncology. Over the past twenty-five years, proton therapy has become more prominent worldwide, as it is an important component of clinical radiation therapy for both adult and pediatric clinical care. Proton therapy has the potential to alter the landscape of daily radiation therapy treatment due to its inherent ability to spare normal tissue. Colleagues contributing to this book have provided insight into the history and footprint of proton care, the status of protons in registries and clinical trials, and future directions.

Proton therapy has a rich history and historically was limited to a few centers of excellence. The systems required unique expertise in the field of radiation therapy both for treatment planning and treatment execution. Because of the unique nature of treatment delivery, often single fields were treated each day using compensation devices designed to modulate dose distribution. The devices used were early-stage three-dimensional models that became radioactive themselves, therefore cost associated with maintenance of equipment and disposal were unique even in the field of radiation oncology. Pioneers of care at both Massachusetts General Hospital and Loma Linda, CA played important roles in the genesis and application of proton care in the United States.

Because of the unique properties of proton dosimetry, and with exit dose conspicuous by absence, investigators had envisioned strategies for proton care to be delivered at an enterprise level. Design changes with pencil beam applications coupled with miniaturization of the cyclotron design, smaller units became commercially available and proton care became available in a more geographically transparent manner. Today, nearly 100 centers have proton capability, which will expand as cost and production adjust with the demand. Of equal importance, proton applications are now disease sites and anatomically transparent with advantages in all areas of the body. The advantage for pediatric patients has always been clear with decrease dose to normal tissue. Modern applications are now applied for lymphoma for cardio-pulmonary tissue sparing, head/neck, central nervous system, abdomen, pelvis, and extremities with advantages in tissue sparing in all regions. The modern proton unit has image guidance, tracking, and multi-leaf collimation in a manner similar to photons, thus bringing the nimble advantage of photon care to proton treatment execution. Radiosurgery can now be performed with protons in a facile manner in all target areas and investigators are evaluating the role of ultra-rapid dose rate delivery of protons to further exploit the therapeutic advantage of particle care.

This book reviews many aspects of proton care including the application of protons in modern clinical trials. It also reviews problems associated with the migration of proton care worldwide. Finally, the book examines the future direction of proton care and the expectation that years from now, proton care will be as applicable

to the cancer patient as photon care. As our colleague Herman Suit once said, the advantage of proton care is self-evident as the dose distribution is simply better. It is our responsibility to ensure the process improvements predicted by Dr. Suit.

I would like to thank IntechOpen and Romina Rovan who managed this project. It has been a privilege to help coordinate the text and chapters designed to acknowledge the history, footprint, and growing interest of proton care worldwide.

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Section 1

Introduction

Chapter 1

History and Overview of Proton Therapy

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Abstract

The use of proton therapy in oncology is not a new idea. The unique physical properties of protons and potential advantages in radiation therapy were initially recognized in the 1940s. Since the first patients were treated in the 1950s, technology and clinical applications have evolved as evidenced by the increasing number of proton therapy centers and patients being treated throughout the world. This chapter will review the history of proton therapy providing a detailed overview of the cyclotron and synchrotron techniques used and how they have advanced with time.

Keywords: proton therapy, charged particle, history, oncology

1. Introduction

Radiation therapy is a standard local treatment in oncology with nearly 50% of cancer patients receiving radiation at some point in their disease course [1, 2]. This is most often used in combination with surgery, chemotherapy and, more recently, immunotherapy [3, 4]. The underlying principle of using ionizing radiation in oncology is based on its transfer of energy to tissues resulting in DNA damage, the acquisition of mutations that disrupt cell physiology and cell death [5, 6]. Determining the optimal radiation delivery modality, dose, treatment strategy and combination of other therapies have been an active area of investigation for decades [7, 8]. Advances in physics, radiology and radiobiology have allowed the field of radiation oncology to evolve resulting in more favorable clinical responses while minimizing toxicity to normal structures [9].

Several discoveries near the end of the 19th century gave birth to the discipline of radiation sciences. At Würzberg University in Germany, Wilhelm Conrad Roentgen's experiments using a cathode-ray tube led to the discovery of x-rays. His seminal findings that a "ray" can pass through most solid objects, but not bone or metal is, of course, still a central tenet in radiology practice today. The discovery of radioactivity by Henri Becquerel and identification of polonium and radium by Marie Curie soon followed that resulted in scientific advances that would lead to a new era bridging the gap between modern technology and medical sciences [10].

The discoveries made by Roentgen, Becquerel and Curie laid the groundwork for industries in healthcare to begin the production of devices to generate high-energy beams for diagnostic and therapeutic purposes throughout the early to mid-20th century. The roots of proton therapy can be traced to these initial technological undertakings [11]. In more recent years, radiation oncology entered a new era with the advent of three-dimensional (3D) treatment planning systems. This allowed physicians, physicists and dosimetrists to computationally derive solutions to prior limitations in external beam radiation therapy planning. Intensity modulated radiation therapy is one such fundamental advance that optimizes conformal radiation delivery to a 3D target volume [12]. This widespread use of conformal radiation therapy with a focus on increasing tumor cell effect has revamped interest in the applications of proton therapy in oncology [13].

For this reason, this chapter will review the history and evolution of proton therapy to provide a framework for the later discussion of treatment planning, efficacy and future directions.

2. Proton discovery

Atoms are comprised of subatomic particles with a unit positive charge (protons), negative charge (electrons) and neutral charge (neutrons). Ernest Rutherford's initial studies on subatomic particles found that α and β rays derived from uranium and helium atoms consist of nuclei of α rays. These findings were substantial because they led to studies that revealed that when nitrogen gas is irradiated by an α particle it produces oxygen atoms and the nuclei of hydrogen atoms, which have a net positive charge. This unit with a net positive charge was termed the proton. Rutherford concluded that a nitrogen atom is composed of positively charged protons and negatively charged electrons, and that a nitrogen atom can be converted to oxygen and a proton (hydrogen atom nucleus) [14, 15]. Following the discovery of the proton, James Chadwick at Lawrence Berkeley Laboratory discovered the neutron and studies subsequently began assessing potential applications of fast neutron radiation therapy [16–18].

3. Protons vs. photons

Photons are high-energy x-rays and are the traditional modality used in external beam radiation therapy. Photon therapy typically relies on several beam directions to achieve a uniform dose distribution to a target volume in order to treat disease and minimize toxicity to structures at risk. This is because, within tissues, photons exhibit a decreasing energy deposition with higher depth. Proton therapy, a form of charged-particle therapy, differs from photon therapy regarding energy transfer within tissues as proton velocity is inversely proportional to the energy transferred within tissues [19]. Therefore, by reducing their velocity based on electromagnetic interactions with atoms in tissue, the higher energy they can transfer to a pre-determined depth.

This concept of a "peak" was initially discovered by William Bragg in the early 1900's and is known as the "Bragg peak." The Bragg peak, or energy deposition as a function of tissue depth, has potential to deliver higher doses to a target volume while maintaining dose-constraints of nearby critical structures [20]. The potential for increased tumor cell effect while reducing dose to structures at risk is one of the underlying factors in the medical interest of proton therapy.

4. Early stages of proton therapy in medicine

In 1946, Robert Wilson was the first to recognize the potential medical applications of proton therapy [21]. By utilizing the concept of the Bragg peak and knowledge that protons exhibit decreasing velocity as they travel through tissue, Wilson postulated that these physical properties could be advantageous for targeting disease deep within healthy tissue. Needless to say, his idea was well ahead of the time. Wilson stated,

> *"These properties make it possible to irradiate intensely a strictly localized region within the body, with but little skin dose. It will be easy to produce well collimated narrow beams of fast protons, and since the range of the beam is easily controllable, precision exposure of well-defined small volumes within the body will soon be feasible" [21].*

Of course, Wilson highlighted concepts that are still fundamental in the modern practice of radiation oncology.

In 1954, the first patients were treated at Lawrence Berkeley Laboratory with proton therapy using a cross-firing technique with a 340 MeV proton beam [22]. The target was the pituitary gland for hormone suppression in patients with metastatic breast cancer. In these patients, the Bragg peak was not used due to difficulties in approximating the range. This technique was able to concentrate the dose to the pituitary with a single-fraction. In 1958, a three-fraction schedule was utilized for pituitary radiation [23].

The Gustav Werner Institute in Uppsala, Sweden was the first to incorporate the Bragg peak and concepts proposed by Robert Wilson into proton therapy studies. A 185 MeV cyclotron was used to treat the initial set of patients in the late 1950s to early 1960s, which included work by stereotactic radiosurgery pioneer Lars Leksell [24–27]. Interestingly, high doses per fraction were used due to time constraints at the cyclotron. The spread-out Bragg peak with a rotating technique was used in order to produce range-modulated beams [28, 29]. Together, the use of protons as a "neurosurgical tool" for "cerebral surgery" was used to treat dozens of patients during this time [30]. The applications of delivering larger doses of intracranial radiation to precisely defined targets are still prominent today. The innovation of Larsson, Leksell and others is best demonstrated by quoting their 1958 Nature article that says,

> *"with high-energy protons a sharply delimited lesion can be made at any desired site in the central nervous system" [30].*

In collaboration with Massachusetts General Hospital, the Harvard Cyclotron Laboratory launched their program in the 1960s using a 160 MeV cyclotron also incorporating the Bragg peak proposed by Wilson [31]. Again, neurological targets were identified for radiosurgery, with a focus on pituitary irradiation [32]. Patients with conditions such as acromegaly and Cushing's disease had their skull placed in a head frame in order to target the "beam spot" within the sella turica [32]. The authors reported satisfactory results, which included the reduction of complications with added experience. Their success gained recognition and received funding by agencies such as the National Cancer Institute.

In the early 1970s, the Department of Radiation Oncology at Massachusetts General Hospital expanded proton therapy to patients with sarcoma, head and neck cancer and melanoma [33–35]. In 1979, another oncologic advance developed

by this department was the idea of the use of proton therapy for men with prostate cancer [36]. Seventeen men with localized prostate cancer were treated with boost proton therapy. During the 12 to 27-month follow-up, 16 of these patients were locally controlled. In general, side-effects were mild, which included urethral stricture in two patients. Minimal rectal toxicity was reported in follow-up.

Throughout the 1970s, Russia initiated several proton therapy programs. These occurred at several institutions including the Joint Center for Nuclear Research, the Institute of Theoretical and Experimental Physics and a collaboration between the Petersburg Nuclear Physics Institute and the Central Research Institute of Roentgenology and Radiology. The Institute of Theoretical and Experimental Physics was the largest of these programs [37], which used a 7.2 GeV proton synchrotron. Using the Bragg peak, pituitary irradiation of breast and prostate cancer patients was performed. By 1981, nearly 600 patients with breast and prostate cancer as well as others with bone metastases, lymph node malignancies, osteosarcoma, melanoma, cervical cancer and eye tumors were treated [37, 38]. This expanded the applications of proton therapy not only for pituitary irradiation, but for several extracranial conditions.

Although Japan is a large user of proton therapy today [39], they had only treated 11 patients with proton therapy alone and 18 patients with a proton boost into the early 1980s [40]. Their efforts took place at the National Institute of Radiological Sciences in Chiba and subsequently at the Particle Radiation Medical Science Center in Tsukuba. Since that time, proton therapy has greatly expanded in Japan with more than 10 centers available for treating patients [39].

5. Expansion of proton therapy

Throughout the 1980s, proton therapy was primarily used for intracranial stereotactic radiosurgery [41]. However, clear advantages of proton therapy were demonstrated in treating patients with conditions with otherwise limited therapeutic options such as chondroma and choroidal melanoma [42–44]. While proton therapy centers had provided benefit to many patients throughout the world, in the 1970s and 1980s, a severe limitation was that they were located at research institutions. This limited the number of patients being treated since these centers had several ongoing research projects that required beam time. Moreover, it inconvenienced both the medical team and patients due to the requirement to travel to the research centers for treatment.

In 1990, the first proton therapy center based out of a hospital was built at the Loma Linda University Medical Center [45]. This was an undertaking that required Fermilab to develop the synchrotron and the Harvard Cyclotron Laboratory to design the gantries. Soon after its implementation, Loma Linda University Medical Center established itself as a leader in proton therapy. The large number of patients treated during the 1990s at Loma Linda provided evidence that proton therapy had the potential to be an important modality in radiation oncology. Since its operation began, Loma Linda University Medical Center has remained a prominent proton therapy institute and research center [46].

Following the initial success of Loma Linda University Medical Center, the proton therapy center at the Harvard Cyclotron Laboratory was transferred to the Massachusetts General Hospital for clinical use in 2001. Around this time, Indiana University also implemented a hospital-based proton therapy center. This increase in hospital-based proton therapy centers and technological advances allowed radiation oncology departments to recognize the possibility of widespread use that

could lead to continued advances in clinical settings. This is evidenced by a drastic increase over time in the number of proton therapy facilities worldwide [47].

6. Evolution of proton therapy technology

As detailed above, initial proton therapy centers utilized a cyclotron, which circulates particles using an electromagnetic field and accelerates them based on an energy selection system [48]. This process continually produces a single batch of protons. The major advance of synchrotron systems was the ability to accelerate particles of different energy levels, which produces pulses of protons and results in a more energy efficient process [48].

Initially, cyclotron and synchrotron systems produced beams the width of a "pencil", which made treating larger targets difficult. Thus, scattering foils were used to broaden beam width. However, use of a single scattering foil was insufficient due to limitations in achieving reproducible beam flatness. In the late 1970s, the double scattering system was incorporated at the Harvard Cyclotron Laboratory, which could accurately reproduce beam flatness to homogenously cover larger treatment volumes [49]. This required materials with specific physical properties to ensure a beam of desired width [50].

At the Gustav Werner Institute in Uppsala, Sweden, Larsson introduced the concept of magnetic beam scanning to replace the previously used scattering techniques [25]. Many types of magnetic beam scanning techniques have been proposed. Initially, spot scanning was developed, but 3D continuous scanning soon became widely used. Technological advances in 3D beam scanning techniques were later developed that produced more conformal beams that were highly effective at reducing the dose to structures at risk [51]. As the advent of intensity modulated radiation therapy changed the modern practice of radiation oncology, intensity modulated proton therapy has become increasingly used at proton centers. The physical properties of protons and ability to modulate dose along the beam axis has highlighted the advantages of intensity modulated proton therapy and its ability to improve tumor cell effect while sparing structures at risk when compared to photon therapy [52].

7. Conclusion

The advantages of proton therapy were recognized early in its history by Wilson as well as the early treatment centers at Lawrence Berkeley Laboratory, the Gustav Werner Institute and the Harvard Cyclotron Laboratory. Since proton therapy is particularly attractive for cases where there is a risk of important structures being irradiated, intracranial targets, such as the pituitary gland, were the first to be treated [22, 23]. This evolved from single fraction to multiple fraction treatments [23]. The benefits of sparing nearby, sensitive structures were later highlighted by treating chondroma and choroidal melanomas [35, 42–44]. In fact, these became some of the most commonly treating conditions at the Harvard Cyclotron Laboratory.

Proton therapy has demonstrated more favorable dose distributions when compared to photon therapy in several tumor types [53–55]. However, it is unclear if these superior dose distributions will translate to better outcomes and, if so, the patients who would receive the most benefit will need to be identified. Moreover, hospital facilities will need to weigh these potential benefits with the financial and

space requirements of a proton beam. Although there is strong evidence for advantages in pediatric patients [56], there continues to be debate in other diseases such as prostate cancer [57]. Clinical trials are ongoing to identify the optimal radiation modality in various clinical scenarios [58].

Conflict of interest

The Authors declare no conflict of interest.

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Section 2

Design and Structure of a Proton Facility

Chapter 2

Proton Therapy Center Layout and Interface

Ameer L. Elaimy, Linda Ding, Jonathan Glanzman, Lakshmi Shanmugham, Beth Herrick, Jody Morr, Dan Han, Jeffrey C. Buchsbaum and Thomas J. FitzGerald

Abstract

Due to space requirements and a substantial financial burden, the feasibility of health systems adopting proton therapy has been called into question. However, advances in facility design and treatment delivery have allowed institutions offering proton therapy to reduce footprint while incorporating technological improvements at reduced costs. As the number of centers and patients treated continue to increase, this chapter will review the layout and interface of proton therapy facilities providing a detailed overview of the design, costs and faculty and staff considerations.

Keywords: proton therapy, layout, footprint, radiotherapy

1. Introduction

The use of proton radiotherapy in oncology has gained renewed interest in recent years. The unique physical properties of protons and potential applications in radiation oncology were initially recognized by Robert Wilson in 1946 [1]. Soon after, the first patients were treated with proton therapy in the 1950's at the Lawrence Berkeley Laboratory [2]. Throughout the 1950's to 1970's, other institutions including the Harvard Cyclotron Laboratory, the Gustaf Werner Institute in Uppsala, Sweden and several facilities in Russia pioneered seminal studies that provided important insight demonstrating the advantages of proton therapy in the treatment of patients with cancers of the brain, eye, head and neck and skin [3–17]. This laid the groundwork for the transition of proton facilities from research institutes into hospital settings. Loma Linda University Medical Center was the first to accomplish this in the 1990's [18]. Since that time, the number of proton therapy centers and patients being treated worldwide has substantially increased [19].

As the demand for proton therapy has amplified, several vendors and facilities have attempted to address these needs through the development of new technology that reduces dose to surrounding structures. One such example is the advent of pencil-beam scanning that limits entry and exit dose to targets of large volume while achieving superior conformity when compared to photon therapy [20]. Although the use of proton therapy has increased with more centers being constructed in the United States and throughout the world, questions remain regarding core patient cohorts that will benefit from its use. Moreover, the clinical

scenarios where the dose distribution advantages will provide better outcomes are still being elucidated [21]. This has led to hospital facilities questioning whether these potential benefits outweigh the financial and space requirements of a proton therapy center. Vendors have responded by supplying cutting-edge equipment, treatment planning systems, variations to existing proton beams and determining new ways to limit space. This has led to further innovations in proton therapy systems and a smoother integration with departments of radiation oncology and their existing photon system network.

In light of the continued evolution regarding footprint of proton therapy centers, this chapter will discuss facility design and equipment interface in order to provide an overview of the applicability of hospital-based proton systems.

2. Vendors

Mevion Medical Systems, IBA (Ion Beam Applications S.A.) Proton Therapy, Hitachi and Varian Medical Systems are the major proton therapy manufacturers throughout the world. Each vendor offers unique and advantageous proton therapy technology that allows health systems to construct a proton facility based on their specific requirements.

Mevion Medical Systems has developed many proton facilities throughout the United States with the most prominent located at the S. Lee Kling Proton Therapy Center at Siteman Cancer Center of Washington University School of Medicine and Barnes-Jewish Hospital [22]. Mevion developed the S250 proton accelerator system, which is a superconducting synchrocyclotron with a gantry-mounted proton source that rotates 190 degrees around the patient to facilitate optimal beam access. Specifically, the S250i series incorporates pencil-beam scanning for intensity modulated proton therapy by using a low-profile multi-leaf collimator system. For high volume proton centers, the S250MX system offers multiple room configurations and independent gantries.

IBA has established itself as an industry leader in proton therapy and has constructed numerous facilities throughout the world [23]. The Proteus system by IBA is also synchrocyclotron-based with the ability of pencil-beam scanning for intensity modulated proton therapy but incorporates a compact gantry that rotates 360 degrees around the patient. The general layout of a proteus-based treatment room consists of an open treatment enclosure, gantry rolling floor and in-room imaging control that, together, is about the size of two linear accelerator vaults. The reduced footprint and freedom in treatment plans are highly favorable characteristics for both hospital facilities and physicians.

Hitachi is also a leader in proton facility development as evidenced not only by the success of the University of Texas MD Anderson Cancer Center, but by several centers in Japan [24]. Hitachi offers a low footprint synchrotron with variations in gantries, which include full-sized 360-degree, compact 360-degree and 190-degree options. The type/s of gantry selected can be constructed into single room or multi-room designs to deliver intensity modulated proton therapy and real-time image gated proton therapy.

The development of the ProBeam 360 by Varian Medical Systems uses a superconducting cyclotron and 360-degree gantry to deliver intensity modulated proton therapy in single or multiple room configurations [25]. Each vendor offers effective technology that limits footprint, which leaves health systems options to determine number of treatment rooms, 360 vs. 190-degree gantry angle and if a synchrocyclotron, synchrotron or cyclotron is most appropriate for their needs.

3. Proton therapy center example-based layout

The design and layout of a proton therapy center is dependent on if it will be a part of a larger, hospital-based organization or a stand-alone facility. If a component of a radiation oncology department, then it will need to be determined if the proton therapy center will be located within the core department along with photon therapy equipment or at another location. Treatment rooms to be designed include the gantry, beam and control rooms as well as beam line and accelerator vault rooms, which include space for experimental setup and storage. As with any radiation oncology treatment facility, procedure rooms, examination rooms, reception area and administrative offices will need to be included in the overall layout.

The space requirements for a proton center are dependent on the number and size of treatment rooms as well as other medical and patient areas. The University of Texas MD Anderson Cancer Center proton facility was the first to be part of a National Cancer Institute (NCI)-designated comprehensive cancer center [26]. It is comprised of four rooms within a unit that is 96,000 total square feet. This includes a single beam room with two fixed horizontal lines, one for large volume targets and another for small volume targets (such as structures within the eye) while the other three rooms contain isocentric gantries. Proton therapy equipment at MD Anderson was acquired through Hitachi and treatment planning occurs through use of technology by Varian Medical Systems. Hitachi also developed the proton therapy center at St. Jude Children's Research Hospital, which consists of two rotating gantry rooms and one fixed horizontal beam room [27]. Proton therapy has demonstrated favorable results for several pediatric cancers [28], and this undertaking by St. Jude Children's Research Hospital further demonstrated the clinical importance of proton therapy for pediatric patients.

As mentioned above, IBA has constructed some of the largest proton centers in the country. The Roberts Proton Therapy Center at Penn Medicine is regarded as one of the world's largest centers, which offers both proton and photon therapy. It consists of four gantry rooms, a fixed beam room designated for treating conditions of the eye and a research room using the Proteus system by IBA [29] Similarly, the University of Florida Proton Therapy Institute is comprised of four gantry rooms and one fixed beam room, while the Francis H. Burr Proton Therapy Center at Massachusetts General Hospital has a fixed beam room for eye treatments and two gantry rooms [30]. Of note, the Francis H. Burr Proton Therapy at Massachusetts General Hospital initiated operations in 2002 after transfer from the Harvard Cyclotron Laboratory.

Another important example that highlights the versatility of proton facilities is the S. Lee Kling Proton Therapy Center at Siteman Cancer Center of Washington University School of Medicine and Barnes-Jewish Hospital, which was initiated in 2013 [31]. This system was the first gantry-mounted cyclotron and, accordingly, the first single-room proton center of its kind. The rotating gantry used by this system provides a platform for the beam to enter the treatment room from a 190 degree angle [31].

In 2020, the S. Lee Kling Proton Therapy Center expanded its operations through the addition of the Mevion S250i Proton Therapy System, which was installed directly next to the original system. This 1 + 1 expansion has substantial implications for limiting space requirements while increasing patient volume and delivering more efficient treatments, which incorporates Adaptive Aperture and Hyperscan technology. Of note, a collaboration between radiation oncologists at the S. Lee Kling Proton Therapy Center and Mevion Medical Systems have conducted research studying FLASH irradiation, which can deliver 200 Gy/s average dose rate

at the Bragg peak and has potential in achieving higher tumor control rates than previously reported [32]. Collaborations between vendors and proton facilitates not only has potential for advances in research but facilitates the incorporation of clinical considerations into improvements in technology and treatment delivery.

4. Cost

In addition to space requirements, another major factor for health systems to consider in the implementation of a proton therapy center is the financial burden. The cost of the construction, equipment, technological considerations and staffing must all be taken into account. Although proton therapy has demonstrated more favorable dose distributions when compared to photon therapy [21], determining specific patients within a department of radiation oncology who are most likely to benefit may be a challenge. Moreover, it may also be helpful for health systems to consider the vicinity of other proton therapy centers and how this might affect their patient base.

Proton therapy centers have been reported to cost up to 235 million USD [33]. However, since vendors have developed technology that substantially reduces footprint, this has led to more feasible costs for health systems. Of course, this is dependent on the size of the facility, number of treatment rooms as well as if they are fixed-beam or gantry. In more recent years, proton therapy centers have been reported to cost closer to 25 million USD, which makes the cost/benefit analysis more reasonable for health systems. Perhaps not surprisingly, proton treatments have been reported to cost more than photon treatments [33], and this should also be considered when assessing facility returns and navigating the insurance process.

5. Faculty and staff considerations

Optimal efficiency of a proton therapy facility is dependent on an expert staff and smooth transition for patients during each aspect of their treatment (check-in, waiting area, consult rooms, on-treatment visit (OTV) rooms, simulation, mold preparation, and guidance to a treatment room being used for a patient's specific condition). Due to the generally large space of a proton center and the technical complexities it requires, having well-trained faculty and staff is imperative for execution of day-to-day operations. This includes physicians, physicists, dosimetrists, radiation therapists, radiation oncology nurses, machinists, operations engineers and administrative staff. The number of faculty and staff at a given time will depend on the size of the facility, number of patients being treated and quality assurance protocols for the specific equipment being used.

As photon therapy delivery requires specific training and experience, this is also the case with proton therapy. However, several potential challenges, which include the intricate details of proton therapy and lack of experience by faculty and staff predominately trained in photon techniques may result in a new proton center encountering delays and issues when it treats its initial set of patients. To minimize these potential issues, it may be helpful for radiation oncology departments who plan to construct a proton center to encourage faculty and staff to enroll in courses to familiarize themselves with the technical details and workflow. Organizations including the Particle Therapy Co-Operative Group and European Society for Radiotherapy and Oncology as well as institutions including the University of Pennsylvania, University of Texas MD Anderson Cancer Center and Mayo Clinic

have offered courses, seminars and workshops to educate those who plan to or are currently involved in administering proton therapy.

6. Conclusion and future directions

As proton therapy evolves and become more prevalent, advances in facility design and treatment delivery are likely to continue that will make it more feasible for health systems to consider adopting. Vendors have responded by developing more affordable systems that reduce footprint while offering flexibility in number of fixed-beam or gantry treatment rooms. Pencil-beam scanning and variations in gantry angle are other advances that have shown considerable promise. Together, when also considering the favorable dose distributions of proton therapy, it is likely that the number of institutions offering proton therapy will continue to rise.

Going forward, it is critical that proton therapy facilities, vendors and physicists and engineers in both academia and the private sector continue to form collaborations that improve treatment delivery and imaging technology while reducing footprint. As proton therapy facilities gain more experience by treating larger numbers of patients, the knowledge they acquire should be relayed to vendors in order to improve patient care, develop more effective equipment and maintain a high-standard of quality assurance. Vendors should continue to have smooth processes that replace or upgrade outdated equipment. As always, questions and ideas should continue to be shared in society meetings, educational sessions and other forums.

Conflict of interest

The Authors declare no conflict of interest.

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Section 3

Clinical Trials in Proton Therapy

Chapter 3

Multi-Institutional Data Collection and Analysis via the Pediatric Proton/Photon Consortium Registry

Nicholas J. DeNunzio, Miranda P. Lawell and Torunn I. Yock

Abstract

Care of patients with proton therapy has increased in the past decade. It is important to report on outcomes and disease specific utilization of particle therapy. In this chapter, we review our experience in developing a registry for pediatric patients treated with radiation to assess outcomes and provide a platform for shared research interests.

Keywords: Pediatric cancer, radiation therapy, particle therapy, proton registry

1. Introduction

Pediatric cancers comprise a simultaneously rare but highly varied cadre of diseases. They account for less than 1% of all new cancer diagnoses made in the United States each year with nearly 17,000 projected in 2020 for patients under 20 years of age [1]. These can be classified as liquid tumors (leukemias and lymphomas) and solid tumors originating in central nervous system (CNS) and non-CNS sites. While many patients undergo radiotherapy (RT) as part of standard disease management, a significant portion of treatment paradigms does not include RT outright or requires RT to the entire body (e.g. total body irradiation in conditioning for stem cell transplants in patients with leukemia), thereby obviating the need for highly technical delivery methods such as proton radiotherapy (PRT). The number of patients available for study, therefore, is substantially less such that studying treatment outcomes is challenging and limits the ability of any one radiation center to amass clinical data and generate timely empirical results.

Survival and toxicity outcomes associated with PRT, as with photon radiotherapy (XRT), can be obtained through inquiries ranging in quality from single-institution retrospective studies to prospective randomized phase three clinical trials. However, in the pediatric population, randomized trials are not feasible given lack of equipoise among parents of patients and caregivers between proton- and photon-based radiation. In addition, low disease prevalence, varied disease management options, and varied anatomic sites can result in limited data availability. Consequently, collaboration among institutions is needed to obtain a critical mass of data that enables meaningful outcomes research. Children's Oncology Group (COG) and the International Society of Pediatric Oncology (SIOP) are cooperative

groups that work together to try to answer critical treatment-related questions on the more common pediatric malignancies. However, access to cooperative group data for ad hoc studies is limited, even among cooperative group members. Furthermore, these groups are focused on primary disease-specific endpoints and typically do not prioritize the collection of data on health outcomes and morbidity that can affect health-related quality of life. Importantly, COG has a registry called Project:EveryChild that attempts to capture limited information and biological specimens on all patients with a pediatric malignancy or benign tumor. However, the only information collected on RT is whether a patient was treated with it but no information on dose, site, timing of radiotherapy, or other factors that can play a role in disease control and other health outcomes [2].

To address these challenges, the Pediatric Proton/Photon Consortium Registry (PPCR) was initiated in 2010 [3–5], first focusing exclusively on studying clinical outcomes after PRT. Herein we describe the PPCR's administrative structure and processes, collected data (including patient demographics), and our vision for how the PPCR may further evolve.

2. PPCR overview

The PPCR is a consented registry established by and centrally coordinated through a team at Massachusetts General Hospital (MGH). Nineteen institutions are currently contributing data while 11 are in the process of joining [6]. Pediatric patients treated with radiation prior to 22 years of age are offered enrollment and all treatment exposures and baseline patient health and tumor characteristics are collected. The registry also tracks survival and treatment-related toxicity for all and patient-reported quality-of-life (PedsQL) data on a voluntary basis at 14 institutions. The PPCR enrolled its first participant in October, 2012 and was initially designed to collect data on the pediatric proton cohort. Then in 2018, after input from the National Cancer Institute (NCI) and various stakeholders, patients treated with any radiation modality became eligible to enroll. The PPCR was jointly funded by the NCI/MGH Federal Share of Proton Income research fund until 2019 and is now funded predominantly through MGH research funds and philanthropic donations.

2.1 Site acquisition

All radiation centers that treat pediatric patients are welcome to join, although current laws hinder some centers from joining among those based outside the United States, Canada, and Australia. Once clinicians at an institution express interest in participating, they are provided the current protocol, informed consent form, financial disclosure form, signature and delegation of responsibilities logs, and investigator agreement. The interested investigator(s) will then begin the regulatory proceedings needed to open the study at their institution. Unlike involvement in other registries and cooperative groups, there is no central cost to join though institutions are responsible for supporting the staff needed to complete study-related tasks.

2.2 Team composition

The coordinating team at MGH consists of five individuals: principal investigator (PI), project manager, biostatistician, and two clinical research coordinators (CRC). The coordinating team is responsible for central registry oversight and

reporting, patient registration, database management, monitoring, and quality assurance. Individual site team composition is dependent on available resources and ranges from a single physician up to a staff of eight. Notably, limited institutional resources is the most commonly reported barrier to participation.

2.3 Regulatory structure

Each site uses its own Institutional Review Board (IRB) and abides by its own institutional regulations. The site's protocol and consent forms are approved by the coordinating team at MGH. Eight centers use the Western Institutional Review Board, Inc., in lieu of a local IRB. To streamline ongoing review and protocol changes, the coordinating team compiles study changes into a single annual amendment submission that is implemented study-wide.

2.4 Consent and enrollment

All children and young adults (<22 years of age) who receive radiation at one of our participating institutions are eligible and invited to enroll. For this minimal-risk study, informed consent may be obtained by any member of the study team (e.g. CRC, research nurse, advanced practice provider, physician/PI) and must be obtained prior to completing any study-related procedures. Most patients are enrolled at some point during their primary treatment, although prior radiation treatment does not exclude them from being eligible. PedsQL study consent is sought in the first week of treatment to facilitate timely completion of the baseline survey. All patients are centrally registered at the coordinating center and assigned a study identification number (SIDN). The registry's goal is to capture all pediatric patients treated with RT. However, some patients decline to enroll, which can introduce bias in the collected data. To mitigate this effect, basic, non-identifying demographic information is gathered on patients who decline to participate, including their reason for doing so. This facilitates identifying barriers to registry enrollment and meaningful disparities between participants and patients who do not consent. Participants remain on study until death, withdrawal of consent, or study termination.

2.5 Data infrastructure and collection

Clinical data and patient-reported outcomes are collected and managed using the REDCap platform available through the National Institutes of Health [7–9]. This is a no-cost, web-based software platform for collecting and managing data and administering online surveys. Each study site is assigned its own data access group and can only see records entered by users within this group.

Participants are entered into the database using their assigned SIDN. Data are collected at the following time points, each with its own specifications: baseline (pre-RT), during treatment, and follow-up. A total of 1,604 data variables provide information on demographics, diagnosis and associated genetic factors, imaging dates and results, all cancer-related treatments, survival outcomes, and all treatment-related toxicities. Question formats allow for quantitative and qualitative responses and include drop-down boxes, radio buttons, check-boxes (multiple selections), text with validation (dates, numbers), and text without validation. Branching logic streamlines data input by displaying relevant data variables based on prior selections. Radiation plans (inclusive of planning scan, contours, and dose files) and pertinent diagnostic imaging (e.g. magnetic resonance imaging) are collected and managed using MIM Software Inc.'s MIMcloud (Cleveland, OH; [10]), which is a

secure internet-based file transfer service. Files that are uploaded to MIMcloud are anonymized by SIDN and then stored on a centrally housed server that is maintained by the coordinating center.

PedsQL Core Module surveys, added in September, 2015 as a voluntary component of the PPCR, collect data on physical, emotional, social, and cognitive functioning [11, 12]. Surveys are administered to patients at the beginning and end of treatment, and annually thereafter. For patients under five years of age, surveys are completed by the parent only. For patients aged 5–18 years, both the parent and child complete the surveys. For patients over the age of 18, no parental survey is given. REDCap's survey functionality allows participants to complete the survey electronically as well as receive a secure link by email or text to access follow-up surveys. This REDCap function directly deposits the patient's responses into the database, thereby obviating the need for manual data entry.

Each site has permission through the consent process to contact their site's participants, families, and home physicians to request outside medical records and update the database. This is critical as proton therapy centers are quaternary referral centers and the majority of patients return to their home institution for continued oncologic care, which makes longitudinal follow up more difficult [13].

2.6 Data safety and monitoring

All data entered into REDCap are monitored for timeliness of submission, completeness, and adherence to protocol requirements. Ongoing monitoring procedures include: (1) review of all participant consents and study eligibility at registration; (2) database review for discrepancies and potential errors; (3) remote or on-site monitoring; (4) monthly reports that identify missing data that are vital to the integrity and completeness of the dataset and are subject to a higher standard of data monitoring.

2.7 Data usage

All institutions have unfettered access to their own data and can use their data for operational planning, quality purposes, or research purposes. Data can be extracted manually or via REDCap's built-in reporting features. For use of multi-center data, investigators may submit a "Request for Data" (RFD) through a REDCap questionnaire. RFDs are then reviewed by the PPCR coordinating center and each site PI. Each PI can decide whether to include their site's data in the requested project. Data are available for investigator-initiated research and for investigators wishing to partner with the PPCR to answer questions in pediatric oncology.

3. Data and patient characteristics

This collaborative effort aims to expedite investigations into and understanding of pediatric patient survival, treatment toxicity, and impacts on quality of life after RT by pooling data from multiple institutions and making them available for study to participating investigators. Data are qualitative and quantitative in nature, inclusive of patient demographics, dosimetric statistics of the radiation target and healthy tissues, and neoadjuvant and/or adjuvant treatments that are administered as part of standard comprehensive cancer care. In addition, dose distribution data are curated, which are critical in providing a higher level of granularity in dosimetric studies.

To date, the PPCR has enrolled more than 3,200 patients, with a steady annual accrual of about 450 patients in recent years. Notably, the COVID pandemic has

slowed accrual in 2020 due to the various institutional responses that put non-COVID research on hold to focus attention on the health crisis. Patients have a median age of ten years and are mostly residents of the United States (76%), male (57%), White/Caucasian (71%), and non-Hispanic/Latino (71%) (**Table 1**, **Figures 1**, **2**). RT has been delivered using protons in 99% of participants, reflecting that the bulk of institutions that joined were proton centers prior to 2018 when enrollment criteria

	Total (n = 3260)
Characteristics	
Age at RT (years)	9.74 (<1–27.7)
Sex	
Male	1860 (57.1%)
Female	1400 (42.9%)
Race [α]	
Black or African American	242 (7.4%)
Arabic/Middle Eastern	35 (1.1%)
Asian	171 (5.2%)
White/Caucasian	2329 (71.4%)
Native American/Alaska Native	16 (0.5%)
Native Hawaiian or Other Pacific Islander	11 (0.3%)
Unknown/Not Specified	425 (13.0%)
Other	29 (0.9%)
Missing	42 (1.3%)
Ethnicity	
Hispanic or Latino	353 (10.8%)
Not Hispanic or Latino	2305 (70.7%)
Unknown or Not Reported	602 (18.5%)
United States Residency[β]	
United States	2461 (75.5%)
Non-United States	542 (16.6%)
Not Reported	257 (7.9%)
Tumor Site	
CNS	1929 (59.2%)
Non-CNS	1299 (39.8%)
Missing	32 (1.0%)
Radiation Modality[α]	
Protons	3238 (99.3%)
Photons	188 (5.8%)
Electrons	7 (0.2%)

[α]*Totals sum >100% due to multiple selections per patient.*
[β]*Due to IRB restrictions, patient residency is not reported for some patients.*

Table 1.
Characteristics of PPCR participants.

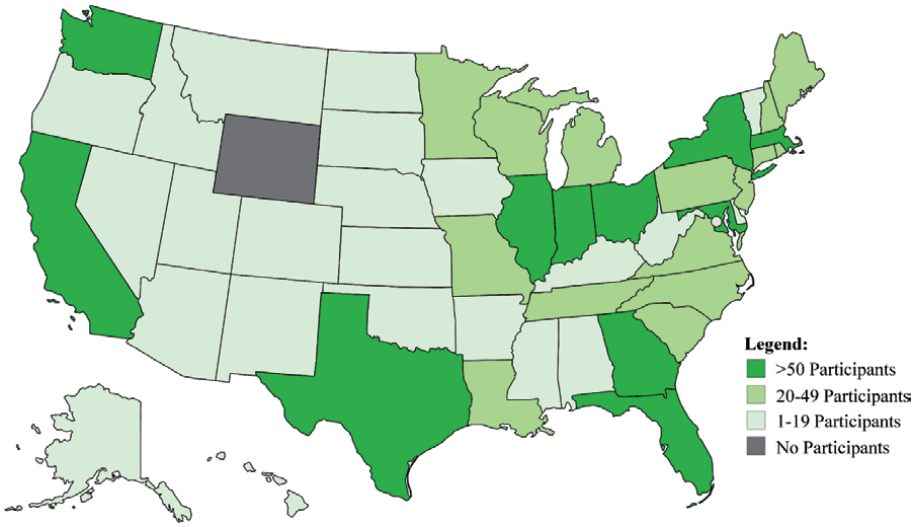

Figure 1.
Participant residency by state in the United States.

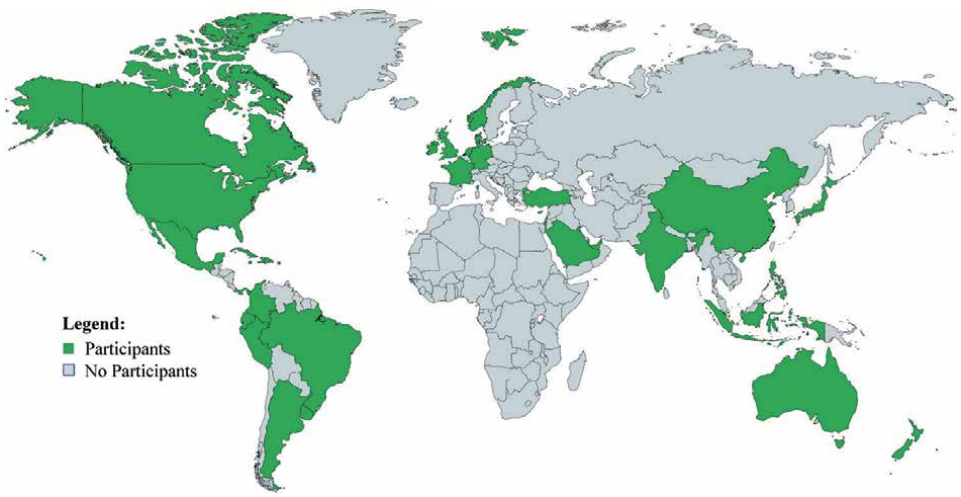

Figure 2.
Participant residency by country.

became agnostic of radiation modality. Nearly 60% of the tumors treated in this cohort originated in the CNS (**Table 1**, **Figure 3**), which is the most common site of solid tumors in the pediatric population.

Since its inception, the PPCR's structure and scope have developed and expanded to adapt to the ongoing treatment landscape to address this unmet need within pediatric radiation medicine. For instance, in 2018 patients treated with XRT were made eligible for enrollment [14]. Incorporation of these data will facilitate photon/proton comparison studies that are critical for better understanding the strengths and weaknesses of PRT. This is especially true for developing dose constraints for organs at risk as these may not be identical across RT modalities. Such is the case for the brainstem, whose PRT dose limit was reduced on the most recent COG ependymoma protocol (ACNS0831). While the topic is controversial, there is some concern that there may be an increased risk of brainstem injury with PRT compared to XRT using a typical relative biological effectiveness dose conversion of 1.1 for PRT [15–18].

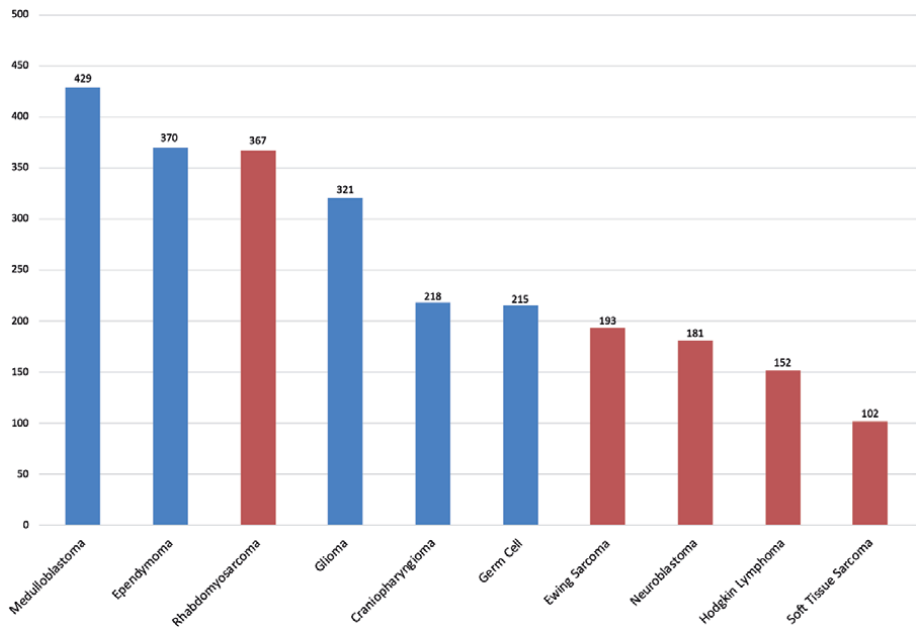

Figure 3.
Histogram showing the ten most-represented histologies in the PPCR. CNS tumors are shown in blue and non-CNS tumors are shown in red.

4. Future objectives

The PPCR has established a centralized, collaborative, and adaptive framework for data acquisition in pediatric patients receiving RT, with respect to treatment parameters and quality of life. This registry resource is now robustly able to better evaluate differences in practice patterns, dosimetric changes, and the clinical impacts of the treatments we deliver. The platform we have created is now being leveraged by the Epidemiology branch of the NCI to allow for large-scale cohort research. Furthermore, the PPCR study staff are also participating in the larger effort of the Childhood Cancer Data Initiative [19] recently started to accelerate the speed of research with the ultimate goal of improving cancer treatment and outcomes for pediatric patients.

Looking forward, we aim to continue to expand the network of participating institutions not only domestically, but also internationally - first into Canada and Australia and then into other countries that allow sharing of de-identified data. This will not only serve to continue to amass data for rare tumors for which single-institution studies are simply not feasible, but will also yield insights into variations in practice patterns and which treatment regimens are the most effective and safest. In addition, the dynamic nature of the registry facilitates incorporation of data from other treatment modalities (e.g. FLASH radiotherapy, other particle therapies, etc.), much like how photon-based treatment data have been incorporated recently. This will further expand our understanding of how to best manage pediatric malignancies by adapting data acquisition to ongoing technologic developments and changes in practice patterns. We encourage all to use this resource to improve cancer care and outcomes for pediatric cancer patients undergoing treatment as well as those who have completed therapy.

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Chapter 4

Credentialing Proton Centers for Clinical Trials

Paige A. Taylor

Abstract

This chapter will provide an overview of quality assurance processes to credential proton therapy centers for clinical trial participation. There are a number of credentialing audit steps, including independent output verification, anthropomorphic phantom audits, image guidance credentialing, knowledge assessments, and on-site dosimetry review. The purpose of these credentialing steps is to ensure consistency across proton centers participating in clinical trials, and well as comparability with photon centers for randomized trials. This uniformity ensures high quality data for measuring patient outcomes, which are pivotal at a time when proton therapy is being assessed for superior outcomes.

Keywords: proton therapy, quality assurance, credentialing, Imaging and Radiation Oncology Core, phantoms, dosimeters, image guidance, benchmarks, audits

1. Introduction

1.1 Importance of clinical trial quality assurance (QA)

Clinical trials are designed to give us confidence in a course of care. For cancer treatment, clinical trials have played a crucial role in the advancement of treatment for a variety of disease sites over the last century. As discussed in the chapter on clinical trials, there are a number of active protocols seeking to better understand the role of proton therapy within modern radiotherapy. Clinical trials have varied points of emphasis and radiation therapy may be an important aspect of the trial but not the trial endpoint. Phase II and III trials often require many participants to reach a statistically significant conclusion. With limited numbers of patients of various disease sites seen at an individual institution, it is common for proton therapy trials to be conducted among multiple institutions. When a trial includes multiple institutions, variability in treatment practices increases. One way to minimize differences across participating centers is to require QA of the trial treatment. QA helps minimize deviations within trials, and can improve clinical outcomes such as overall and progression-free survival [1–4]. This is particularly important for many proton therapy clinical trials, as insurance companies want to see quantification of superior outcomes before agreeing to cover the cost of therapy.

1.2 National Cancer Institute (NCI) proton guidelines

In 2007, the NCI formed an ad-hoc panel of proton experts to outline guidelines for the use of proton therapy in clinical trials. The original guidelines included

recommendations about beam calibration protocol, relative biological effectiveness (RBE), target volumes, and clinical trial audits. The guidelines have been updated several times since then, most recently in 2019, to include requirements for modulated pencil beam scanning delivery, robust optimization, advanced treatment planning algorithms, and recommendations about clinical trial credentialing [5].

2. General proton approval

2.1 Output checks

Regular remote output checks are part of clinical trial QA around the world [6]. In the United States (US), output checks are required on an annual basis for all proton beams used in the NCI's National Clinical Trial Network (NCTN) protocols. The purpose of these QA audits is to verify the output of a uniform field. Typically institutions use their reference calibration (International Atomic Energy Agency Technical Report Series 398) field for this purpose. Use of the same field year after year can catch drifts in output or dramatic changes that may be caused by an error in calibration.

2.2 On-site audit

In addition to the remote output check, all proton therapy centers in the US receive an on-site dosimetry audit as part of the baseline approval process for clinical trial participation. With relatively few proton centers in the US (as compared to photon clinics), many personnel are coming to work at new proton facilities without prior experience with proton therapy. On-site audits are perhaps the most crucial component of proton approval, as they allow a deep dive into the dosimetry and clinical operations of a facility, and check for practice consistency across these new facilities.

The on-sites audit consists of a number of dosimetric measurements, including beam calibration, calibration equipment intercomparison, depth dose profiles, lateral beam profiles of reference and patient fields, imaging vs. radiation isocenter coincidence, and Hounsfield Unit (HU) – Relative Linear Stopping Power (RLSP) calibration. On-site audits allow for greater dosimetric accuracy and complexity than remote audits. Recommendations are made to the institution about how they can improve their clinical practice and make it more consistent with other proton centers on multi-institutional trials. The most common recommendation relates to the HU-RLSP conversion curve that institutions use to predict proton range within a patient [7, 8]. The curve is sensitive to errors at low densities (e.g. lung tissue) and variability is observed across institutions at both low and high densities. Accuracy of this calibration is critical to accurate proton beam modeling and by minimizing deviations in the calibration, treatment delivery deviations can also be mitigated.

The on-site audit also includes a review of clinical practices, covering topics like CT simulation and re-simulation over the course of treatment, patient immobilization, treatment planning and robustness evaluation, and image guidance. The goal is to ensure consistency across institutions, in an effort to minimize deviations on trials. For example, if an institution is not performing any kind of rectal sparing technique for prostate treatment, a recommendation might be made to investigate and adopt a technique in order to follow standard clinical practices. The machine QA practices are also reviewed to ensure compliance with recommended standards [9–12]. The proton QA standards are relatively new, so the review of QA practices provides useful feedback on ways to implement different tests, benefits and drawbacks of different equipment, and failure modes within the system.

3. Protocol-specific credentialing

3.1 Anthropomorphic phantoms

Anthropomorphic phantoms are one of the most robust options for remote audits of a radiotherapy modality. They encompass an end-to-end test of simulation, treatment planning, setup, and delivery of radiation. Proton therapy presents some unique challenges for phantom tests. The plastics typically used for QA of photon beams are not necessarily "tissue-equivalent" in a proton beam, thus appropriate phantom materials need to be tested to ensure they fall on a clinical proton HU-RLSP curve [8].

The phantoms currently available for proton credentialing test a variety of different clinical requirements: conformality (brain, head and neck (H&N), spine), organs at risk (OAR) avoidance (H&N, prostate), motion management (liver, lung), heterogeneities (lung, spine), and multiple targets (liver) [13, 14]. Proton anthropomorphic phantom credentialing has already led to improvements in accuracy of treatment dose calculations for clinical trials. The lung phantom credentialing for the Radiation Therapy Oncology Group's (RTOG) randomized proton vs. photon trial for non-small cell lung cancer (NSCLC) (RTOG 1308) found gross overestimates of dose when using an analytic algorithm for dose calculations in low-density heterogeneities [15]. The NCI has updated their proton therapy guidelines to require Monte Carlo or advanced algorithms for future trials with low density heterogeneities [5].

3.2 Image guidance

Image guidance is a crucial component of proton therapy because the beam range is dependent on the density of the material in its path. If you plan a field in soft tissue and then a bone is in the beam path at the time of treatment, you could entirely miss your target. Alternatively, if high density tissue is in the beam path at the time of planning but not at the time of treatment delivery, you risk delivering full dose to the tissue distal to the target. Most proton centers began by using orthogonal kV image guidance, but many now have in-room volumetric imaging capabilities with CT or cone-beam CT (CBCT) [16, 17].

There are many components of image guidance that are important to verify: image quality, geometric accuracy, imaging dose, imaging system communication, and safety [9–11]. Some of these components, like imaging dose and image-guided radiotherapy (IGRT) safety checks, are left to the institution's physics team to test. Other elements are verified through clinical trial credentialing. Many protocols require IGRT credentialing for both photon and proton therapy if "reduced margins" (typically less than 5 mm) are used. The IGRT credentialing requires submission of actual patient IGRT data for central review, as well as completion of a questionnaire outlining IGRT practices. The images are reviewed for registration to reference treatment planning data as well as consistency from day-to-day. The goal of this credentialing is to ensure consistency of IGRT processes and quality across institutions.

Of course, there could be accurate in-room images, but if the proton beam is not coincident with the IGRT isocenter, the accuracy of the beam delivery is negatively impacted. For this reason, the coincidence of the IGRT and proton beam isocenters is verified for proton therapy centers participating in clinical trials. This is done with a Winston-Lutz type test as part of the baseline approval process for clinical trial participation [18].

3.3 Motion management

Motion management is of particular importance in proton therapy due to the sensitivity of the beam range to changes in tissue density [19, 20]. Several anthropomorphic phantoms (liver, lung) assess the end-to-end process of motion management, but there are some clinical trials that also require a motion management questionnaire. This questionnaire assesses the standard clinical practices for assessing and accommodating target motion, such as the upper limit for motion magnitude, simulation practices, respiratory management system, and patient setup requirements. Many of these aspects are also reviewed during the on-site audit, so a separate motion management questionnaire for a specific clinical trial may not be necessary.

3.4 Knowledge assessments

A knowledge assessment asks questions about a clinical trial to ensure that participants have carefully reviewed the protocol and understand its requirements. Knowledge assessments are used for credentialing in a handful of NCTN clinical trials. Knowledge assessments can be useful for randomized proton vs. photon trials because there are intricacies of treating with two modalities, such as accounting for RBE, different definitions of target structures, and partnerships among multiple institutions. Unfortunately the knowledge assessment only captures the knowledge of a few personnel at a specific point in time, so it does not ensure that everyone involved over the course of the trial has carefully read the protocol. For this reason, most new NCTN proton clinical trials do not require knowledge assessments.

3.5 Benchmark cases

Benchmark cases have commonly been used for clinical trial credentialing [21, 22]. The objective is to have a standard sample case that all participants plan on. The reviewer can then assess quality of contours, beam arrangement, and target coverage. Often an independent dose recalculation is also performed to assess the accuracy of the institutions' treatment plan dose calculations. Benchmarks can be a great way to identify variability across centers and offer a platform to provide feedback to participants for improving their practices.

In addition to planning benchmark cases, there is also an image-fusion benchmark case that is used for some central nervous system (CNS) trials. The benchmark reviews an institution's fusion of CT and MR images. For proton therapy, this benchmark can be particularly useful. Proton therapy cannot be planned directly on MR images because the HU values from CT are required for beam range calculations, and the proton range is sensitive to anatomical changes, so proper fusion of MR and CT images is important for treatment delivery accuracy.

There are two challenges with benchmarks; one general and one proton-specific. There have been a few instances where a clinical trial required a benchmark and hundreds of institutions completed the benchmark, but then when it came to patient enrollment, only a small fraction of those initial institutions enrolled patients on-protocol. Reviewing benchmarks is time-intensive for the QA office and at times this method of up-front verification does not yield commensurate reward. For proton therapy specifically, the NCTN QA group does not yet have an independent dose calculation that can be used for all proton therapy centers, so benchmarks can only be used as a qualitative assessment rather than a quantitative one. For these reasons, clinical trial QA is shifting away from standard benchmark cases.

3.6 Pre-treatment, on-treatment and post-treatment review

In lieu of benchmark cases, many clinical trials are shifting toward pre-treatment or on-treatment review of actual patients enrolled in the trials. A pre-treatment review is the submission of the actual treatment plan for a patient intended to be treated on protocol. The plan is rapidly reviewed by clinical trial staff or volunteers and feedback is provided to the participating institution before the start of that patient's treatment. Most commonly, the contours, target dose coverage, and dose to critical structures are reviewed. For proton therapy, the beam arrangement and potential sources of range uncertainty are also evaluated.

The advantage of pre-treatment review is that it can reduce the number of protocol deviations. If an institution receives feedback about ways to improve one patient's treatment, this benefits the individual patient and can also benefit subsequent patients treated at the same institution. The biggest drawback of pre-treatment review is the time-sensitivity of the plan review. Typically the turnaround for such reviews is three business days, but sometimes this is done more quickly. This requires that there is always personnel available to review cases, and does not allow for the reviewer to batch reviews at a time convenient to them. To balance the demands of pre-treatment review, some protocols will require pre-treatment review for the first few (e.g. five) patients from an individual institution. Other trials might place a quantitative criterion for when to require pre-treatment review; one trial requires pre-treatment review if the high dose goal for the target is not met. This is a good compromise to allow early feedback to shape an institution's practices throughout the protocol.

On-treatment reviews, performed while the patient is being treated, can allow similar timely feedback as pre-treatment reviews. They are less time-sensitive, but can have a similar positive down-stream impact on subsequent patients treated by the same institution. Another benefit of the pre- and on-treatment reviews is they give the reviewers a chance to see common issues across multiple institutions, which can be addressed during investigator discussions during the trial and help ensure consistency as the trial moves forward.

Post-treatment reviews are typically performed for all plans, regardless of whether pre- or on-treatment reviews were performed. They assess many of the same criteria, as well as protocol compliance for duration of treatment time.

4. Conclusion

Independent peer review is an important component in clinical trials with radiation therapy, particularly in the emerging field of proton therapy. The credentialing efforts required by the NCI are a paradigm for other proton clinical trials. With the future of proton therapy relying on results of many clinical trials, it is important to get the basics right. Through standard checks of consistency and comparability, we ensure high quality trial data for strong statistical analysis of outcomes.

Conflict of interest

The author declares no conflict of interest.

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Chapter 5

Clinical Trials Evaluating Proton Therapy

Paige A. Taylor

Abstract

Although proton therapy was developed almost 80 years ago, widespread clinical implementation has been limited until the past decade. With the growing use of proton therapy, there is a desire to prove the equivalence or superiority of proton therapy across a number of cancer disease sites. Dozens of clinical trials have been developed to accomplish this within individual institutions, among a few centers, and across national and international networks such as the National Cancer Institute's National Clinical Trial Network. The protocols include proton therapy imbedded in trials with photon therapy as well as randomized photon vs. proton trials. This chapter provides an overview of the design of such trials as well as some of the challenges facing protocols with proton therapy.

Keywords: proton therapy, clinical trials, protocols, randomized, phase II, phase III, National Cancer Institute, National Clinical Trial Network

1. Introduction

1.1 Clinical trial importance

Clinical trials are an important step to ensuring the safety and efficacy of medical treatment. For radiation therapy, clinical trials have allowed us to look at important questions like dose escalation, fractionation, and new radiotherapy technologies. Much like the use of instensity-modulated radiation therapy (IMRT) was critically reviewed in the early 2000s, proton therapy has come under careful scrutiny over the past decade. Many radiation therapy departments commissioned proton therapy centers and began to integrate protons into their clinical practice.

1.1.1 Safety and efficacy

Most people who work in radiation therapy have seen the striking treatment plan comparisons between proton therapy and traditional photon therapy for a pediatric craniospinal case, noting the marked reduction in dose to organs at risk and normal tissue outside of the target region [1]. These in-silico studies are even more exciting given the potential reduction in secondary cancer for pediatric patients. The potential benefits in these studies come with corresponding risk; if the beam modeling or treatment delivery positioning is not accurate, there is a risk of high overdose to normal tissue or severe underdose of the target. For this reason, the National Cancer Institute (NCI), the American Society for Radiation Oncology (ASTRO), and other

groups have encouraged methodical, careful study of the clinical benefits of proton therapy through clinical trials [2].

The potential benefits of proton therapy are also complicated by the higher biological effectiveness of protons as compared with photons. The current clinical practice in the US is to use a relative biological effectiveness (RBE) of 1.1 for protons, but studies have shown that the true biological response is more complicated and variable [3]. While the higher RBE of protons is a potential benefit for killing tumor cells, there is potential increased biological risk to critical organs proximate to the target. Clinical trials with proton therapy can allow us to look at both sides of the coin by analyzing the correlation between RBE and clinical outcomes.

1.1.2 Evidence for insurance

Insurance companies have played a role in driving the development of randomized proton vs. photon clinical trials as well. Due to the higher up-front cost of proton therapy for many disease sites, insurance companies have asked for data showing marked improvement in survival outcomes for patients treated with proton therapy in order to cover treatment costs. As discussed later in the chapter, this presents a bit of a catch-22 in clinical trial accrual, as insurers are waiting for trial data to approve coverage, but trial data is nearly impossible to collect without insurance coverage for patients enrolled on-study.

1.2 Clinical trial landscape in the US

1.2.1 Clinical trial groups

The largest clinical trial system that supports proton therapy protocols in the US is the National Clinical Trial Network (NCTN), funded by the NCI. The NCTN is made up of four adult and one pediatric clinical trial groups, as well as a partnership with the Canadian Cancer Trials Group. Most of the proton therapy studies run through the NCTN are large-scale, multi-institutional Phase II and Phase III trials. These trials either randomize patients to proton or photon therapy to compare treatment outcomes or imbed proton therapy as a possible treatment modality in a study designed to answer a different clinical question. The NCI has also funded proton clinical trials outside of the NCTN [4–7]. These are often run by a single proton center "sponsor" in partnership with other proton facilities and funded through NCI grants.

Outside of the NCI, there are several other groups that help sponsor clinical trials for proton therapy. The National Association for Proton Therapy (NAPT) is a nonprofit group that helps facilitate proton therapy research collaborations. Most of the operational proton therapy centers in the US are members of NAPT. The Patient-Centered Outcomes Research Institute (PCORI) provides funding for clinical trials comparing proton vs. photon therapy for prostate and breast treatment. The NCI also has a Childhood Cancer Data Initiative (CCDI) that collects standard patient data, including proton therapy data, in a central repository for data sharing and analysis within the research community.

Outside of the US, several groups in Europe and Asia have proton therapy protocols open or in development. The Japan Clinical Oncology Group (JCOG) is funded by Japan's National Cancer Center Research and Development Fund and conducts studies with proton therapy [8]. The European Organization for Research and Treatment of Cancer (EORTC) operates clinical trials within Europe and currently has two protocols with proton therapy embedded [9]. The European Society for Radiotherapy (ESTRO) recently established the European Particle

Therapy Network (EPTN), which conducts a number of prospective studies looking at proton (and carbon) therapy, and works in concert with the EORTC [10, 11]. Global collaborations on clinical trials have been limited so far. The US has the largest catalog of proton therapy clinical trials and has sought participation of international proton centers, but the many steps to opening the protocols (NCTN membership, state department clearance, baseline approval quality assurance) have slowed down collaboration. The clinical trial groups are working on streamlining these processes to allow for expanded international partnerships in the future.

2. Randomized proton vs. photon trials

In order to move past in-silico studies that promise superior dosimetry with proton therapy, clinical evidence is needed. One of the best ways to get these data are through randomized clinical trials. For proton therapy trials, randomization is generally structured with two arms: proton vs. photon. In order to get enough patients for statistical significance, these trials require a lot of patients (usually hundreds) and are typically run as multi-institutional studies. These large randomized studies may be designed to show superiority of proton therapy or to demonstrate non-inferiority [12]. Most NCTN randomized proton vs. photon trials have a primary endpoint of assessing overall survival. Secondary endpoints include progression-free survival, local control, toxicities, cognitive outcomes, symptoms burden, quality of life, cost effectiveness, and cost–benefit economics. While proton therapy generally has a higher up-front cost, it is hypothesized that proton therapy may be more cost-effective for some disease sites due to reduction in acute and long-term toxicities and associated medical costs.

Typically NCTN clinical trial data is only assessed for objectives explicitly listed in the protocol and analysis outside the original scope is only permitted after the trial has been closed several years. For this reason, somewhat indefinite exploratory objectives are written into the protocol to allow for analyses that may not be understood at the time of protocol development. For randomized proton vs. photon trials within the NCTN, exploratory objectives include biospecimen and imaging data collection for the assessment of biomarkers.

Most randomized proton vs. photon studies randomize 1:1, though some protocols have randomize 2:1 in favor of proton therapy. The two arms typically have the same radiobiological dose prescription, though some studies like NRG Oncology/RTOG 1308 have low dose and high dose arms.

2.1 Challenges of randomized proton vs. photon trials

Clinical trials can be challenging for a number of reasons - increased personnel effort to coordinate patient enrollment and data submission, increased operational costs, low patient interest, and low physician engagement – but randomized proton vs. photon trials face a number of unique challenges.

2.1.1 Treatment planning

One unique aspect of proton vs. photon trials is that it is common to create treatment plans for patients using both modalities to ensure that both can meet the planning dose constraints required by the protocol [13]. This may require increased time on the part of the participating institutions, though many proton centers may already be creating double plans for insurance purposes.

Treatment planning itself is different between proton therapy and photon therapy. The planning target volume (PTV) that is commonly used for photon plans is generally not used in the same way for proton therapy. Instead of uniform expansion from clinical target volume (CTV) to the PTV, proton treatment plans may have one pre-defined lateral margin, and a different margin in the direction of the beam range that depends on the maximum beam energy [14, 15]. In this way, the proton "PTV" is beam-specific. This presents a challenge for clinical trial data analysis, as most protocols are written with historical photon PTV constraints. Future protocols should be designed with this in mind.

Furthermore, proton therapy treatment planning has started to shift away from the standard lateral and range margins in favor of robust optimization of the CTV [16, 17]. There are many different ways to report dose when using robust optimization (e.g. voxel-wise worst-case approach, scenario-wise worst-case approach, delivered dose variance) [18]. Clinical trials should soon consider how robustly optimized treatment planning data will be collected to ensure appropriate data comparison between the proton and photon arm. This highlights the crucial role that physicists and data (i.e. Digital Imaging and Communications in Medicine (DICOM)) experts play in the development of clinical trials.

In addition to the nuances of physical dose, randomized proton vs. photon trials need to consider the implications of radiobiology. The NCTN currently uses an RBE of 1.1, but many proton centers are starting to consider variable RBE in their treatment planning practices [19, 20]. If variable RBE treatment planning becomes standard, clinical trials will need to incorporate it into treatment planning constraints, and determine what patient data needs to be collected to appropriately compare different treatment plans.

2.1.2 Patient preference

One challenge with randomized clinical trials comparing proton therapy with photon therapy is patient preference. This manifests when a patient is randomized to one arm but has a strong desire to be treated on the other arm, and thus goes off protocol. Patients randomized to the photon arm may decide they want proton therapy instead due to an impression gathered through independent online research or a preference for the "latest and greatest" technology. Conversely, some patients randomized to the proton arm may go off protocol to receive photon therapy due to mistrust of a new, "unproven" technology.

2.1.3 Insurance denial

Another challenge of proton trial accrual is insurance denial for proton therapy [21]. This is particularly challenging in the case of randomized proton vs. photon trials because it can make it harder to reach accrual goals on the proton arm of the protocol. Insurance denials of proton therapy can also skew the patient demographics of the proton arm. For example, Medicare is significantly more likely to cover proton therapy than private insurers, which can skew the age of the proton cohort toward older participants [22]. This older patient cohort might have comorbidities or other characteristics that make it challenging to compare outcomes data between the two arms. Lastly, the process of appealing insurance denials can lead to delays in the start of radiation treatment [23]. Clinical trial patients may already wait slightly longer for treatment to start due to clinical trial requirements such as pre-treatment reviews of the treatment plan. These delays might result in a patient going off trial to pursue treatment sooner.

One way to counteract the deleterious effect of proton insurance denial on randomization is to use a 2:1 randomization in favor of proton therapy. This gives the trial more opportunities to accrue proton patients, even if insurance challenges persist. But most proton centers choose to challenge insurance denials, and the best way to combat insurance denial is through support networks and sharing of resources. The NAPT offers a guide for patients on steps to deal with insurance denial, many of which are applicable to clinical teams as well [24]. Many proton centers have dedicated personnel to manage insurance appeals. For the NCTN, proton insurance denials are a frequent topic at operations management and proton working group meetings. These forums allow physicians to share successful techniques to overcome insurance barriers. Physicians have banded together to publish pleas for insurance companies to change the insurance approval process for proton therapy [25]. Some proton therapy centers have negotiated with insurance companies to reimburse proton therapy at the cost of IMRT, picking up the rest of the costs themselves [25]. The NCI has also advocated on behalf of proton therapy centers in the context of clinical trial insurance reimbursement for randomized NCTN protocols [26].

2.1.4 Logistics of partnerships with proton centers in other cities, countries

Due to the limited number of proton therapy centers, many randomized proton vs. photon trials encourage partnerships between one proton center and any number of photon clinics. There are many considerations when establishing a partnership between two institutions, such as who gets "credit" for the clinical trial accrual, how clinical trial reimbursement is allocated between the institutions, which personnel have rights to upload patient data to the appropriate portals, etc. There is a possibility that a photon clinic might partner with a proton center in another country. In this case, the logistics of travel reimbursement (if provided) should be addressed, as well as clinical trial membership and state approval if the trial is run through the NCTN. This type of partnership may become increasingly common as clinical trials for carbon therapy are being developed, with most carbon centers located in Europe and Eastern Asia. A few concepts have been proposed that randomize IMRT treatment to centers in the US, and carbon therapy to centers abroad [27].

3. Imbedded proton trials

In addition to randomized proton vs. photon clinical trials, there are a number of trials that imbed proton therapy as one of several allowed treatment modalities. This practice was most common this past decade in pediatric trials, such as those conducted by the Children's Oncology Group (COG), but has been applied to adult trials as well. While the superiority of proton therapy outcomes might not be the primary endpoint of these studies, the hope is that with enough data, secondary analyses can be performed to look at proton patient cohorts compared to others.

3.1 Pediatric trials

To date, the standard method of including proton therapy in pediatric clinical trials has been to imbed protons in the protocols. The strategy recognizes the challenges of accrual to disease-specific radiation therapy protocols in pediatric patients and permits parallel treatment strategies for both photon and proton care to

successfully manage the study. Approximately 50% of pediatric malignancies are in the leukemia domain, therefore protocols requiring radiation therapy are directed to tumors of the central nervous system, sarcoma, renal, orbit including retinoblastoma, and lymphoma. Therapy volumes and target dose are uniform between proton and photon care with guidelines imbedded in the study to insure synergistic care for tumor control acknowledging subtle differences in planning target volumes and dose distribution to normal tissue. Both proton and photon patients need to meet the identical dose to tumor and normal tissue. Dose to normal tissue in most situations is more easily achieved with proton therapy. In pediatric studies, outcome analysis including imaging are part of the longitudinal aspect of protocol management, therefore colleagues in the COG and the Imaging and Radiation Oncology Core (IROC) can evaluate normal tissue endpoints with outcome imaging validation to review comparison plans in retrospect to acquire important outcome analysis for secondary study endpoints between proton and photon care.

One challenge pediatric trials have faced is the apparent racial disparities between who receives proton therapy, with non-Hispanic white pediatric patients significantly more likely to be treated with protons than black patients [28]. This presents a challenge to proportional racial representation in clinical trial data.

3.2 Adult trials

In the US, adult clinical trial groups have imbedded proton therapy in dozens of clinical trials. At times, proton therapy has been added through clinical trial amendments with the hope of boosting accrual to protocols struggling to accrue patients. For a number of reasons (small number of proton centers, insurance denials, competing proton-specific trials), this has not proven to be the silver bullet, however, and generally it's not recommended to add proton therapy as an allowable modality solely to improve trial accrual for adult protocols. Despite lower accrual numbers, proton therapy can be a good addition to a trial, adding the possibility of secondary analyses to look at proton therapy outcomes in relation to other treatment modalities.

4. Proton therapy registries

Outside of prospective clinical trials with proton therapy, there are a number of proton therapy registries. These are generally less structured than Phase II/Phase III trials and allow for more flexibility in which data are analyzed. The Proton Collaborative Group (PCG) is a registry of nearly six thousand proton patients in the US [29]. The PCG looks at survival outcomes and quality of life, and fosters peer review collaboration across centers for clinical trial development. The Pediatric Proton Consortium Registry (PPCR) is a multi-institutional collaborative registry of demographic and clinical data for pediatric patients treated with proton and photon therapy [30]. The goal of the PPCR is to compare benefits of the two radiotherapy techniques, such as disease outcomes and quality of life. Washington University School of Medicine and Radialogica, LLC have a Proton Therapy Registry for adult and pediatric patients that collects clinical and dosimetric data [31].

5. Conclusions

Proton therapy has great potential and in some cases, proven clinical benefit. The best way to gather evidence to secure proton therapy as a standard of care for

cancer treatment is through thoughtful, controlled clinical trials. Much work has already been done to this effect, and with so many clinical trials for proton therapy currently accruing, we will soon have data to answer the myriad questions related to proton therapy treatment outcomes.

Conflict of interest

The author declares no conflict of interest.

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Chapter 6

Adaptive Proton Therapy in Head and Neck Cancer

Nagarjuna Burela

Abstract

Anatomic and dosimetric changes occur in head and neck cancer during fractionated proton radiotherapy, and the actual dose received by patient is considerably different from original plan. Adaptive radiotherapy aims to modify treatment according to changes that occur during proton therapy. Intensity modulated proton therapy for head and neck cancer (HNC) patients benefitted by adaptation to correct the dose perturbations caused by weight loss, tumor volume changes, setup and range uncertainties. The following sections have elaborated the rationale of adaptation in HNC, proton physics in HNC, studies comparing non-adaptive and adaptive intensity modulated proton therapy (IMPT) plans, reasons for adaptation and how to mitigate these changes.

Keywords: adaptative radiotherapy, proton, intensity modulated, head and neck cancer, anatomic changes, dosimetric changes, uncertainties

1. Introduction

Intensity Modulated Radiation Therapy (IMRT) with photons has become standard treatment for locally advanced head and neck cancer (HNC) because of its high conformality and better sparing of critical structures [1–3]. However proton therapy using spot scanning (Intensity Modulated Proton Therapy-IMPT) has shown superior dose distribution compared to IMRT in head and neck cancer patients [4–8]. The physical characteristics of proton i.e., its ability of sharp distal fall of inside tissue made substantial advantages over photon therapy. The unnecessary radiation to organ at risks (OARs) and nearby healthy tissues was significantly reduced with proton when compared with photons. The advantages of proton therapy (over photon) in head and neck malignancies have already documented in literature [9, 10]. Protons significantly reduce the risk of xerostomia, dysgeusia, dysphagia, tube feeding dependence and hypothyroidism.

During radiation treatment of Head and neck cancer, changes in anatomy occur like shrinkage of tumor and normal tissues, which is in response to radiation and combined chemotherapy. So plan adaptation is desirable to optimally treat these patients undergoing anatomical modifications and weight loss. These little alterations during proton therapy lead to huge dosimetric changes (like high dose to normal structures and low dose to target volume) because of sharp dose fall off between target volume (TV) and OAR, thus leading to increased complications and marginal failure. The influence of anatomical changes for proton therapy is more pronounced due to range uncertainties. To counteract these limitations, the best

possible strategy is Adaptive Radiotherapy (ART) of proton, i.e., repeat imaging and repeat planning to adapt to actual patient anatomy.

2. Physics: HNC

The anatomy of head and neck is complex and tumor is surrounded by many critical structures or organ at risk (OAR) like parotid, spinal cord, constrictors, thyroid etc.

The physical properties of protons are very useful for the treatment of these cancers. The physical properties of photon Vs proton are depicted in **Table 1**. Protons travel a well-defined distance, losing energy at an increasing rate before stopping, forming the characteristic Bragg peak. The distal penumbra is limited and is well adapted to the treatment of head and neck cancer. Besides this, a therapeutic beam can be produced by (a) Passive Scattering Proton Therapy (PSPT), i.e., where narrow monoenergetic beam pass through a range modulation wheel and scattering it laterally to cover the tumor volume, (b) Pencil Beam Scanning (PBS), i.e., scanning the narrow (pencil) beams magnetically by energy layers. To create homogenous depth dose, the Spread Out Bragg Peak (SOBP) is created by summing of all pristine Bragg peaks.

Passive Scattering PT is not well adapted to the complex anatomies of head and neck cancer compared to pencil beam scanning. In PSPT, the dose distribution is conformed laterally with an aperture, and range uncertainties are minimized through range compensator smearing. In large volume tumors, field junctions are used, known as beam patching. While beam patching is sensitive to set-up uncertainties. However, in Pencil Beam Scanning (PBS), the beam is scanned magnetically which facilitates intensity modulation and allowing to treat tumor surrounded by complex anatomies.

In PBS, there are two different optimization techniques:

i. Single-field optimization (SFO) and

ii. Multi-field optimization (MFO/IMPT).

In the SFO approach, each beam is optimized independently to achieve a uniform dose to the target. SFO is quite robust to changes. With IMPT, the optimization

Variable	Photon	Proton
At beam entrance	i. Maximum dose in beam path	i. No maximum dose, Flat entrance dose
	ii. Skin sparing effect present (build up dose after certain depth)	ii. No skin sparing effect
Around target	No distal fall off	Distal fall off seen (proton stop)
After target	Exit dose seen	No exit dose (no dose behind target)
Laterally	Lateral penumbra is stable relative to depth	Lateral penumbra increase with depth
Everywhere	Electron contamination	Neutron contamination

Table 1.
Physics: photon vs proton.

process simultaneously optimizes the intensities of the spots from all of the beams, thereby irradiating the tumor heterogeneously with each beam but providing a uniform dose to it. IMPT is therefore more relevant for the complex head and neck anatomy and OAR constraints. IMPT is clearly less robust than SFO in the presence of uncertainties.

The advantage in IMPT, we can use multiple field arrangements for better curvilinear dose distributions around critical structures and this is less easily achieved with single field optimization. The critical structures are better spared in MFO/IMPT than SFO. The MFO plan can be made more robust by taking into account setup and range uncertainties during optimization.

3. Dosimetric studies

In photons, adaptive planning is done mainly because of change in size of tumor and relative shift in critical structures. While in protons, the sharp dose fall off and air-borne interface (different stopping power) makes proton very sensitive to variations in treatment depths. Proton therapy is more susceptible to tissue density heterogeneities as proton range is density dependent. In the proton beam path if bone is present the beam is pulled back, while beam is pushed forward if air is in the path.

Multiple studies have shown that proton therapy in head and neck malignancies produce similar or better target coverage and conformity than IMRT. Minor variations in change in anatomy would result in significant change in dose distribution in proton therapy. Very few studies have quantified the degree of dose variations during treatment for patients undergoing IMPT. The three studies are summarized in **Table 2**.

Parameter	**Simone et al., 2011 [11]**		**J Gora et al., 2015 [12]**		**Wu et al., 2017 [13]**	
Number	n = 10		n = 6		n = 10	
Location	oropharynx		oropharynx, hypopharynx		oropharynx	
Prescribed dose (GyE)	70		70, 63, 56		70	
Timing of replanning	After 36 Gy (week 4)		Week 4		Week 4	
IMPT plan	Non-adaptive	Adaptive	Non-adaptive	Adaptive	Non-adaptive	Adaptive
BS (Dmax, Gy)	31.3	29	24.7	21.1	10.15	9.8
SC (Dmax, Gy)	30.5	28.4	25.3	20.8	10.95	10.58
I/L parotid (Dmean, Gy)	32.9	29.8	—	—	7.64 (Rt parotid)	7.26 (Rt parotid)
C/L parotid (Dmean, Gy)	19.5	18.3	20.7	20.8	8.73 (Lt parotid)	8.75(Lt parotid)
Glottic larynx (Dmean, Gy)	35.3	31	39.4	45.9	—	—

IMPT-intensity modulated proton therapy, BS-brain stem, SC-spinal cord, I/L-ipsilateral, C/L-contralateral.

Table 2.
Studies showing dosimetric results and comparison between non-adaptive and adaptive IMPT plans.

4. Reasons for adaptation

i. Target deformation:

In patients of head and neck cancer treated with photons, various studies shown that the reduction in target volume ranges from 5 to 13% during treatment [14–16]. In Gunn et al. [17], out of 50 patients of oropharyngeal cancers treated with IMPT, in view of weight loss and tumor volume changes 19 patients (38%) had adaptive replanning.

ii. Anatomical and OAR deformation

The potential anatomical changes are weight loss, decrease in size of surgical flap, reduction in swelling, parotid gland shrinkage etc. [16, 18, 19]. **Figure 1** depicts the reasons of replanning.

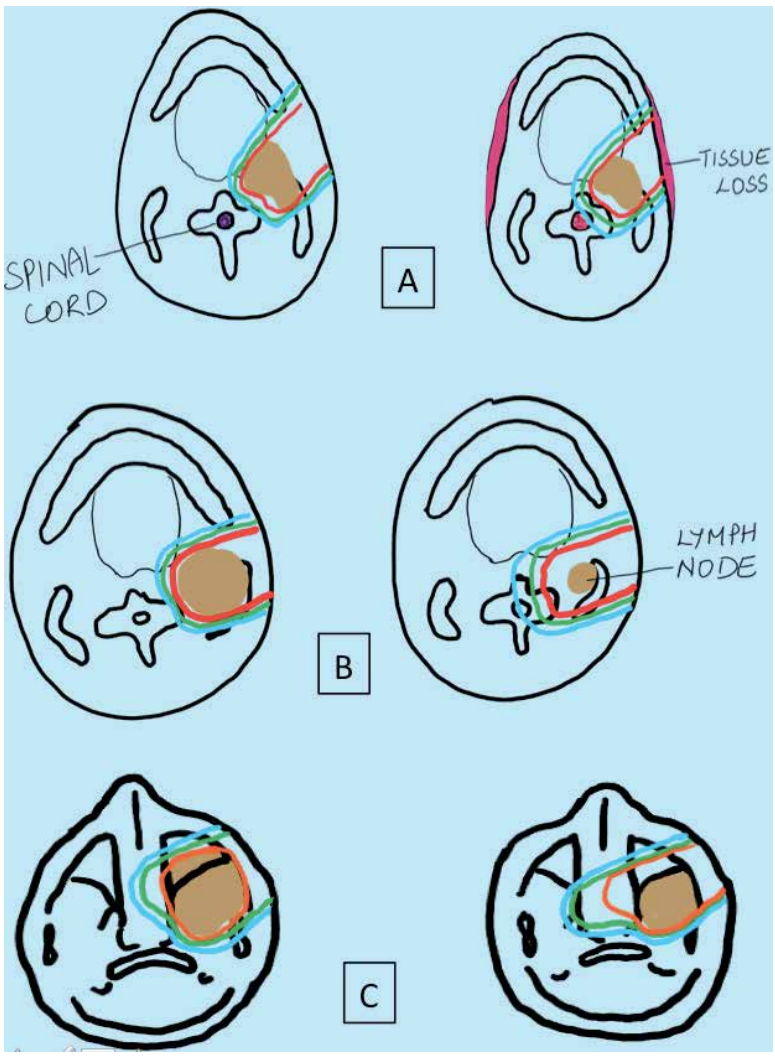

Figure 1.
Reasons for adaptation: (A) anatomical change – weight loss, (B) target deformation – nodal response, and (C) beam path change.

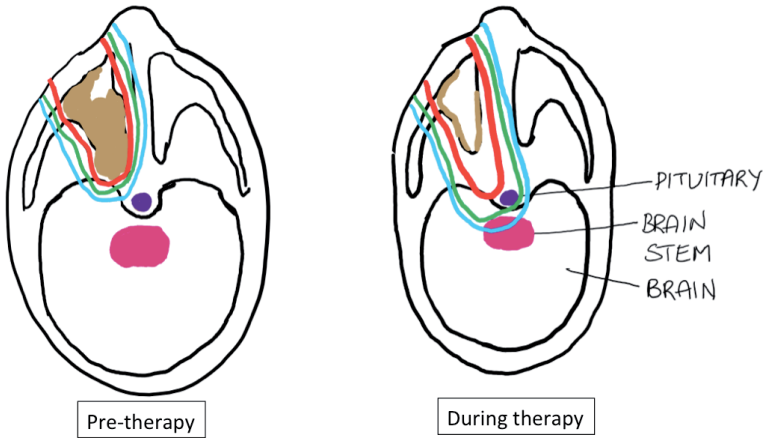

Figure 2.
The variation in filling of maxillary sinus affecting dose distribution during treatment.

iii. Beam path change

As proton range is density dependent, it is more susceptible than photons. The nasal cavity and paranasal sinuses region contains variable amount of complicated structures such as bone, mucosa, tumor tissue, collected fluid, and air, which can alter the different proton beam ranges. Variations in air and fluid content in the nasal cavity and paranasal sinuses during the course of radiotherapy could affect the proton dose distribution. Clearing or opacification of sinuses may result in shift of the high dose deposition, potentially lead to change in dose to the targets and critical structures (**Figure 2**). Late toxicities such as brain injury, cerebrospinal fluid leakage, and vision loss have been reported for patients with head and neck cancer patients treated with proton or carbon therapy [20–22].

In a study by Fukumitsu et al., twenty patients of nasal and paranasal sinuses received proton therapy and in 18 out of 20 cases, the air content in the cavities increased. This resulted an increase in dose to brainstem above 60Gy in 3 patients and increase in dose above 50Gy in 10 patients [23]. Susharina et al. also demonstrated that change in aeration in vicinity of target lead to decreased dose to target (5%) and increased dose to optic structures and brain stem [24].

iv. Uncertainties

The main factors leading to range uncertainty are

a. Range calculation in TPS

   i. Inaccuracies arising from CT (HU to stopping power conversion, CT reconstruction, HU uncertainty like metal artifacts, partial volume effect)

   ii. Inaccuracies arising from dose algorithm

b. Discrepancies between planned and delivered dose – like geometric changes (setup and motion) and density heterogeneities.

5. Practical considerations

The process of adaptive radiotherapy identified by weight loss, mask fitting, changes in patient setup, regularly planned intervals, treatment response assessed by CBCT scans, diagnostic CT or MRI scans (tumor shrinkage), recalculating the dose delivered to targets and OARs.

The other approaches are planning QACT (quality assurance CT) at regular intervals (after every 10 fractions) as reduction in parotid and target volumes occur in early third week resulting in huge dosimetric differences. In the modern proton therapy, image guidance with daily CBCT helps in identifying the anatomical changes and early treatment response.

The IMPT treatment uncertainties can be mitigated by robust optimization. The robust optimization technique is a robust plan generated using CTV as primary target and not requiring geometrically expanded PTV. The robust optimization method takes into account setup and range uncertainty directly during spot weighting. Therefore it does not need extra volume to be irradiated.

There is no consensus on most appropriate timing regimen for adaptation/ replanning during proton therapy.

6. Conclusion

Proton therapy in head and neck cancer is associated with tissue and target volume changes leading to higher doses to normal tissues (salivary glands/DARS). Adaptation once or twice in middle of treatment will reduce unnecessary doses to parotid, swallowing structures etc., thus improving patient's quality of life by reducing the risk of xerostomia and tube feeding dependence.

Acknowledgements

I would like to express my sincere gratitude to my teachers and colleagues for their guidance and support. I especially thank my wife for her continuous support in completing the chapter.

Conflict of interest

Nil.

Nomenclature

ART	adaptive radiotherapy
BS	brain stem
CBCT	cone beam computed tomography
CT	computed tomography
C/L	parotid-contralateral parotid
DARS	dysphagia/aspiration at risk structures
HU	Hounsfield Unit
HNC	head and neck cancer
I/L	parotid-ipsilateral parotid
IMRT	intensity modulated radiation therapy

IMPT	intensity modulated proton therapy
MFO	multi field optimization
MRI	magnetic resonance imaging
OARs	organ at risk
PBS	pencil beam scanning
PSPT	passive scanning proton therapy
SFO	single field optimization
SC	spinal cord
TV	target volume

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Section 4

Current Challenges in Proton Therapy

Chapter 7

Proton Therapy in Lower-Middle-Income Countries: From Facts and Reality to Desire, Challenges and Limitations

Sandra Ileana Pérez Álvarez, Francisco Javier Lozano Ruiz, Federico Maldonado Magos and Aida Mota García

Abstract

Around 50% of cancer patients will require radiotherapy (RT) and 10–15% of these patients could be eligible for proton beam radiotherapy (PBT). Dosimetric advantages are undeniable, mainly in pediatric and reirradiation scenarios. Though, PBT facilities are scarce worldwide and the IAEA has reported 116 functional particle facilities, of which 98 are PBT, virtually absent in low- and middle-income countries (LMIC). The Latin America and Caribbean region represent a unique opportunity for a PBT center, as there are currently no functional facilities and current RT needs are significant. The challenges can be summarized as high initial investment and maintenance, geographic coverage, required baseline technology and certification, over-optimistic workload, unclear rates and reimbursement, unmet business plan and revenue expectations, and lack of trained human resources. Investment costs for a PBT facility are estimated to be at around 140 million euros; therefore, this seems unsuitable for LMIC. Mexico's geographical advantage, GDP, baseline technologies and high demand for RT makes it an ideal candidate. Nevertheless, a PBT center would account for a third of Mexico's annual health expenditure for 2020. Enormous efforts must be made by both the private sector and governmental authorities to provide funding.

Keywords: proton therapy, cost-effectiveness, low-to-middle-income countries, infrastructure

1. Introduction

Radiotherapy (RT) is an integral component of contemporary cancer treatment, both as curative and palliative therapy. Around 50% of patients will, at some point during their cancer history, require RT. Its contribution to cancer survival is estimated at around 40% versus 49% for surgery and 11% for systemic treatment modalities. [1] In the past decade, ongoing research in systemic therapies has broadened the indications for RT, since as long-term survival increases so does the prevalence of the disease. Oligometastatic cancer recurrence is increasingly managed with RT, as well as oligoprogressive disease. This in addition to its more common applications, such as local control in curable or metastatic settings. However,

dose-limiting toxicity remains the main problem for RT, especially for in-field recurrences where reirradiation is a bigger concern.

Proton beam radiotherapy (PBT) is a novel technique with endless possibilities. Different simulation models have estimated that 10–15% of all radiated patients from various European countries could be eligible for PBT, but only less than 1% receive it. [2] Since toxicity and dosimetry advantages are undeniable, and although there is still scarce clinical practice, indications and applications are on the rise mainly in pediatric and reirradiation scenarios, without excluding common indications for radiation treatments, especially when dose constraints are an issue. Still, PBT remains non-existent in Latin America and virtually absent in low- and middle-income countries (LMIC). The following chapter will focus on how a PBT can be suitable for proven clinical indications in LMIC, particularly in Latin America and Mexico, where cancer and epidemiology registries—although insufficient—present a broader view of current RT needs when compared to other LMIC across Africa and Asia. A general overview of the facts and realities of RT, as well as the challenges and limitations expected for a proton facility in these countries, will be presented.

The Latin America and Caribbean (LAC) region represents a unique clinical opportunity for a proton radiation therapy center, as there are currently no functional facilities and because current radiotherapy needs are significant. Nevertheless, auxiliary diagnostic facilities required for a functional PBT center, such as computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI) and pathology departments, although insufficient, are found in some LAC cities, meeting the highest quality requirements and the most rigorous international certifications. There is an upcoming PBT center in Buenos Aires, Argentina with operations due to start in 2022. Even with this center, availability for this type of treatment is evidently not enough for the 629 million inhabitants living/distributed in the 192 million km^2 of Latin American territory. [3]

2. Proton therapy in low- and middle-income countries

2.1 Facts and reality

According to the IAEA Directory of Radiotherapy Centres, there are 116 functional proton/ion facilities (107 in high-income countries, 8 in upper-middle-income countries and 1 in LMIC) around the world, out of which 98 are PBT. Most are located in high-income countries in North America, Europe and Asia, countries that coincidentally have the highest number of photon radiotherapy equipment, and none in LAC. [4] **Figure 1** shows available PBT facilities according to their operation status. Even LAC has RT available only in 70% of its countries, with approximately 1 megavoltage machine per 650,000 inhabitants. Distribution varies according to income groups, creating an unequal environment for adequate cancer care, particularly from a radiotherapy standpoint. [5]

Cancer accounts for 10% of the global healthcare budget, out of which RT takes up only about 5%; therefore, RT expenditure is about 0.25–1% of the total healthcare budget. [6] This represents a very small fraction of the total healthcare budget if we consider that up to 25% of the population is expected to go through radiation treatment at some point in their life. [7] Although RT is regarded as the cheapest cancer treatment modality, limited resources are available in Latin America due to absence of domestic and international funding. Approximately 90% of the population in these countries will lack access to RT.

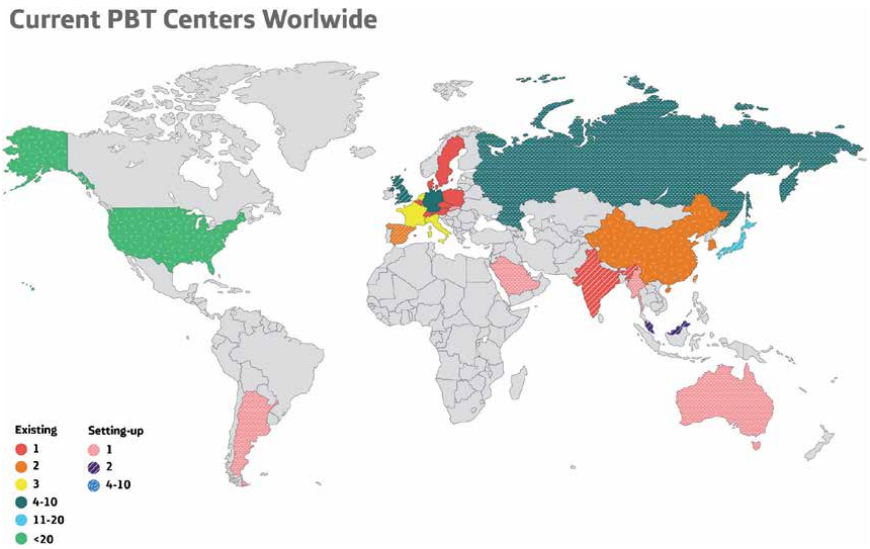

Figure 1.
Available proton therapy facilities in clinical operation and under construction.

Insufficient detailed information about attainability for radiotherapy and auxiliary diagnostic tools in LMIC is a constant. Currently very few countries in LAC have submitted recent data. Thus, planning for a PBT center requires data regarding general availability, not only for radiotherapy but also for auxiliary diagnostic tools, such as PET, MRI, CT scans and pathology laboratories, many of which are either partially or completely unavailable across the LAC region. Developing a PBT center with full access to all therapeutic and diagnostic tools involved in proton therapy must therefore be contemplated in at least one of the main cities of the region; otherwise, PBT center usage could be suboptimal. LAC presents a complex paradox, where most of childhood cancer and reirradiation scenario candidates for PBT are much more frequent than in developed countries—where most PBT centers exist—but is simultaneously the region facing the most difficulties for a functional PBT center, not due to the obvious economic challenges, but because of the lack of complementary and auxiliary tools required for it.

Another issue is that currently around 8% of LAC residents are 65 years or older, which represents the population with the highest risk for malignant neoplasms. By 2050, this figure is expected to double to 17.5% and to exceed 30% by the end of the century. In 2018, this represented over 1.3 million new cancer cases and over 660,000 cancer-related deaths; therefore, at least twice this number will reflect cancer deaths by 2050 unless international efforts to reduce mortality are effectively implemented. [8]

2.1.1 Adult tumors suitable for PBT in Latin America and their relevance for a proton facility

The LAC region encompasses 33 countries and 15 dependencies or territories with a total population of 646 million in 2019. [9] With a combined gross domestic product (GDP) of United States dollars (USD) 5.7 trillion, LAC is a region of growing importance to the world economy. [10, 11] GDP per capita ranges from USD 754 in Haiti to USD 85,477 in the Cayman Islands. Haiti is considered the only low-income country in the region; 7%, 49% and 41% are considered lower-middle-, upper-middle- and high-income countries, respectively. [12] According to Bishr

et al., there is a total of 593 RT centers in 28 countries, with up to 983 megavoltage machines, of which 23.9% are telecobalt machines. Twelve countries (30%), containing 2% of the LAC population (estimated population of 12.5 million), lack RT facilities. [13]

Although the number of needed radiotherapy machines varies between reports and despite underestimation due to lack of cancer registries, the overall conclusion is that around 50% of cases requiring radiotherapy in LMIC never receive treatment, and this goes up to 90% in low-income countries. [7] Additionally, the economic burden of lost productivity due to morbidity and premature death from cancer accounts for nearly 60% of the total economic burden associated with cancer in European Union countries. [14]

2.1.2 Pediatric tumors in Latin America and their relevance for a proton facility

Although pediatric cancers represent 10–13% of patients treated with PBT in the US, PBT has proven clinical applications, especially for pediatric brain tumors since important toxicities such as growth deficiencies, hearing loss, intelligence quotient impairment, learning disabilities and secondary malignant neoplasms will potentially be avoided in childhood survivors. Among potential tumors treated with PBT, medulloblastoma and other pediatric central nervous system (CNS) malignancies in people under 21 are highly prevalent in LAC. LMIC countries have younger populations; for example, according to UNICEF, there are over 193 million minors registered in LAC. [15] Therefore, the expected number of children with cancer is larger. It is estimated that around 84% of childhood cancer occurs in these countries, simply because nearly 90% of the world's children population lives in LMIC. Moreover, 45% suffer from child poverty, which limits their access to RT.

GLOBOCAN estimates the incidence of childhood cancer varies between 50 and 200 cases per million children each year in different LMIC. However, this data is not reliable due to many undiagnosed childhood cancers, especially in rural areas of LAC, where diagnostic tools, such as MRI or even CT scanning, are not available [16]. Under-recording is another main issue since LMIC have weaker epidemiology networks and death certificates may be incomplete or absent. All of these factors contribute to inaccurate data.

Childhood cancer survival rates vary widely by region, particularly in LMIC, where lack of access to diagnoses is just the tip of the iceberg. Access to optimal treatments is often limited to private and selected tertiary public institutions. These out-of-pocket expenditures are often prohibitive for most of the LMIC population and, among many other factors, are essential components for this foreboding result. A simulation-based analysis for global childhood cancer survival estimates shows large variation by region, ranging from 8.1% (4.4–13.7) in low-income countries in Eastern Africa to 83% in high-income countries in North America, placing Latin America central nervous system cancer survival estimates at around 50%. [17]

2.1.3 Advantages and limitations of PBT

PBT has been used for almost seven decades. Even so, indications of PBT for cancer treatment have had an alarmingly slow development, often being displaced by other radiotherapy techniques, such as stereotactic body RT (SBRT) or intensity-modulated RT (IMRT) /volumetric arc therapy (VMAT). PBT has an important and undeniable radiobiological advantage over SBRT and VMAT techniques, [18] since it significantly reduces the absorbed dose by normal tissue and lowers whole body integral radiation doses due to the requirement of fewer treatment fields, [14, 19] which means there is overall less acute and late toxicity. This has been

proven in multiple clinical trials, particularly in pediatric cancer and specific adult malignancies (skull base, head and neck, hepatocellular, central nervous system, breast, lung, prostate, testicular and ocular tumors), among other fewer common scenarios, such as reirradiation, where it allows for dose escalation in patients who otherwise would not be optimal candidates for photon therapy. [2]

Challenges for investment in particle therapy treatment centers reported by the European Investment Bank can be summarized in a) PBT is currently indicated for only a small number of cancers; b) treatment is very costly and time consuming; c) geographic coverage; d) limited research activity. Main issues for project implementation include a) delays and problems with technology specifications and certification; b) overflow of patients seeking treatment and over-optimistic workload; c) unclear rates and reimbursement schemes; d) unmet business plan and revenue expectations; e) limited number of trained human resources. Surprisingly, limitations for PBT are mainly economical, not only because of the high initial investment but also due to the yearly increases in the cost of cancer care, often above inflation rates. This raises the concern that a PBT facility that was once sustainable will not be so in the future due to operational costs, quality assurance, maintenance and continuous training and/or medical education. Lack of high-quality clinical data on outcome and long-term toxicity for PBT contributes to mistrust, but this is a symptom that reflects lack of investment, not a limitation of PBT per se. [20]

2.1.4 Realities of radiotherapy attainability in Latin America and/or Mexico

Starting a PBT center is an enormous challenge and many variables should be accounted for, not only the obvious limitations such as economic capabilities and preexisting infrastructure. But also more subjective and complex variables, such as amenable workforce, solid governmental facilities for diagnosis and oncologic treatment like a national cancer institute, national and international private sector funding, and an organized radiation oncologist society committed to and involved in providing all necessary means for a comprehensive workforce network across the country or the whole LAC region for patient recruitment and referral.

Viability of a PBT center is only possible if a continuous flow of patients is guaranteed, either from locoregional cases or from a referral-based system, and this can only be done by few LAC countries. Based on published information about current demographics, radiotherapy capabilities and diagnostic workup auxiliaries, this might only be possible in few countries. Economic capabilities are fundamental for such type of investment. Even with international support, only cities with a high population and GDP should be considered. **Table 1** ranks the 5 top cities by population and GDP amenable for any PBT projects. As stated before, there is already an ongoing PBT project running in Buenos Aires, Argentina.

It is estimated that two thirds of cancer-related deaths will occur in LMIC and treatment related-morbidity and mortality cause an enormous economic burden, especially in developing countries. Taking into account a PBT center is projected to start soon in Argentina, geographic location, gross domestic income, RT capabilities and diagnostic auxiliary tools available, a following PBT center could be feasible in Mexico. Particularly in the metropolitan area, where most oncology centers in the country are located. Mexico is currently the 14th most powerful world economy and 11th in purchasing power parity, second biggest economy in LAC and 4th in the continent, and is currently classified as an upper-middle-income country with a median age of 28 years old, 7.3% of its population being 65 years or older. [12, 21] Mexico is an exceptionally young country for its economic capabilities, with an incidence of childhood and teenage cancer of 89.6 per million inhabitants (111.4 in children aged 0–9 and 68.1 for teenagers aged 10–18) in 2017 and a prevalence of 18,000 annual

Rank	Country	GDP (PPP) in millions	GDP (PPP) per capita	Highest GDP (city)	Highest population (city)
1	Brazil	3,078,901	14,562	Sao Paulo US$ 699.2 B (2017)	Sao Paulo 21.3 M (2015)
2	Mexico	2,424,511	18,804	Mexico city US$ 411 B (2011)	Mexico city 8.85 M (2015)
3	Argentina	924,539	20,369	Buenos Aires US$ 118 B (2008)	Buenos Aires 2.8 M (2010)
4	Colombia	719,251	14,136	Bogota US$ 221.7 B (2016)	Bogota 8.08 M (2017)
5	Chile	456,394	23,454	Santiago US$ 175 B (2014)	Santiago 7.3 M (2015)

Abbreviations: B: billion; GDP: gross domestic product; M: million; PPP: purchasing power parity; US$: american dollars.

Table 1.
Top 5 cities by population and GDP amenable for any PBT projects.

cases in persons under 18 years of age. [22] The estimated incidence and prevalence of all cancers was 195,499 and 530,602 in 2020, respectively. [23] A busy PBT center is feasible. Mexican radiotherapy demographics have been recently published and this information is not only crucial for any investment on PBT, but also sets a necessary precedent for adequate development.

According to the Mexican radiotherapy certification board, the country lies on an alarmingly low density of radiotherapy facilities, with a density of 1.19 linear accelerators per million inhabitants. [24] Mexico stands out because of this, since it's not only one of the few countries in LAC that could divert health expenditures to a PBT project, but it also currently has an enormous need for radiotherapy facilities. The need for RT centers is huge and will rise in the following years in conjunction with the increasing age of its population and the number of pediatric cancer patients requiring RT (due to its high pediatric population).

2.2 Challenges

2.2.1 Cost evaluation

Van Dyk (2017) evaluated the annual cost of 4 fully independent centers with two linear accelerators each. They reported that capital costs, operational costs per year and cost per treatment course in high-income countries (HIC) are approximately $41,175,000, $18,309,00 and $5,350, respectively; whereas for LMIC, it's $32,035,000, $6,911,000 and $2,020, respectively. [25] In 2003, Goiten estimated that particle therapy was about 2.4 times more expensive than most sophisticated RT techniques, and that this could be reduced to 1.7–2.1 over a decade. [26] The investment costs are estimated to be about 140 million euros or 150–200 million dollars for a 4 to 5-room PBT facility and 40 million for a single-room center, which represent a more affordable option even for high-income countries [26, 27]. The former represents a small, but important, fraction of Mexico's health expenditure (which is approximately 31,700 million USD in 2020) [28].

Lifespan of a PBT facility should also be considered. Although the cost of a 4- or 5-room PBT center can reach several hundred million dollars, a large portion of the cost is attributable to the cyclotron or synchrotron and the huge rotational gantries with a lifespan of more than 30 years. Which is significantly longer than the 7-year average lifespan of a linear accelerator. The direct cost of a modern 4-gantry PBT center is similar to that of a linear accelerator facility with 16 machines over its 30-year lifespan (4 linear accelerators replaced 3 or 4 times over this period). [29].

Several US PBT centers had to accept a reference price as payment for PBT instead of no payment or coverage. In this case, payment is made based on the next most expensive alternative, which does not cover the real cost of delivering the treatment. [30] Additionally, some payers are complaining that they pay for a therapy with no clear evidence of benefit. [31] A focus only on direct up-front costs at the time of the treatment is inaccurate because the indirect costs of managing and surviving with the late adverse effects of radiotherapy could be reduced significantly or even completely with PBT. [29].

2.2.2 Cost-effectiveness analysis and limitations

Investment in high-cost RT facilities will also lead to an increase of the mean treatment cost; however, the cost-effectiveness of PBT may improve if the rate of patients with indications expected to benefit from this innovation increases. [32] PBT cost-effectiveness studies should include costs associated with intervention and secondary benefit comparisons. In summary, all potential costs saved from morbidity and/or mortality reduction versus all possible expenses should be considered. It is very difficult to include and assess every direct and indirect cost related to intervention. This should include construction of the PBT facilities, operational or procedural cost (personnel costs, electricity and maintenance, beam delivery time, number of patients treated). In addition, it should consider potential toxicities and their related costs, such as support medication and/or hospitalization related to RT-induced toxicities, both potentially more frequent in patients with a long life expectancy, close anatomical relationships to organs at risk (OAR), advanced tumor stage, histopathology and pre-existing comorbidities. Others factors that affect cost-effectiveness are treatment volume, treatment fields, treatment duration, total dose and fractionation. [2] A country's health system organization also influences economic cost. Since public (complete coverage versus adjusted-socioeconomical payment) and private services (with or without insurance company, and percentage of reimbursement) differ significantly in availability, reimbursement and cost, this must be considered in the analysis. And even more important is the availability of treatment machines.

PBT use in pediatric cancer is based on integral dose advantages of protons over photon RT. It modulates dosage to avoid OAR when the dose is high and OAR are close and with integral dose minimization. [33] Verma (2016) reported a 2.4-fold increase in initial cost of PBT versus conventional or IMRT in pediatric cancers. However, total costs of adverse effects showed an 8-fold decrease in favor of PBT. This yields a 2.6-fold reduction of overall costs in favor of PBT. [2] Currently, PBT is the most cost-effective option for several pediatric brain tumors. [34] Especially in craniospinal irradiation (CSI) with high dose boost requiring more conformation, such as in medulloblastoma, in which associated adverse effects related to radiotherapy are IQ decline, hearing loss and growth hormone deficiency. In atypical cases, such as high-grade glioma and sarcoma or retreatment of spine lesions, the doses achieved treat less normal tissue and can avoid internal OAR better. [35, 36] Other pediatric tumors suitable for PBT are intracranial and skull base tumors, spine tumors, Hodgkin Lymphoma and retreatment. As such,

PBT is more cost-effective for pediatric cancer due to the decrease in long-term toxicity, long life expectancy after cancer treatment and more remaining years of economic-productive life. Therefore, although the number of cancers that are cured is generally very low, treatment of curable childhood cancer is highly cost-effective. Some issues to be considered include limited data, lack of long-term follow-up and contraindications for PBT (Wilms' tumor classic fields, whole lung classic fields and palliative RT). [2] By contrast, a Brazilian patient volume-based analysis showed that PBT was not cost-effective for pediatric medulloblastoma treatment. [37].

Other outcomes that can be measured include total life-years gained or lost, and quality-adjusted life years (QALYs). [2] For pediatric brain tumor, the incremental cost-effectiveness ratio was $21,716 to 26,419 dollars per QALY, depending on the study. [34].

In adult cases, PBT as standard treatment for breast cancer has not been shown to be cost-effective and is associated with a minimal increase in QALYs. However, specific subgroups that may benefit include patients with high-risk late cardiac toxicity, such as left-sided tumors or internal mammary node irradiation and those with double baseline risk of non-radiotherapy-related cardiac disease. [34, 38] For locoregionally advanced non-small cell lung cancer (NSCLC), PBT increased QALYs compared to conformal or IMRT, and was probably more cost-effective than for early-stage NSCLC. [34, 39, 40] In locally advanced head and neck cancer, intensity-modulated PBT (IMPT) reduces xerostomia and dysphagia rates compared to IMRT; however, cost was increased, [41] with an incremental cost-effectiveness ratio of $4,254 to 143,229 US dollars per QALY, depending on study and radiation technique. [34] In another Chinese study, IMPT was more cost-effective and provided an extra 1.65 QALYs for paranasal sinus and nasal cavity cancers compared to IMRT. [42] For prostate cancer, PBT showed increased costs without increasing QALYs compared to IMRT; in this case, life expectancy determines cost-effectiveness. [43] However, PBT is currently not considered medically necessary for the treatment of lung, prostate, breast, gastro-esophageal, hepatocellular, head and neck, gynecologic cancer or Hodgkin and non-Hodgkin Lymphoma. [44] A review of PBT concluded that no clinical data had shown superiority over advanced RT for treatment of central nervous system lesions. It is only medically necessary for cases with adjacent structures. [45] Given the excellent long-term results with PBT, it is considered medically necessary for the treatment of base skull and sacral chordomas and chondrosarcomas, [46] and uveal melanoma due to lower local recurrence rate, retinopathy and cataract formation. [47] PBT is appropriate for reirradiation where the dose tolerance of adjacent normal structures would be exceeded with conformal or IMRT. [44].

Limitations of cost-effectiveness analyses are short-term follow-up of clinical and toxicity evidence, and lack of standard indications. Therefore, a subgroup of patients that will clinically benefit and gain most QALYs may be identified for an adequate distribution of limited access and availability of PBT facilities.

2.2.3 Human resources

As currently there are no functional PBT centers in LAC, adequate training for radiation oncologists, medical physicists, dosimetrists and radiation therapy technicians is imperative. Although this topic is popular in medical conferences and webinars, the lack of clinical experience is an issue. If a PBT center is considered for LAC, training in all levels of attention will be necessary and this represents an enormous challenge by itself since long term fellowships are required, at least for physicists and radiation oncologists. Periodic supervision from experienced

personal or remote assistant and continuous medical education are two alternatives if intercountry fellowships are not feasible. [48].

2.2.4 Technical needs and limitations

PBT project management requires planning (construction design, permits, functional set-up), implementation (regulatory frame, technical expertise during construction) and operation (treatment planning time, patient logistics, nuclear safety, business plan, financial sustainability). Current PBT facilities require a space the size of a football field. This space is unavailable at or near the main hospitals and could be highly expensive in many capital cities. Therefore, future PBT units that are smaller (single-room PBT), more efficient and less expensive (even as low as $30 million dollars) are expected. [49].

The margins for protons are larger due to range uncertainties, which contribute to less conformality and larger higher dose volumes that include nearest OAR. Techniques to reduce clinical-to-planning target volume (CTV-to-PTV) margin include beam-specific PTV and in-vivo range verification; however, this approach is more expensive. [50, 51] Another limitation is image guidance and adaptive radiotherapy, since this modern technology is lacking in most PBT facilities. [2] Daily reproducibility, setup and anatomical changes are important determinants of dose distribution and thus in tumor control and complications. The treatment time per fraction with proton therapy is longer than for IMRT (22 versus 14 minutes). [52] The ideal PBT facility should have daily volumetric imaging for correct patient setup and identification of anatomical changes, adaptative replanning to compensate variations and setup with respiratory motion management. [53] It is expected that advances will give rise to more compact PBT facilities (1 or 2 treatment rooms) with volumetric image guidance and with a lower cost over time. [2].

2.2.5 Initial investment

PBT has been approved for cancer treatment by the FDA since 1988. Uniform federal government regulations with rigorous evaluation of useful and vital versus inefficient and unworthy technology are necessary since uncontrolled and unregulated healthcare spending on new technology without adequate determination of its effectiveness will eat up funds that could be spent efficiently. It should be considered that private insurers have declined to reimburse PBT for common cancer with no proven benefits compared to other modern techniques.

3. Conclusions

Currently there are virtually no PBT centers in LMIC, and none in LAC. Disparities on PBT distribution around the globe go further than just the obvious—lack of appropriate oncological treatments to alleviate human suffering—but are partially responsible for the slow development of PBT worldwide. At present, most patients amenable for PBT treatments are in LMIC countries, and clinical trials has been halted at least partially because of a lack of recruitment. There is a negative paradox, wherein patients in need of PBT have no access to it and PBT centers around the world with all dosimetric advantages represent less than 1% of all RT treatments. However, a PBT center in any LMIC is economically unviable and requires extensive sociodemographic studies. Mexico could be a strong candidate, not only due to its geographical advantages and total population, but because of its exceptionally young population for its economical capabilities, detailed published

data on current needed access to radiotherapy and a modest but sufficient number of the required auxiliary diagnostic tools, such as PET, MRI and pathology services. Enormous efforts must be made by the private sector (national and international alike) and governmental authorities to provide funding and a comprehensive referral system for the PBT center. As stated previously, following the ALARA principle, PBT provides a clinical benefit to certain patients that is not achievable with photons.

Conflict of interest

The authors declare no conflict of interest.

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Section 5

Future Directions and Management

Chapter 8

Proton Cancer Therapy: Synchrotron-Based Clinical Experiences 2020 Update

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Abstract

Proton therapy is an efficient high-precision radiotherapy technique. The number of installed proton units and the available medical evidence has grown exponentially over the last 10 years. As a technology driven cancer treatment modality, specific sub-analysis based on proton beam characteristics and proton beam generators is feasible and of academic interest. International synchrotron technology-based institutions have been particularly active in evidence generating actions including the design of prospective trials, data registration projects and retrospective analysis of early clinical results. Reported evidence after 2010 of proton therapy from synchrotron based clinical results are reviewed. Physics, molecular, cellular, animal investigation and other non-clinical topics were excluded from the present analysis. The actual literature search (up to January 2020) found 192 publications, including description of results in over 29.000 patients (10 cancer sites and histological subtypes), together with some editorials, reviews or expert updated recommendations. Institutions with synchrotron-based proton therapy technology have shown consistent and reproducible results along the past decade. Bibliometrics of reported clinical experiences from 2008 to early 2020 includes 58% of publications in first quartile (1q) scientific journals classification and 13% in 2q (7% 3q, 5% 4q and 17% not specified). The distribution of reports by cancer sites and histological subtypes shown as dominant areas of clinical research and publication: lung cancer (23%), pediatric (18%), head and neck (17%), central nervous system (7%), gastrointestinal (9%), prostate (8%) and a miscellanea of neplasms including hepatocarcinoma, sarcomas and breast cancer. Over 50% of lung, pediatric, head and neck and gastrointestinal publications were 1q.

Keywords: cancer, proton therapy, synchrotron, oncology, radiotherapy

1. Introduction

1.1 Cancer medicine: precision, interdisciplinary and personalization

Proton beam therapy (PBT) is developing in the context of a substantial increase in the incidence of cancer, the enormous advances made in our understanding of

the biological basis and clinical implications of the disease, and the need to improve the therapeutic index: tumor control promotion and minimal clinically relevant toxicity. PBT is an accessible precision high-energy particle radiation technology, adapted to the therapeutic demands tendencies in health care and health budget of modern clinical practice [1]. Other radiotherapy (RT) solutions using hadron beams (hadron therapy) are too costly in the medium term in most clinical settings [2].

PBT is now firmly established the era of precision medicine [3]. In oncology, the principles of medicine must be well defined: Interdisciplinarity and molecular individuation. Technological excellence will only be achieved when it encompasses the different medical specialties involved in treating each individual patient. Multidisciplinary Tumor Boards (MTD) are an essential part of an efficient approach to cancer management [4]. Personalized cancer treatment is characterized by a detailed analysis of the molecular configuration and evolution of each patient's tumor (gene expression profile and nanobiology) [5]. The latest evidence suggests that tumors are probably unique to each patient, and that each tumor within the same patient (metastasis, primary site or recurrence) has its own biological pattern of progression and host adaptation pathway [6].

1.2 Vectors in radiation oncology: individualized, functional, accurate and precise therapy

RT currently helps to achieve cure over half of all patients that require this treatment; it relieves symptoms in 2 out of every 3 patients, and in general terms is a crucial therapeutic component in 3 out of every 4 cancer patients [7]. Furthermore, RT preserves organs and tissue structures (in contrast to the status resulting from radical extended surgery) and can be used in the context of radical treatment for oligometastatic and oligo-recurrent disease [8, 9]. Forecasts in healthcare systems in countries like the US suggest that by 2020, indications for RT in all types of cancer will have increased by 25%, and by 35% in the case of gastrointestinal malignancies [10].

The foregoing estimations are based on the enormous technological advances made in RT in the last 30 years. If medical advances in clinical oncology have ushered in the era of precision medicine, interdisciplinary approach in recent decades in oncological RT (which specifically uses ionizing radiation to treat cancer) have ushered in the era of accurate precise RT.

Precision RT is very efficient in promoting the local control (LC) of macroscopically identifiable cancer lesions (targeted by image-guided RT), and has an excellent therapeutic index, in other words, minimal, toxicity in normal radiation-sensitive tissue [11]. Because accurate precise RT has minimum effect on the function of the organs, systems (blood, liver, lungs, etc.) and tissues where the tumor is located, it has allowed clinicians to explore the radiobiological effects of hypofractionation, heterogeneous dose distribution within target volumes (adjusted for bio-heterogeneity), and of immunomodulatory, radiation-enhancing, radiation-sensitive and radiation-protective drug interactions [12]. Finally, one of the most promising aspects of accurate precise RT is the potencial of radiation-induced immunogenicity induced by hypofractionated (>8 Gy) RT [13]. Checkpoint inhibitors and other inmunomodulators allow clinicians to explore the potential of combining systemic immunotherapy effects with precision local and atoxic RT [14].

2. Developing proton beam therapy clinical evidence

In the next decade, technological advances in PBT will bring further technological developments in precision RT into mainstream clinical practice. The dosimetric

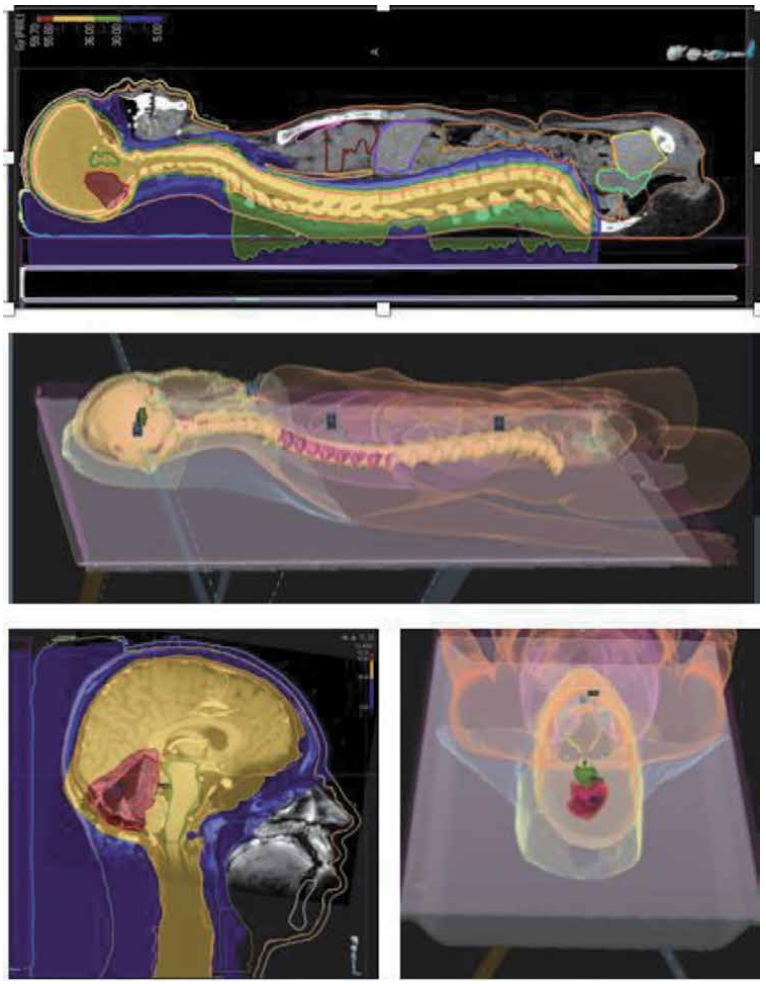

Figure 1.
Clinical practice-based example of dose distribution in a craneospinal irradiation represented in 2D and 3D images. Treatment planning implementation in PBT enhances the perception of clinical benefit expected by protecting normal anatomy from unnecessary irradiation.

precision of PBT compares favorably with photon therapy and, guided by beam homogeneity in the delivery and imaging systems for precision control (4D and quasi-real-time control), its results in clinical practice will be equivalent and reproducible (**Figure 1**).

The value of a treatment is defined as the outcomes obtained divided by the cost, measured over the entire cycle of care [15]. The clinical potential of proton cancer therapy requires sophisticated and realistic assessment of integral cost of care estimations including "costicity" (the cost of toxicity and general health-related supportive care). A collaborative effort between clinicians, patients, and policy makers is needed to design clinical trials with meaningful patient engagement. In particular, patients may help to identify and refine approaches that will lead to improved enrollment and retention in clinical trials as evidence generators sources. One crucial element in arriving at meaningful conclusions from such analyses is the need to account for the costs of managing not only acute RT toxicity but also long-term morbidities that can occur years to decades after RT is completed.

In 2016, Mishra et al. reviewed the context of developing evidence in cancer proton therapy [16]. PBT clinical trials identified from clinicaltrials.gov and the

World Health Organization International Clinical Trials Platform Registry showed a total of 122 active PBT clinical trials, with target enrollment of >42,000 patients worldwide. Ninety-six trials (79%) were interventional and 21% were observational studies. The most common PBT clinical trials focus on gastrointestinal tract tumors (21%), tumors of the central nervous system (15%), and prostate cancer (12%). Five active studies (lung, esophagus, head and neck, prostate, breast) randomize patients between protons and photons, and 3 between protons and carbon ion therapy.

The medical vision in 2020 and ahead, confirms that PBT clinical trial portfolio expands rapidly. Results of PBT studies, generated with synchrotron technology, need additional evaluation in terms of comparative effectiveness, as well as incremental effectiveness and health value offered by PBT in comparison with conventional radiation modalities among other topics of clinical relevance.

Aside from future technological improvements, PBT has already been well received in the international medical community, and is now available in more than 57 centers worldwide [17].

As in other precision RT techniques, phase III randomized clinical trials (RCTs) are not the best research setting, as they have intrinsic limitations in design and data analysis that prevent the positive findings of randomized trials investigating pharmaceuticals agents to be extrapolated to phase III studies with medical technologies. New availability of pencil-beam scanning and the consideration of new biological rationales such as avoidance of bone marrow and circulating blood radiation exposure, may be especially relevant to patients due to the central role of the immune system in cancer therapy.

3. Evolutive and consolidated clinical outcomes

Clinical results based on novel treatments need both time to mature, and a method of comparison that can define the best indications in the context of currently available accurate precise RT. Mature results from some studies recommend PBT for extreme indications in radioresistant, indolent yet highly infiltrative and extensive cancer lesions, and in patients requiring re-irradiation due to symptomatic oligo-recurrence.

The following is a summary of the clinical results of a selective review of the latest, most influential, clinical studies analyzing synchrotron-based PBT institutional outcomes. The data available generally relates to established and developmental indications, together with some comparative analysis with other RT technologies. The information was obtained from a specific literature search and systematic reviews spanning 2010–2020.

3.1 Pediatric tumors

In 2020 PBT is the radiation therapy technology of election for pediatric oncology patients. The evolution towards this practice status has been fast. A survey conducted between July 2017 and June 2018 in all proton centers treating pediatric patients in 2016 worldwide identified a total of 54 centers operating in 11 countries (Particle Therapy Co-Operative Group, PTCOG website). Among the 40 participating centers (74%), a total of 1860 patients were treated in 2016 (North America: 1205, Europe: 432, Asia: 223.

More than 30 pediatric tumor types were identified, mainly treated with curative intent. About half of the patients were treated with pencil beam scanning [18].

Pediatric cancer patients referred to proton therapy centers do benefit from expert dedicated highly specialized care both in terms of normal tissue protection to radiation exposure during treatment delivery and from early access to medical integral care and radiotherapy process (5 weeks median starting time) [19].

A critical milestone to facilitate long-term clinical outcomes research in the modern era has been achieved. The Pediatric Proton Consortium Registry (PPCR) has reported a total of 1854 patients enrolled from October 2012 until September 2017. The cohort is 55% male, 70% Caucasian, and comprised of 79% United States residents. Central nervous system (CNS) tumors were the most frequent group of diseases (61%). The most common non-CNS tumors diagnoses were: rhabdomyosarcoma (n = 191), Ewing sarcoma (n = 105), Hodgkin lymphoma (n = 66), and neuroblastoma (n = 55) (**Table 1**) [20].

3.2 Central nervous system

Radiotherapy confers survival advantages to patients with glioblastoma, medulloblastoma, germ cell, ependymoma and other intracranial neoplasms. This cost-effective and accessible treatment modality has proven efficacy in the adjuvant and definitive setting, as a first-line treatment or after prior lines of therapy. Neuro-radiation oncology has witnessed a burgeoning of new techniques, technologies and strategies that will better optimize the therapeutic ratio. Proton beam therapy (PBT) offers the potential to minimize late-onset toxicities while preserving disease-related outcomes. Multidisciplinary efforts explore synergies between the effects of radiotherapy and novel systemic therapies to tailor the delivery by molecular profile (**Table 2**) [41].

3.3 Head and neck cancer

PBT has emerged as a novel means to reduce toxicity and potentially further improve tumor control in head and neck cancer patients. The unique physical properties of charged particles allow a steep dose gradient with a reduced integral dose delivered to the patient in a proportion that can meaningfully reduce dose-related toxicity.

For the National Comprehensive Cancer Network guidelines, proton therapy is a standard of care for base of skull tumors and is an optimized option for periorbital tumors. The use of proton therapy is expanding for other cancer sites. Novel forms of proton therapy such as IMPT, and technical improvements in dose modeling, patient setup, image guidance and radiobiology, will help further enhance the benefits of proton therapy. The present cost of delivering PBT is approximately 2–3 times higher than for delivering IMRT photons in the head and neck (H&N) cancer model of health care. However, the cost difference is reduced when costs are considered over the entire cycle of care. Predictive models using comorbidity scales could defined a subpopulation of patients for whom proton therapy is likely to reduce side effects and subsequent use of health care resources (**Table 3**) [52].

3.4 Lung cancer

The call for designing and conducting “smart” proton therapy trials for lung cancer patients requires establishing clinical evidence and patient selection criteria to make proton therapy a truly personalized form of treatment. Comparative trials could focus on endpoints such as cardiac toxicity, low-dose radiation bath, and lymphopenia. The enhancement of dosimetric and biological advantages of PBT to improve clinical outcomes requires further developments in image-guided

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Haas-Kogan [21]	2018	671	Posterior fossa tumors: 57% medulloblastoma, 29% ependymoma, 14% gliomas and AT/RT*	Evaluation of brainstem toxicity	54–59.4 Gy	PB	Average rate of symptomatic brainstem toxicity 2.38%.
Mizumoto, [22]	2017	62	Head and neck (24), brain (22), body trunk (9), others (7)	Evaluation of late toxicity	10.8 to 81.2 Gy (median:50.4Gy). Standard fractionation	PB	5-, 10-, 20-year rates for grade ≥ 2 late toxicities: 18%, 35%, 45%. No tumors within irradiated field
Mizumoto, [23]	2016	343	Brain tumor (79), rhabdomyosarcoma(71), neuroblastoma(46), Ewing sarcoma (30), head and neck carcinoma(27), chordoma(14), brain stem tumor (17), cerebral arteriovenous malformation(8), others(51).	Reirradiation ± surgery± concurrent chemotherapy Evaluation of efficacy and late toxicity	10.8 to 100 Gy (median:50.4Gy). Combination PBT and photon: 24	PB ± Photon	Survival rates 1-, 3-, 5-, 10-year: 82.7%, 67.4%, 61.4%, 58.7%. Toxicity: 52 events grade ≥ 2 in 43 pts. Grade 4 in 5pts.
Buszek, [24]	2019	19	Rhabdomyosarcoma: Bladder (14) and prostate (5).	Chemotherapy ± surgical resection	36.0–50.51 Gy(RBE) (median 50.4)/1.8	PB	5-year OS and PFS: 76%. 5-year LC for tumor >5 cm 43% vs. 100% for ≤5 cm (p = 0.006). Acute grade 2 toxicity in 2 pts. (11% proctitis).
Merchant, [25]	2008	40	Optic pathway glioma (10), craniopharyngioma (10), infratentorial ependymoma (10), medulloblastoma (10).	Not reported	Not specified Comparison of toxicity between PB and photons.	PB vs. Photon	PB lower the distribution of low and intermediate (0–20, 20–40 Gy). Large difference in overall dose distribution.
Antonini, [26]	2017	39	Glioma (10), medulloblastoma (14), germ cel tumor (9), craniopharyngioma (4), other(2)	Not reported Evaluation of neurocognitive effect of PB in attention, processing speed, and executive functioning	Median, range(Gy): Focal: 50.40 (45.00–60.00) CSI: 55.80 (45.00–55.80);	PB	Focal: normal limits. CSI: difficulties in underlying component skills (i.e, processing speed)
Kahalley, [27]	2016	150	XRT: Glioma(8), medulloblastoma / PNET(28), ependymoma (13), germ cell tumor (3), other (8). PBRT: Glioma (20),	Comparison Intelligence Quotient (IQ) change after PBRT vs. XRT (60 XRT, 90 PBRT)	Median, range(Gy): Photon: 54.0 (30.6–59.4). PBRT: 54.0 (30.0–60.0)	PB vs. Photon	PBRT: no change in IQ over time. XRT: IQ declined by 1.1 points per year (P = .004).

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
			medulloblastoma/ PNET (34), ependymoma (4), germ cell tumor (17), other (15)				IQ slopes did not differ between groups (P = .509
Taddei, [28]	2018	9	Medulloblastoma	Estimate reductions in projected lifetime SMN incidence and mortality if treated with proton CSI vs. photon CSI	CSI 23.4 Gy-RBE in 1.8 Gy-RBE fractions	PB vs. Photon	Ratio SMN incidence PB CSI to photon CSI: 0.56 (95% CI, 0.37 to 0.75) Ratio SMN mortality PB CSI to photon CSI: 0.64 (95% CI, 0.45 to 0.82)
Peeler, [29]	2016	34	Ependymoma (supratentorial 10, infratentorial 24)	After surgery To determine if areas of normal tissue damage were associated with increased biological dose effectiveness.	54–59.4 Gy	PB	Image changes dependence on increasing LET and dose. TD50 decreased with increasing LET = increase in biological dose effectiveness
Gunther [30]	2015	72	Ependymoma: IMRT: 21 infratentorial PBRT: 26 infratentorial	Postoperative RT ± chemotherapy before RT ± chemotherapy after RT	Median, range(Gy): IMRT 54.0 (50.4–59.4) PB 59.4 (53.0–59.4)	PB and IMRT	PBRT was associated with more frequent imaging changes(OR: 3.89, P < .024).
Sato, [31]	2017	79	Ependymoma (54 infratentorial)	Postoperative RT ± chemotherapy after RT (IMRT 38, PRT 41)	Median, range (cGy): IMRT: 5400 (5040–5940) PB: 5580 (5040–5940)	PBT and IMRT	3-year PFS rates were 60% and 82% with IMRT and PRT, respectively (P = .031)
Adesina, [32]	2019	83	Low grade glioma: Brainstem (19), cerebral hemispheres (6), thalamus (13), optic pathway/hypothalamus (29), other (16).	Surgery ± chemotherapy (IMRT 32, PBT 51)	Median, range (Gy): IMRT: 50.4 (45–59.4) PBT: 50.4 (45–54)	PB	Post-RT enlargement rates PBT vs. IMRT: HR 2.15, 95% CI 1.06–4.38, p = 0.04). RT dose >50.4Gy (RBE) > rates of PsP (HR 2.61, 95% CI 1.20–5.68, p = 0.016)
Zhang [33]	2014	17	Medulloblastoma	Surgery + chemotherapy	CSI 23.4 or 23.4 Gy (RBE) to the age specific target volume at 1.8 Gy/ fraction	PB	Proton superior outcomes (< predicted risks of 2nd cancer and cardiac mortality than photon).

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Bagley, [34]	2018	18	High risk neuroblastoma: retroperitoneum/abdomen (16), thorax/mediastinum (2)	Chemotherapy + resection + autologous stem cell transplant + cis-retinoic acid ± immunotherapy	PT to primary + up to 3 MIBG-avid metastasis: - Primary sites: 21–36 Gy - Metastatic sites: 21–24 Gy	PB (1 IMPT)	2 and 5-year local control rates at primary site: 94% and 87%. 5-year overall survival (OS) 94%
McGovern, [35]	2014	31	AR/RT Tumor CNS	Surgery + Chemotherapy	Focal: 50.4GyRBE (9–54). CSI: 24–30.6 GyRBE. Tumor dose: 54 Gy (43.2–55.8)	PB	Median follow-up 24 months (3–53). PFS 20.8 months. OS 34.3 months. 16% symptoms and brainstem image changes
Grant, [36]	2015	24	Salivary gland tumor: parotid (20), submandibular (4).	Surgery ± concurrent chemotherapy (11 photons, 13 PRT)	X/E RT: 60 (54–66) PRT: 60 (56.4–66) 30 sessions	PB vs. Photons	PRT lower doses to surrounding and contralateral structures.Favorable acute toxicity and dosimetric profile.
Mizumoto, [37]	2018	55	Rhabdomyosarcoma. Histology: 18 alveolar. Localization: Head and neck (37), parameningeal (3), prostate (8), others (7).	Surgical resection ± chemotherapy	36–60 GyE (median: 50.4 GyE). Fractions: 1.8	PB	2-year OS 84.8% (95%CI 75.2–94.3%). 100%, 90.1%, 42.9% for COG low-, intermediate- and high-risk. Not specific toxicity.
Ladra, [38]	2014	54	Rhabdomyosarcoma: Orbital (12), head and neck(3), perineal/ perianal (2), biliary (1), parameningeal (24), bladder/prostate (7), extremities (3), chest/abdomen (2)	Surgical resection ± chemotherapy Dosimetric comparison of PB and IMRT	36–50.4 Gy (median 50.4 Gy)	PB vs. IMRT	Mean integral dose was 1.8 times higher for IMRT
Ladra, [39]	2014	57	Rhabdomyosarcoma: Orbital (13), head and neck (4), perineal (1), biliary (1), parameningeal (27), bladder/prostate (5), extremities (3), chest/abdomen 2, perianal 1.	Surgical resection ± chemotherapy	Radiation dose GyRBE: Median 50.4: Range 36.0–50.4		5-year EFS, OS, LC: 69%, 78%, 81%, respectively. Toxicity: Acute:13 pts. grade 3; Late: 3 pts. grade 3. No toxicities > grade 3.

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Tamura, [40]	2017	26	A. Brain B. Chest C. Abdomen D. Whole CNS(medulloblastoma)	Surgery ± chemotherapy Comparison PBT to IMXT in lifetime attributable risk of radiation-induced secondary cancer (LAR)	**A:** 30.6–57.6 Gy/ 1.8 Gy. **B:** 25.2–60 Gy. /1.8–2.5Gy **C:** 25.2–72.6 Gy/ 1.8–3.3 Gy. **D:** 18–23.4 Gy/ 1.8 Gy	PB	In pts. undergone PBT LAR was lower than IMXT estimated LAR useful marker of secondary cancer induced by radiotherapy

Table 1.
Clinical experiences with synchrotron PBT in pediatric tumors (AT/RT: atypical teratoid rhabdoid tumors; OS: overall survival; PFS: progression-free survival; LC: Local control; SMN: secondary malignant neoplasms; LET: linear energy transfer; TD50; dose at which 50% of patients would experience toxicity; PsP: Pseudoprogression; EFS: event-free survival; PB: passive beam; IMRT: intensity modulated radiotherapy; IMPT: intensity modulated proton therapy; CSI craniospinal irradiation).

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Bronk [42]	2018	99	Grade II-III oligodendroglioma or astrocitoma IDH mut 52%	PB(34) vs. IMRT(65) in development of pseudoprogression	50–54 RBE standard fractionation	PB	No difference in pseudoprogression rate 6 months after proton or photon therapy.
Wilkinson [43]	2016	58	Low-grade gliomas Oligodendroglioma 33% Astrocitoma 38% Mixed 29%	Evaluation of acute toxicity	50–54 RBE standard fractionation	PB	No G3 toxicity 78% G1–2 dermitis, 81% alopecia, 47% fatigue.
Amsbaugh [44]	2012	8	Primary spinal ependymomas n = 6 Grade I; n = 2 grade II.	Surgery before RT	45–54 RBE/25 fx	PB	mFT 26 months. Local control, event-free survival, and overall survival rates were all 100%
Jaramillo [45]	2019	7	Embryonal tumors with multilayered rosettes (ETMRs)	Surgery	52–56 RBE/30 fx	PB	mFT 40 months. mOS 16 months 3 pts. survived ≥36 m 5 pts. had LRF
Vatner [46]	2018	189	Medulloblastoma: 130 Ependymoma: 26 Low grade glioma: 14	CSI ± surgery ± systemic ChT	23.4 Gy/ 1.8 GyRBE	PB	-mFT 4.4y −4-y actuarial rate hormone deficency, GH, TH, ACTH and FSH/LH were 48.8%, 37.4%, 20.5%, 6.9%, and 4.1%, respectively. -Age at start of RT, time interval since treatment, and median dose to the combined hypothalamus and pituitary were correlated with increased incidence of deficiency.
Stoker [47]	2014	10	CNS tumors. 5 adults, 5 pediatric.	Compare field junction robustness and OARs in CSI IMPT vs. PSPT	N/E	IMPT	IMPT vs. PSPT (PB) lowered maximum spinal cord dose, improved spinal dose homogeneity, and reduced exposure to other OARs.
Barney [48]	2014	50	CNS tumors. 38% medulloblastoma.	Surgery + Systemic ChT	CSI 30.6 RBE + Boost 54 RBE	PB	Nausea/vomiting G2 20% Anorexia G2 10% G3 cytopenia 8%

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Brown [49]	2013	40	Medulloblastoma in adults	Surgery. EP: Acute toxicity n = 19 PBT; n = 21 photon CSI	CSI 30.6 RBE + Boost 54 RBE	PB	PBT pts. lost significantly less weight than photon pts., less nausea/vomiting, less cytopenia. Esophagitis 57% vs. 5%
Zhang [50]	2012	1	Medulloblastoma	Risk of second cancer: 3-field 6MV photon vs. 4-field PBT	CSI 23.4 RBE	PB	Lifetime risk second cancer 7.7 vs. 92%. Proton therapy confers lower predicted risk of second cancer for the pediatric medulloblastoma patient compared with photon therapy.
Bielamowicz [51]	2018	95	Medulloblastoma PBT n = 41	MRF surgery + CSI Photons vs. PBI hypothiroidism	23.4 RBE standard CSI 36–39 RBE in HR pts.	PB	Hypothiroidism: mFT PBT 3y 19% mFT photons 9y 46.3%

Table 2.
Clinical experiences in CNS tumors treated with synchrotron technology (2012–2019). OARs: organs at risk; RBE: radiobiological equivalence; CNS: central nervous system; ChT: Chemotherapy).

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Blanchard [53]	2016	50 IMPT 100 IMRT	Locally advanced oropharynx cancer	IMRT vs. IMPT Neck disSection 23%	66–70 RBE/35 fx	IMPT	IMPT is associated with reduced rates of feeding tube dependency and severe weight loss
Frank [54]	2014	15	10 pts. SCC 5 pts. adenoid cystic carcinoma. Locally advanced.	NR	66–70 RBE/35 fx	IMPT	mFT: 28 m cCR: 93.3% Xerostomía G3: 1 patient Mucositis G3: 6 pts.
Bagley [55]	2020	69	Oropharingeal carcinoma stage III-IV	Xerostomia-Related QoL	70 RBE/35 fx	PB	greatest xerostomia-related QoL impairment at 6 weeks. 49% improvement after 10 wks.
Jensen [56]	2017	50 IMPT 100 IMRT	Oropharingeal carcinoma stage III-IV	Prognostic impact of leukocyte counts before and during radiotherapy. IMRT vs. IMPT	70 RBE/35 fx	IMPT	The radiotherapy type (IMRT vs. IMPT) was not associated with lymphopenia. Poor progression-free survival was associated with pretreatment leukocytosis and T status in univariate analysis, and pretreatment neutrophilia and advanced age on multivariate analysis.
Zhang [57]	2017	50 IMPT 534 IMRT	Locally advanced oropharynx cancer	IMRT vs. IMPT	66–70 RBE/35 fx	IMPT	mFT: 33.8 m Osteoradionecrosis rates: 2% IMPT, 7.7% IMRT.
Sio [58]	2016	35 IMPT 46 IMRT	Oropharyngeal Cancer Stage III-IVa.	IMRT vs. IMPT	70 RBE/35 fx	IMPT	Symptom burden was lower among the IMPT patients than among the IMRT patients during the subacute recovery phase after treatment
Gunn [59]	2016	50	Oropharingeal SCC stage III-IV	Concurrent chemo-IMPT 32% IC concurrent chemo-IMPT 30%	66–70 RBE/35 fx	IMPT	mFT: 29 m 2- year actuarial: OS 94.5%; PFS 88.6%. N = 5 recurrence. G3 toxicities: mucositis 58%; dysphagia 12%.
Ludmir [60]	2019	46	H&N alveolar rhabdomyosarcoma in children	Systemic ChT	50.4 RBE/ 25 fx.	PB	mFT: 3.9y 5-y: OS 76% PFS 57%

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
							LC: 84% Tumor size >5 cm, delayed RT after ChT and ICE increased risk.
Ludmir [61]	2018	14	H&N alveolar rhabdomyosarcoma in children 57% localized 43% N+	Systemic ChT	50.4 RBE/ 25 fx.	PB	mFT: 4.3 y 5-y: OS 45% DFS 25% 71% relapsed
Phan [62]	2016	60	SCC 40 pts. Non-SCC 20 pts.	Reirradiation 58% upfront surgery 73% ChT	66 RBE/30 fx	25% IMPT 75% PB	mFT: 13.6 m 1-y: LC 68.4% OS 83.8% PFS 60% DMFS 75% 30% toxicity G3.

Table 3.
Clinical experiences in head and neck cancer treated with synchrotron technology (2014–2019). (mFT: median follow up time).

hypofractionated intensity modulated proton therapy (IMPT) and combinations of hypofractionated proton therapy with immunotherapy [63].

For early-stage non-small cell lung cancer (NSCLC), the optimal clinical context for proton beam therapy (PBT) is challenging due to the increasing evidence demonstrating high rates of local control and good tolerance of stereotactic ablative body radiation (SABR). The potential advantage may be significant in treating larger tumors, multiple tumors, or central tumors. Most of the published studies are based on passive scattering PBT. Dosimetric benefits are likely to increase whith pencil beam scanning/intensity-modulated proton therapy (IMPT) [64]. A prospective longitudinal observational study of 82 patients with unresectable primary or recurrent NSCLC treated with 3-dimensional conformal radiation therapy (3DCRT), IMRT, or proton therapy included patient-reported symptom burden, assessed weekly for up to 12 weeks with the validated MD Anderson Symptom Inventory. Despite the fact that the proton group received significantly higher target radiation doses ($P < 0.001$), patients receiving proton therapy reported significantly less severe symptoms than did patients receiving IMRT or 3DCRT [63]. (**Table 4**).

3.5 Esophageal cancer

Radiation therapy (RT) has become an important component in the curative management of esophageal cancer (EC). Since most of the ECs seen in the Western hemisphere (i.e., Europe and the United States) are located in the mid- to distal-esophageal locations, heart and lungs invariably receive significant radiation doses. Proton beam therapy (PBT) provides the ability to further reduce normal tissue exposure because of its lack of exit dose, which is expected to provide clinically meaningful benefit for at least some EC patients [90].

Investigators at MD Anderson Cancer Center have reported a phase IIb randomized trial comparing PBT and IMRT for patients with EC (NCT01512589). The primary endpoints are progression-free survival and total toxicity burden, which is a composite endpoint including serious adverse events and postoperative complications. Among the 145 patients randomized, total toxicity burden was 2.3 times higher for photon IMRT and the postoperative complications (50% of patients were operated) was 7.6 times higher in photon IMRT cohort. The 3-year overall survival was similar in both groups (44%) [91]. Results from prospective clinical trials will greatly improve our knowledge regarding the role and benefits expected from proton therapy for EC. (**Table 5**).

3.6 Hepatocellular cancer

Proton beam therapy has the unique dosimetric performance, particularly valuable for the treatment of hepatocellular carcinoma (HCC). Clinical data is available in a limited number of patients, especially from Japan. In a systematic review from 1983 to June 2016 to identify clinical studies on charged particle therapy for HCC, a total of 13 cohorts from 11 papers. The reported actuarial local control rates ranged from 71 to 95% at 3 years, and the overall survival rates ranged from 25–42% at 5 years. Late severe radiation morbidities were uncommon, and a total of 18 patients with grade ≥ 3 late adverse events were reported among the 787 patients included in the analysis.

The American Society for Radiation Oncology (ASTRO) issued a Model Policy on PBT in 2014 and PBT for HCC is covered by medical insurance in the United States. The Japanese Clinical Study Group of Particle Therapy (JCPT), the Japanese Society for Radiation Oncology (JASTRO), the Japanese Radiation Oncology Study

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Lin [65]	2016	11	II-III NSCLC	4D versus 3D Robust Optimization	66 RBE/33 fx	PB	4D robust optimization improved dosimetry in comparable targets.
Welsh [66]	2013	260	Primary NSCLC	SBRT photon vs. SBRT proton dosimetric comparison	50 Gy/4 fx	PB	SBRT protons: Same coverage, significant reduction dose in chest wall and lung.
Matney [67]	2013	20	NSCLC IIB-III	Randomized IMRT vs. PSPT. 4D-3D dose variables	60–70 Gy/ 30–35 fx	PB	-Target coverage maintained up to 17 mm in both. −2/11 pts. less susceptible to respiratory motion PSPT
Nguyen [68]	2015	134	NSCLC II-III inoperable	Concurrent CT −21 stage II −113 stage III	60–70 Gy/30–35 fx	PB	−4.7 y follow-up -mOS stage II: 40 months Stage III: 30 months. OS, DFS, LC no difference by stage.
Niedzielski [69]	2017	134	NSCLC stage III.	IMRT(85 pts) vs. PSPT(49 pts) Esophageal toxicity (clinical and image)	60–70 Gy/30–35 fx	PB	No significant difference in esophageal toxicity found between proton and photon-based radiation therapy for the study cohort, based on imaging biomarker or CTCAE grade
Ohnishi [70]	2019	669	NSCLS stage I 38% T1a; 31% T1b; 29% T2a.	Efficacy and safety PBT	74–113 Gy	PB	3-y OS 79,5%. >100 GyE improved outcomes
Elhammali [71]	2019	51	Advanced inoperable NSCLC	Concurrent Cht	67.3 Gy	IMPT	3-y LC 78%. mOS 33 months,DFS 12 months. G3 toxicity 18%
Nakajima [72]	2018	55	Stage I NSCLC IA 33 pts. IB 22 pts	Image-guided fiducials (71%)	66 Gy/10fx 72 Gy/ 22 fx	PB	3-y OS 87%; 74% DFS; 96% LC No G3 toxicities.
Nantavithya [73]	2018	19	Inoperable stage NSCLC with HR features.	SBRT vs. SBPT	50 Gy/4 fx	PB	3-y OS 27% LC 90%

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
McAvoy [74]	2013	33	Recurrent after RT 63 Gy/33fx. III 20 pts.	Area of failure after initial RT: 19 pts. "in field". 31 pts. concurrent ChT.	63 Gy/33 fx	PB	1-y OS 47% DFS 28% LC 54% Toxicity≥3G pulmonary 21%
Gomez [75]	2013	25	NSCLC, thymic, carcinoid tumors.	Phase I. Dose-escalation hypofractionated PBT	45–52.5-60 Gy/15 fx.	PB	Dose-limiting toxicity: 2 pts. experienced fistula (52,5Gy). 60 Gy pneumonitis G4
Xiang [76]	2012	84	Stage III NSCLC	Concurrent Cht FDG uptake correlate (SUV1 pre, SUV2 post)	74 RBE/35 fx	PB	KPS and SUV2 were independently prognostic for LRFS, DMFS, PFS and OS.
Gomez [77]	2012	108	Stage III NSCLC (50–70% pts)	Esophagitis Concurrent ChT 405 3DCRT 139 IMRT 108 PBT	≥50 Gy/25–30 fx	PB	Esophagitis ≥ G3 -3DCRT 28% -IMRT 8% -PBT 6%
Koay [78]	2012	44	Stage III NSCLC	Concurrent ChT Analyze dosimetric variables and outcomes after adaptive replanning	74 RBE/37 fx	PB	-Adaptative planning more often performed in large tumors. −107.1 cm^3 adaptive VS 86.4 cm^3 nonadaptive. - Median n° fx: 13 -Improvement in esophagus and SC.
Register [79]	2011	15	Stage I NSCLC	Central or superior tumors. Photon SBRT vs. PSPT vs. IMPT	50 Gy/4 fx	PB/IMPT	When the PTV was within 2 cm of the critical structures, the PSPT and IMPT plans significantly reduced the mean maximal dose to the aorta, brachial plexus, heart, pulmonary vessels, and spinal cord.
Chang [80]	2011	44	Stage III NSCLC	Phase II study Concurrent ChT	74 RBE/35 fx	PB	1-y OS 86%; PFS 63% Non-haematological G3 toxicity: 5 dermatitis, 5 esophagitis, 1 pneumonitis. n = 9 local recurrence.

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Shusharina [81]	2018	83	Inoperable II-III stage. Oligo-mtx NSCLC	Compare lung injury IMRT vs. PBT revealed by ^{18}F-FDG post-treatment uptake	74 RBE/ 37fx	PB	The slope of linear 18F-FDG-uptake – dose response did not differ significantly between the two modalities
Jeter [82]	2018	15	Stage II-III NSCLC	Phase I study. Integrated simultaneous boost for dose-escalation IMRT (6) vs. IMPT (9).	72 Gy IMRT 78 RBE IMPT	IMPT	Grade ≥ 3 pneumonitis developed in 2 of the 6 patients treated to 78 Gy(CGE) IMPT SIB
Chang [83]	2017	64	Unresectable stage III NSCLC -IIIA 47% -IIIB 53%	Phase II study Concurrent ChT	74 RBE/37fx	PB	mOS 26 months 5y PFS 22%; LRR 28% Late pneumonitis G2 16% G3 12% 3% bronchial stricture.
Chang [84]	2017	35	Early stage (IA-II). 12 T1N0 23 T2–3 N0	Phase I-II prospective inoperable dose-escalated PBT	87 RBE/35fx	PB	-Median follow up: 83 months. −5-y OS 28% LC 54% Pneumonitis G2 11%; G3 3% Heart G2 5,7%; Chest wall 2,9%.
Chao [85]	2017	52	IIIA 51%. Recurrent NSCLC	Re-irradiation 67% concurrent ChT	66 Gy 30–74 RBE	PB	42% ≥ G3 toxicity. The 1-year rates of overall and progression-free survival were 59% and 58%, respectively.
Giaddui [86]	2016	52	Inoperable stage II-IIIB	Compliance criteria RTOG 1308: Phase III 26 IMRT vs. 26 PBT	70 RBE/35fx	PB	RTOG 1308 dosimetric compliance criteria are feasible and achievable
Wang [87]	2016	82	Locally advanced NSCLC.	3DCRT (22) vs. IMRT(34)vs. PBT(26) Patient-reported symptom burden	Higher radiation target dose used PBT	PB	Patients reported significantly less severe symptoms (pain, fatigue, lack of appetite, sleep and drowsiness).
McAvoy [88]	2014	99	Reirradiation for intrathoracic recurrent NSCLC	Concurrent ChT	60 EQD2 Reirradiation dose. 70 Gy median inital dose.	IMPT	Toxicity ≥ G3 7% esophageal and 10% pulmonary. Median LC,DMFS, and OS times were 11.43 months, 11.43 months, and 14.71, respectively.

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Lopez Guerra [89]	2012	60	−80% stage III-IV. −40% squamous cell −35% adenocarcinoma	-Change in pulmonary function over time with PBT -Concurrent ChT. -PBT (60) vs. 3DCRT (93) vs. IMRT (97)	74 RBE	PB	Lung diffusing capacity for carbon monoxide is reduced in the majority of patients after radiotherapy with modern techniques. Multiple factors, including gross tumor volume, preradiation lung function, and dosimetric parameters, are associated with the DLCO decline.

Table 4.
Clinical experiences in lung cancer treated with synchrotron technology (2011–2019).

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Ono [92]	2019	202	100 patients stage III/IV	90 inoperable patients.	87,2 median BED	4 PB centers	5y OS 56,3% 5Y LC 64,4%
Fang [93]	2017	448	IA-IVA III 56%	IMRT vs. PBT Lymphopenia	50.4 Gy/28 fx	PB	Significant less lymphopenia in lower esophagus
Xi [94]	2017	343	I-III III 65%	CRT definitive IMRT vs. PBT	≤50,4 Gy/28 fx 87%	Only 7 IMPT (5,3%)	PBT significant better OS,PFS,DMFS,LRFFS
Shiraishi [95]	2017	272	IIA-IVA III 59% 94% lower third 94% adenoca.	Neoadyuvant CRT IMRT vs. PBT lymphopenia	50,4 Gy/28 fx	PB	G4 lymphopenia 40% vs. 17% during nCRT
Prayongrat [96]	2017	19	IIB + III 80% 63% Distal third	CRT (4 surgery)	50,4 Gy/28 fx	IMPT single field 13	84% complete response. 4% surgery. G3 esophagitis (3 pts) 1-y OS 100% Mean heart dose 7.5 Gy
Shiraishi [97]	2017	727	I-IVA III 60% 89% Distal third	477 IMRT 250 PB DVH comparisons//Cardiac dose// Surgery 50%	50,4 Gy/28 fx	IMPT 13	Significant lower radiation exposure, MHD (chambers and coronary arteries).
Lin [98]	2017	580	I-IV III 63%	37% 3D 44% IMRT 19% PB Postop morbidity+outcome lenght in hospital. Stay LOS	50,4 Gy/28 fx	3 institutions (1/3 PB)	LOS: 3D 13.2d IMRT 11.6 d PB 9.3 d Pulmonary+cardiac+wound complications
Yu [99]	2016	11	100% Distal and GEJ	4D robust CT calculations	Dosimetric comparison	IMPT	Changes of water equivalent thickness ΔWET inspirations and espiration
Echeverria [100]	2012	100	I-IV III 51% 82% Distal third	Pneumonitis CTCAEv4 Re-staging PET-CT FDG 100%	50,4 Gy/28 fx	PB	Linear dose–response on FDG PET-CT. Symptomatic pts. had higher dose response slope.

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Lin [101]	2012	62	I-IV II-III 84%	CRT + surgery (46%) Stage II + III (84%) Adenocarcinomas (76%)	50,4 Gy/28 fx	PB	Esophagitis 46% ypT0N0 28% 5y OS 37% Mean CR 50%
Zhang [102]	2008	15	I-IV	4DCT scan VS IMRT	50,4 Gy/28 fx	PB	3D vs. 4D plans % Gy sparing spinal cord MaxD. 2 fields vs. 3 fields: Better lung sparing, less conformality target.
Lin [103]	2020	145	II-III	Induction ChT IMRT vs. PBT randomized	50,4 Gy/28 fx	PB IMPT (20%)	Total toxicity burden and postoperative complications significantly lower in PBT cohort. 3-y OS 44%.

Table 5.
Clinical experiences in esophageal cancer treated with synchrotron technology (2012–2019).

Group (JROSG) and other groups are conducting multi-institutional prospective clinical trials in order to obtain approval for national health insurance for HCC and other cancers. The NCCN guidelines recommend that PBT may be appropriate in specific situations. In the Japanese guidelines, can be considered for HCCs that are difficult to treat with other local therapies, such as those with portal vein or inferior vena cava tumor thrombus and large lesions. The Korean Liver Cancer Study Group also mentioned the efficacy of PBT in their guidelines [104]. Guidelines from expert hepatologists evaluating the of data available for HCC patients will influence on the pattern of clinical practice considering the option of PBT as upfront therapy in the decision-making process (**Table 6**) [105].

3.7 Lymphoma

In adult lymphoma survivors, radiation treatment with increase excess of radiation dose to organs at risk (OARs) does increase the risk for side effects, especially late toxicities. Minimizing radiation to organs at risk (OARs) in adult patients with Hodgkin and non-Hodgkin lymphomas involving the mediastinum is the decisive factor to select the treatment modality.

Proton therapy reduces the unnecessary radiation to the OARs and reduces toxicities, especially the risks for cardiac morbidity and second cancers. In modern guidelines for adult lymphoma patients, the benefit from proton therapy and the advantages and disadvantages of proton treatment are considered. The dosimetric advantage of reducing the unnecessary dose to lung, breast, heart, spinal cord, vessels, vertebrae, thyroid and other structures in certain lymphoma involvements can be significant and highly desirable for patients that will be extreme long-term survivors at risk for severe chronic conditions and second malignancies [112] (**Table 7**).

3.8 Prostate

PBT for prostate cancer patients has been a continuously growing option due to its promising characteristics of high precision dose distribution in the target and a sharp distal fall-off. Considering the large number of proton beam facilities in Japan, the further increase of patients undergoing this treatment will be related to the policies of the Japanese National Health Insurance (NHI) together with the development of medical equipment and technology. A review conducted review to identify and discuss research studies of proton beam therapy for prostate cancer in Japan (up to June 2018) included 23 articles (14 observational, focused on the adverse effects), and 7 interventional on treatment planning, equipment parts, as well as target positioning. Favorable clinical results of PBT were consistent and future research should focus on longer follow-up clinical data. PBT is a suitable treatment option for localized prostate cancer [116].

At present, as particle beam therapy for prostate cancer is covered by the Japanese national health insurance system (since April 2018), and the number of facilities practicing particle beam therapy has increased recently, the number of prostate cancer patients treated with particle beam therapy in Japan is expected to increase drastically [117]. (**Table 8**).

3.9 Miscellaneous neoplasms and oncological clinical conditions

PBT has been explored in a variety of cancer sites, histological subtypes and disease stages, including localized breast cancer, seminoma, pancreatic cancer, oligo-recurrences and other cancer conditions. (**Table 9**).

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Takahashi [106]	2019	31	HCC recurrent after PBT. Child-Pugh class A (90%)	Angiography+TACE or TA in previous PB	77 RBE/35 fx 72 RBE/ 22 fx 66 RBE/ 10 fx	PB	Abnormal staining of the irradiated liver parenchyma was observed in 22 patients
Chadha [107]	2019	46	Unresectable HCC Child-Pugh class A-B 1–3 tumors.	22% multiple 28% vascular 57% recurrent	97 RBE/ 15 fx BED ≥90 GyE BED <90 GyE	PB	2-y LC 81% OS 62% 13% G3 toxicity
Hsieh [108]	2019	136	85%Posthepatectomy No RT Stage I-II: 49% Stage III: 39% BCLC-C 60%	RILD	66 RBE/10 fx 72 RBE/22 fx 67 RBE/15 fx	PB	Unirradiated tumor volumen/gross tumor volumen and Child-Pugh independently predicts RILD in patients with HCC undergoing PBT
Sanford [109]	2019	133	Unresectable HCC PB 37%. Child-Pugh class A 83% Child-Pugh class B-C 17%.	Protons vs. photons ablative	45 Gy/15fx 30 Gy/5–6 fx Liver GTV: 24 Gy/ 15 mean dose	PB	Improved 2y OS 59 vs. 28%. Decrease RILD Less liver descompensations
Hong [110]	2016	92	Unresectable or locally recurrent HCC or ICC 47 HCC 37 ICC	No prior RT 29% vascular thrombosis. 27.3% mutiple tumors	67.2 RBE / 15 fx	PB	2-y LC 94% OS 63%; 46%
Grassberger [111]	2018	43	22 HCC 21 ICC	Flow citometry lymphocite populations. CTLs NK prior/during/ after.	67.5 RBE / 15 fx	PB	• mOS 0.6 months for HCC and 14.5 months for ICC patients. • Longer OS significantly correlated with CTLs. • 42 months follow-up.

Table 6.
Clinical experiences in liver cancer treated with synchrotron technology (2016–2019); RILD: radiation induced liver disease; mOS: median overall survival.

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Ricardi [113]	2017	138	I-II 73% III-IV 27% Mediastinal involvement 96% Bulky 57%. No-relapse; No-refractory	Consolidation ChT	21 RBE pediatric 30.6 RBE adults	PB	3-y DFS 92% No G3 radiation toxicities
Rechner [114]	2017	22	Early-stage HL: Mediastinal	-Dosimetric comparisons. -IMRT vs. PBT -DIBH vs. free breathing.	30.6 RBE/17 fx	PB	DIBH with PBT significantly reduced life of year lost compared to IMRT in FB
Zeng [115]	2016	10	Early-stage HL: Mediastinal	Dosimetric comparison IMRT vs. 3DCRT vs. IMPT	30.6 RBE/17 fx	IMPT	IMPT significantly reduced lung and cardiac doses.

Table 7.
Clinical experiences in malignant lymphoma treated with synchrotron technology (2016–2017).

A special challenge for defining PBT health value are geriatric cancer patients. Aging and chronic comorbidity is a medical reality in the present and future of oncology practice. It is projected that 1 of 5 Americans will be aged ≥65 years in 2050 and that 60% of cancers will occur in this group. As PBT resources are limited, centers have designed decision-making systems for prioritization. Elderly cancer patients are as fragile as pediatric oncology patients in terms of "normal" tissues protection importance, their tissues are not that "normal" at all but link to comorbid and biological senescence. A small pilot survey of international academic radiation oncologists with particular experience in geriatric care recommended a preference for irradiation with PBT, due to the age condition and cancer stage. Although this finding may sound provocative, it shows that, while currently inclined toward pediatrics, many practitioners see strong indications in the elderly population.

The Eurocare showed that the age-standardized death rate for cancer was ≥12 times higher among elderly persons than among younger persons, in part, because treatments most commonly associated with cancer cure are less commonly given to elderly patients. The use of PBT will, through reducing morbidity, make the delivery of curative therapy more possible, merits a serious thought. Older patients are more likely to be admitted for cancer treatment as a result of an emergency or at an advanced stage. These factors may be associated with increased costs. The societal cost of delayed or inadequate treatment will require formal measurement against the cost of these advanced radiation technologies. PT should now be regarded as a relevant method to limit the short- and long-term toxicity of irradiation and reduce the need for costly supportive care.

While research protocols no longer exclude patients based solely on age, many currently do so because of these patients' comorbidities. It is time to consider the inclusion of comprehensively assessed elderly men and women in clinical trials of PBT. It is among these patients that some of the greatest benefits may yet be revealed. Until specific trials report their findings, a proactive guidance for the

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Deville [118]	2018	100	Risk organ-confined.	Post-prostatectomy. 34% ADT	70.2 RBE	86% IMPT	• Favorable GU-GI toxicity. • Acute max toxicity: G0 14%, G1 71%, G2 15%, G3 0%.
Pan [119]	2018	693	3465 IMRT 312 SBRT	Radical RT		PB	2y: • Erectile dysfunction 21 vs. 28% • Urinary toxicity 33 vs. 42% • Bowel toxicity 20 vs. 15%
Iwata [120]	2018	520	7 institutions. Organ confined.	21% ADT	63–66 RBE/ 22fx	PB	5y bRFS: LR 97% IR 91% HR 83% Toxicity ≥G2 GI-GU 4%
Nakajima [121]	2018	526	Urinary toxicity Organ confined	NR	74 RBE/ 37 fx 78 RBE/ 39 fx 60 RBE/ 20 fx	PB	No G3 toxicity. G2 hypofractionation 5,9%.
Takagi [122]	2018	1375	Long- term. Organ confined	56% ADT	74 RBE/37 fx	PB	Toxicities GU 2% GI 3% 5y bRFS: LR 99% IR 91% HR 86% VHR 66%
Rana [123]	2016	10	Dosimetric comparisons: IMP vs. IMRT	Rectum Bladder Femoral Head	79.2 RBE	IMPT	Better dosimetric results with IMPT
Pugh [124]	2013	226	Passive scattered VS IMPT	QoL Sexual function GU-GI toxicity	76 RBE/ 38 fx	22 PB 65 IMPT	No toxicity or QoL differences between PB and IMPT.

Table 8.
Clinical experiences in prostate cancer treated with synchrotron technology (2013–2018); GU: genitourologic; GI: gastrointestinal; QoL: Quality of life; ADT: androgen deprivation.

Authors	year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Guttmann [125]	2017	23	Reirradiation for recurrent and secondary soft tissue sarcoma	Reirradation. 1°: Acute toxicities.	68.4 RBE/ 30–35 fx.	PB 78%.	mFT 36 months mOS 44 m 3-y LF 41% Extremity-spared amputation 70%.
Hashimoto [126]	2016	10	Cervix Locally advanced (IIB/IIIA)	WPRT: 3DCRT vs. IMRT vs. PBT	50.4 RBE/ 25 fx	IMPT	IMPT spared the small intestine, colon, bilateral femoral heads, skin and pelvic bone to a greater extent than the other modalities.
Haque [127]	2015	1	Seminoma.Initial stage IA. Salvage radiation	IMRT vs. PBT	30 RBE/15 fx	PB	Complete response with no radiation-related side effects at the 3-month follow-up.
Pan [128]	2015	7	Mesothelioma IMRT n = 3 IMPT = 4	Pleurectomy n = 6	60RBE/ 25fx Integrated boost	IMPT	Dosimetric benefit shown in OARs. Lower mean doses to the contralateral lung, heart, esophagus, liver, and ipsilateral kidney, with increased contralateral lung sparing when mediastinal boost was required for nodal disease.
Demizu [129]	2017	96	Skull base n = 68 Cervical spine n = 8 Lumbar spine = 5 Sacral spine = 15	Surgery performed in 68 pts	<70Gy RBE (50pts) >70 Gy RBE (46pts)	PB	5-y OS 75% PFS 50% LC 71%
Smith [130]	2019	51	Reconstructed + − nodes	Post-mastectomy inmediate reconstruction	50 Gy/25 fx (73%) 40 Gy/15 fx (27%)	IMPT	Low rates of acute toxicity. More complications with hypofractionation. Max dermatitis G1 63%.
Mutter [131]	2016	12	I-III	Post-mastectomy inmediate reconstruction	50 Gy/25 fx (73%)	IMPT	Skin radiodermitis G3 in 1 patient.

Table 9.
Clinical experiences in miscellaneous neoplasms and cancer conditions treated with synchrotron technology (2015–2017); LC: Local Control.

allocation of geriatric patients to PBT in the non-study situation is needed urgently [132].

4. Clinica Universidad de Navarra Proton Unit: early clinical experience

In March 2020, after a 28 months installation period, the first cancer patient was treated. This is the first synchrotron equipment for PBT operating in Europe (**Figure 2**) and the third 360° gantry available for clinical use worldwide. (**Figure 3**). It is important to emphasize that the initiation of clinical activities was coincident with COVID pandemic, in one of the cities in the world (Madrid, Spain) with the more devastating epidemiologic and medical compromise. Under the strict institutional protective policy, none of the professionals involved in PBT

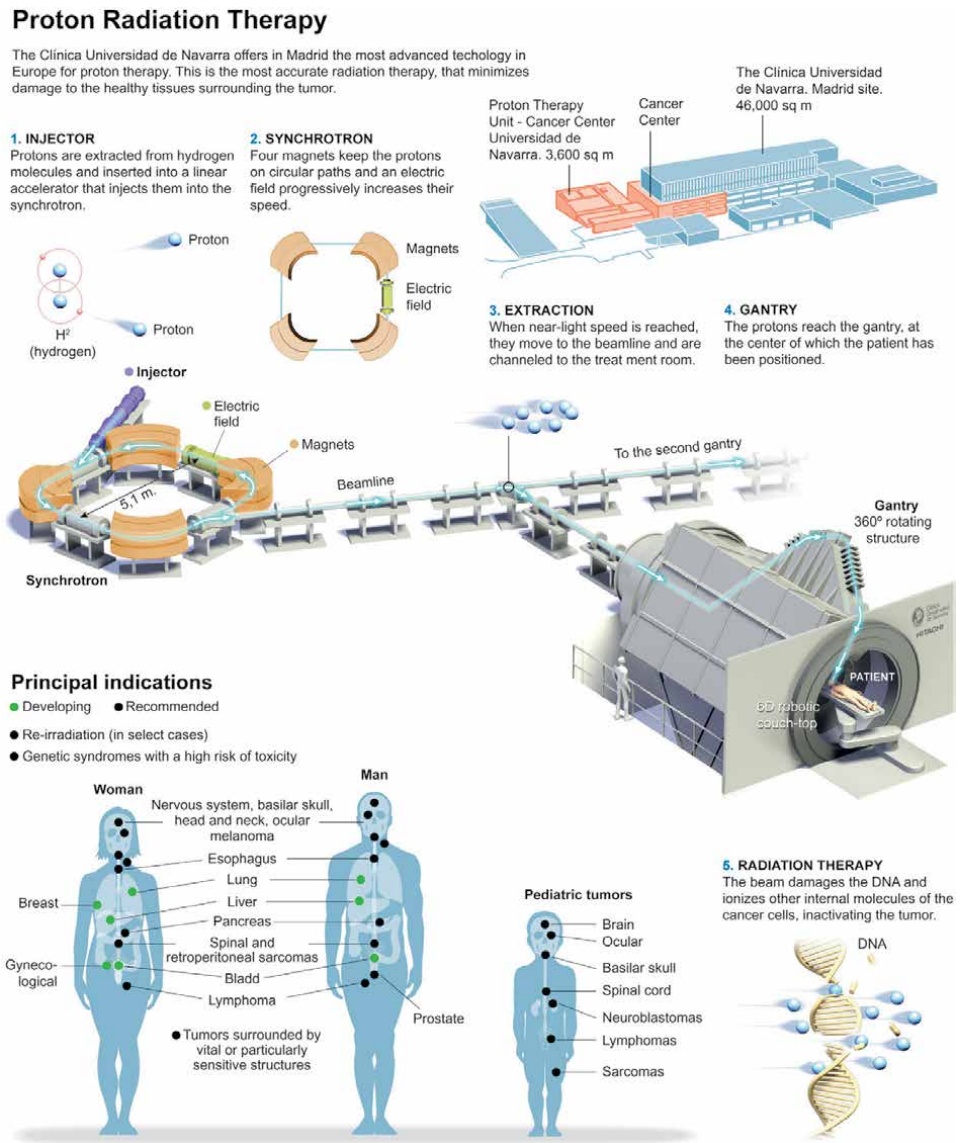

Figure 2.
Characteristics of the Proton Beam Therapy Unit structure at the Cancer Center Universidad de Navarra, CCUN (Madrid Campus, Spain).

Figure 3.
Distribution of exclusive synchrotron technology for PBT in the world. Institutions with active 360° gantry equipment available.

intra-hospital process have had a positive test for COVID infection (up to the moment of writing the present manuscript October 2020), but several patients (11%) under treatment were detected to be infected along the treatment period (**Table 10**).

Patient characteristics		
	#	%
N° patients		
	55	100
Age, years		
Median (range)	42 (3–86)	
<30	20	36.3%
>30	35	63.6%
Gender		
Female	29	52.7%
Male	26	47.3%
Reirradiation		
Yes	19	34.5%
No	36	65.4%
COVID-19		
Positive	6	11%
TUMOR		
Site		
Brain	17	30.9%
Skull base	4	7.3%
Head & Neck	7	12.7%
Thorax	5	9%
Spine	8	14.5%
Upper abdomen	2	3.6%

Patient characteristics		
	#	%
Pelvis	12	21.8%
Histology		
Chordoma/chondrosarcoma	9	16.3%
Rhabdomyosarcoma/Soft Tissue Sarcoma	3	5.4%
Medulloblastoma	5	9%
Ependimoma	3	5.4%
Craneopharingioma	2	3.6%
Malignant glioma	7	12.7%
Lymphoma	2	3.6%
Adenocarcinoma	11	20%
Squamous Cell	6	10.9%
Others	7	12.7%
TREATMENT		
Previous surgery Previous radiotherapy Concomitant ChT	33 19 10	60% 34.5% 18.1%
Proton Beam technique		
IMPT MFO synchrotron	55	100%
N° incidences (median, range)	3 (1–4)	
1 2 3 >3	1 15 27 12	1.8% 27.3% 49% 21.8%
Total doses		
<30 Gy RBE >30 Gy RBE	2 53	3.7% 96.3%
Fractionation (median, range)	24 (5–37)	
<10 10–20 >20	2 20 33	3.6% 36.3% 60%
Volume		
-Focal -Extended	32 23	58.2% 41.8%

Table 10.
Early clinical demographic data in patients treated in the Clinica Universidad de Navarra synchrotron PBT system: 6 months period (March–October 2020).

5. Conclusions

In principle, PBT offers a substantial clinical advantage over conventional photon therapy. This is because of the unique dose-deposition characteristics of protons, which can be exploited to achieve significant reductions in normal tissue doses proximal and distal to the target volume. These may allow escalation of tumor doses and greater sparing of normal tissues from unnecessary irradiation exposure, thus

potentially improving local control and survival while at the same time reducing toxicity, carcinogenesis and improving quality of life. Synchrotron technology matches these benefits with proven reproducibility of its dosimetric properties and clinical observations.

Despite the high potential of PBT, the clinical evidence supporting the broad use of protons is still under consolidation. The clinical data generated in institutions with synchrotron technology is abundant and of high scientific quality in terms of bibliometric records. An update has been summarized in the present publication. Clinical scientists operating with synchrotron proton beams are remarkably active in generating knowledge on topics such as cost effectiveness, the implementation of randomized trials and the collection of outcomes data in multi-institutional registries.

Some fundamental issues to understand clinical outcomes are unsolved. This includes the equivalence of passive beams versus pencil beam radiation delivery and the relative biological effectiveness (RBE) of protons which is simplistically assumed to have a constant value of 1.1. In reality, the RBE is variable and a complex function of the energy of protons, dose per fraction, tissue and cell type, end point, etc.

From 2012 to 2017, both ASTRO's Emerging Technology Committee report and ASTRO Model Policy document on proton beam therapy consider its recommendation 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. Based on the medical necessity requirements or the generation of clinical evidence in IRB-approved clinical trials or in multi-institutional patient registries adhering to Medicare requirements, PBT is expanding widely in clinical practice [133].

For a practicing oncologist evaluating treatment plans has uncertainties about the radiobiological equivalences (RBE) and other dosimetric elements that are taken into current models, which means that, the dose displayed on a commercial treatment plan is likely to be less accurate. These features are not intuitive for oncologists and allied cancer specialties clinicians and need further refinement in the assessment of dosimetric displays. It means the dose effects may extend past the isodose lines shown on paper, not considering certain uncertainties and this effect beyond the target will always be in non-target normal tissues [134].

Synchrotron technology is a component of the integral health care of a patient requiring radiotherapy and all the elements involved in the medical process need to be optimized to achieve an improved quality and safety standards in proton cancer therapy [135].

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Conflict of interest

The authors declare no conflict of interest.

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Chapter 9

The Future of Proton Therapy

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Abstract

Proton therapy is increasing in utilization worldwide at a rapid rate. With process improvements in costs, footprints, and continued advances in the delivery of care, including intensity modulation and image guidance, proton therapy may evolve into standard treatment with photon radiation therapy. This chapter reviews process improvements in proton therapy and the application in modern care.

Keywords: proton therapy, particle therapy, radiotherapy reimbursement

1. Introduction

In this chapter, issues associated with the current practice and future of proton therapy are presented including the costs of operation and financial risks involved with developing a program. With process improvements in costs, footprints, and continued advances in the delivery of care, including intensity modulation and image guidance, proton therapy may evolve into standard treatment with photon radiation therapy. In this chapter, process improvements in proton therapy and the application in modern care are reviewed.

2. The influence of process improvements in proton delivery systems

Historically, proton therapy has always been perceived as an advantage for radiation oncology. With the first generation of proton therapy units, the advantage of sparing normal tissue with precision manipulation of the Bragg peak limiting exit dose to normal tissue structures has been viewed as an opportunity to escalate dose to tumor targets less amenable to photon therapy and limit dose to normal tissues in all body areas. Successful application of proton therapy for patient care has been acknowledged as self-evident in areas where sparing of normal tissue was of considerable importance. These situations include critical body locations where exit dose would be a distinct disadvantage. Lesions at the skull base treated with curative

intent and pediatric malignancies where limiting exit and integral dose would be a distinct advantage for amelioration of long-term effects on normal tissue, are some examples.

Up until the past decade, there were a limited number of proton facilities world wide and access to proton therapy was challenging and elusive. Footprints were extremely large and maintenance costs were significant. The planning for proton care required unique personnel. Devices to alter the Bragg peak had to be constructed for each proton field based on a rigorous process further complicated by the lack of volumetric three- and four-dimensional image anatomy to mill devices for the appropriate treatment. The team of physicists, dosimetrists, and therapists were often not aligned with other department efforts as the processes involved with proton therapy care required unique radiation therapy planning tools and different manners of therapy execution disparate from those applied to photon care. Proton therapy delivery, accordingly, could not function at an enterprise level and remained an eclectic subset of patient care units limited by access and availability. Accordingly, only a few institutions worldwide were able to provide proton care treatment delivery. Early generation units were difficult to maintain as they required unique engineering skills for daily therapy. Vehicles were not available to image validate daily therapy and, often due to the complexity of geometries, only a limited number of therapy fields could be treated in a single day further limiting the ability of proton therapy to function at a level commensurate with photon management.

Photon therapy delivery processes moved forward more quickly due to the nimble application of x-ray therapy tools and the ability to add diagnostic quality image guidance and extended collimation to linear accelerators for intensity modulation with and without modulated arc therapy. The footprint for linear accelerators was small by relative comparison and many corporate strategies aligned to integrate advanced technology imaging and therapeutic process improvements into them. As accelerators become more computer controlled, their down time became less associated with mechanical failure and more associated with computer driven issues. Cerrobend blocks were replaced by multi-leaf collimators which provided enhanced shaping of the beam both at the beam edge and in a dynamic manner within the field itself. Dynamic motion of the multi-leafs permitted alteration in beam intensity creating "beamlets" of radiation which could be aligned to the inverse topography of the target and normal tissue. Fluence profiles for photon therapy could be modulated and daily treatment reproducibility could be optimized and validated with portal dosimeters and adaptive therapy design.

Volume modulated arc therapy for photons has compressed treatment time with dynamic and simultaneous harmonization of gantry motion coupled with multileaf motion. This influenced and simplified motion management for radiosurgery and daily traditional therapy applications by significantly decreasing the time required for daily therapy. As a positive consequence, the risk of patient movement and motion of the target away from the intended target of therapy was limited, providing more security that the targets were correctly treated enhancing the quality of daily care. In many series, the quality of care has direct impact on patient outcome, therefore improved quality has the potential of maximizing tumor control and titration of the therapy effect on normal tissue function [1, 2]. Successful improvements in the application of photon care have moved the field forward at a rapid pace and vendors are evaluating the applicability of these improvements to proton care.

In contrast, proton care remained challenged by the footprint and strategy behind therapy application. The mechanics of particle delivery improved with the development of pencil beam application systems as these systems were more facile to apply care than passive scatter systems. Nevertheless, despite the

limitations in application strategy, the ability of limiting exit dose and improving the geometry of the application of radiation therapy for patient care remained alive in the minds of many radiation oncologists, physics application specialists, and cyclotron engineers; and, by the early part of the 21st Century, the ideas supporting proton delivery became increasingly realistic and able to function at an enterprise level [3–7].

Initially, proton systems placed emphasis on traditional models of care which had multiple therapy gantries including research gantries aligned with a single central source to generate particles. The facilities cost hundreds of millions of dollars to construct and maintain, therefore considerable commitment and investment were required by all involved to insure a successful outcome for institutions and patients. The enthusiasm was generated by clinical altruism and institutional visibility. Institutions and facilities used multiple business models to achieve the objectives for design, construction, and implementation of care. Often the models were built on partnerships between otherwise competing institutions to manage costs. Institutions would also partner with business venture firms to share cost and profit. Multiple cottage industries grew from these partnerships. Disease areas of high patient volume were targeted for application to support the fiscal infrastructure of the program. Informatics tools permitted off-site management and planning, facilitating the integration of business models [8–15].

The most important change occurred with miniaturization of proton design coupled with the integration of tools that have made photon care nimble and precise. The production of single gantry systems that could be directly integrated into department function has become a working model for the future of particle care (**Figure 1**). These systems offered a much smaller footprint at a significant cost reduction, thus making proton care achievable for institutions who otherwise could not consider particle therapy. This has evolved into a powerful tool and has permitted particle therapy to mature in many parts of the world. Proton care is no longer an eclectic sub-specialty of radiation therapy but a dynamic growing component of radiation therapy maturing at a rapid rate in parallel to photon care. There have been many challenges in reaching this point and more challenges lie ahead.

Figure 1.
Single gantry radiation therapy system. Copyright. Creative commons attribution license (CC BY) [16].

Nevertheless, proton care now has a solid footprint in clinical radiation therapy and will continue to grow moving forward [17–24].

3. Financial considerations

Proton therapy systems require a strong financial commitment from institutions and financial partners. Investments of $200 million and higher were required to build centers with multiple gantries. Investors and institutions needed security to insure their investment would merit the expense required for construction, operation, and maintenance. Business models were designed anticipating predictable high-volume radiation therapy. Many of these models were based on the treatment of prostate cancer anticipating a paradigm shift away from surgery and photon-based therapy strategies. This was an attractive model as dose distribution to normal tissues including bladder and rectum appeared superior and would accordingly be supported by insurers and third-party support systems.

Many payors, however, chose not to support proton therapy for prostate care due in part to the successful application of advancements in using photons. The ability to alter fluence profiles over the entire radiation therapy treatment field coupled with the ability to document positioning with kilovoltage (kV) fiducial tracking and volumetric computer tomography created a significant paradigm shift in the treatment of prostate cancer. Multiple photon-based trials demonstrated both outstanding local control and minimal treatment sequelae with photon based image-guided intensity-modulated radiation therapy (IMRT) and, as such, it was challenging to demonstrate clinical improvement with the use of protons despite unambiguous improvements in dose distribution to normal tissue with proton care. Because a statistically significant improvement in normal tissue outcome could not be demonstrated between photon and proton therapy, many payors decided not to support the cost of proton therapy for prostate cancer. A typical comparable American Medical Accounting and Consulting (AMAC) reimbursement for a cancer patient treated with proton therapy versus intensity modulated photon therapy results in a greater than $16 thousand increase per patient revenue for proton therapy, hence the reason for pause in approval and requirement of clinical improvement outcome data to re-visit the discussion.

For most radiation therapy departments, the three largest disease treatment groups are breast cancer, thoracic/lung cancer, and genitourinary (GU)/prostate cancer. In many departments with standard surgical sub-specialty care institutional colleagues, these disease groups in aggregate, comprise 25–35% of the patient population on treatment. Therefore, to justify proton care with multiple gantry platforms, a common therapy disease site would help secure the fiscal security required for investment. Business models were often driven by predictions for prostate cancer management and when reimbursement models changed, and prostate cancer therapy was no longer supported by insurance carriers, many proton centers faced fiscal uncertainty. There were centers in the United States that entered bankruptcy and one center closed because of fiscal challenges maintaining the facility. The future of multiple gantry centers became less certain. Institutions in large metropolitan areas with an integrated prominent bandwidth for a referral network remained successful, however it became less certain that proton care could successfully enter geographic regions of more limited population centers in medical markets with competition. For proton centers to survive the new era of fiscal compromise where reimbursement may not be commensurate with investment and cost, proton application would need to become more cost effective and demonstrate clinical advantage in multiple disease groups.

Approximately 12 years ago, single gantry proton units came to market and the paradigm of care changed. The units had a more attractive cost at a fraction of multi-gantry facilities with a smaller footprint for construction and maintenance. Although the initial units had challenges with image guidance and nimble platforms for treatment execution, over the past decade process improvements in these areas have made the execution of proton treatment the near equivalent of photon therapy. Coupled with the advantage of dose distribution, institutions have been able to revisit their cancer center specific strategic plans and incorporate proton units into their capital equipment plans for the next generation of radiation oncology. Companies manufacturing proton single gantry cyclotrons may or may not be aligned with the production of photon linear accelerators. Those aligned may have a long-term advantage in their ability to integrate photon and proton planning into a single overarching system and more easily transfer patient care between units on an as needed basis. Nevertheless, it is a unique time in the history of radiation therapy as proton care has now moved to enterprise function with multiple proton facilities throughout the United States and the world. Many institutions are planning for proton construction in the near future. The investment must be planned with a strategy for growth. Although the cost is significantly less than previous multiple gantry systems, cost remains significantly higher than photon therapy and the advantages must balance the investment for financial security. Although in selected circumstances proton care is reimbursed by insurance carriers at a higher level per treatment, it is not clear and in fact unlikely the reimbursement models will remain at current levels. Proposals over the past several years have suggested movement to a single model of reimbursement agnostic of therapy approach, implying that proton and photon case reimbursement including the use of advanced technologies would be identical. Although these models for reimbursement have not yet been implemented, institutions planning on developing proton care must remain cognizant that reimbursement models will likely change in the near future and a strategy for both growth and cost containment must be incorporated into the business plan for proton development moving forward [25, 26].

4. Adjustments in proton footprint for future care

Significant progress has been made in the development of proton delivery systems and cost has evolved to become achievable with effort for institutions who could otherwise not consider particle therapy. The technology has made considerable progress over the past two decades and will continue to improve. The footprint will become smaller and more compressed. This will increase the likelihood that proton facilities can be located in closer approximation to traditional photon facilities and conceivably be placed in photon vaults, saving cost of construction. Current single gantry optimal building strategies build out from facilities with a general cost of $6 million for construction costs. Being able to build and install particle therapy into traditional departments and photon vaults will save cost and serve to bring particle therapy to the staff creating synergy for all department full time employees (FTE). Photon care today has extraordinary image guidance and intensity modulation with tools for optical tracking and patient care has never been better. This has created nimble treatment that can be validated and treated in a few minutes. The goal for proton care moving forward is to integrate to advantages of photon care into the proton footprint. This would include tools for image guidance, beam precision, and optical tracking as well as create synergy and integration among the physics and therapy staff [25, 26].

This idea has begun to mature. Image guidance has played an important role in providing security in daily patient setup well beyond what could be achieved with kV imaging. The addition of both diagnostic kV imaging and cone beam computer tomography has brought a new era to radiation treatments and has permitted radiation oncologists to titrate target volumes due to the confidence in daily set up. Proton centers are beginning to integrate imaging strategies into daily care including ring-based geometries to secure volumetric set up for treatment. Many centers now use multi-leaf collimators to provide intensity modulation including strategies to apply small volume radiosurgery with proton therapy. Flash therapy is being applied with electrons, photons, and now protons. The more particle care can synergize with the advances in photon care, proton care can be easily integrated into the work flow of department management.

Artificial intelligence will play an increasing role in the daily practice of radiation oncology. Even early iterations of artificial intelligence have provided both consistent normal tissue contouring and enhancement of planning function for dosimetry and physics planning staff. This saves time and effort permitting planning staff to focus more on the important planning tasks at hand and could serve to introduce particle planning strategies to all planning staff. An appropriate economy of scale for staff could be created so not to segregate staff into separate divisions as contouring of normal tissue and tumor targets is therapy agnostic. The ultimate therapy approach can be applied for photon/proton per assessment of benefit to the patient including insurance requirements. Department functions can become more transparent between staff as artificial intelligence matures and ultimately resides in a single planning system that manufacturers that participate in developing both photon and proton treatment units. Staff can become familiar with the tools of therapy as the processes of plan development and therapy execution become more parallel and aligned [27].

5. Strategy for the future

Historical models of radiation oncology departments offering photon and proton care had FTE including physicists and therapists that were skilled in their specific area with little overlap in function, therefore there were redundancies and no economy of scale for the FTE. This was due to the disparate nature of treatment planning and treatment delivery creating silos in the department without hybrid function. Even engineering skills and requirements were disparate and FTE functioned in independent areas with minimal overlap in work flow, resulting in increased cost and challenging to function with backfill staff support between the teams. The process of care and the planning of care were and currently remain different requiring separate computer operation systems further separating work flow. The infrastructure required for proton care was unique and planning for care required separate modeling systems. This was necessary by default and hybrid strategies to provide an economy of scale for individual FTE could not be developed because the employee skill set could not co-exist in a hybrid model. Even today, many proton manufacturers do not participate in developing photon patient care. As reimbursement models change and become agnostic to radiation therapy technique, there will be more effort to move this strategy into a different pathway as reimbursement for proton care will become more aligned with photon care. It will be necessary for departments to provide hybrid strategies as reimbursement becomes photon/particle transparent and internal economies of scale for patient care will need to be enhanced [25–38].

To accomplish these important objectives, proton care of the future will need to become more cost aligned with current costs of photon care. Cost for photon care has increased over the past decade as process improvements in intensity modulation, image guidance, and optical tracking have become commonplace in a department. Computer operations require cost including upgrades and institutions need to be prepared to undergo constant process improvements and support these improvements for cost. Cost of vault construction and modern linear accelerators can now exceed $5 million for photon care as the cost includes tools for optical tracking, intensity modulation, and image guidance.

The current cost of vault construction and build out for single gantry cyclotron function is now in the minimal range of $30 million with $6 million dedicated to vault construction as a build out from the primary facility and $24 million for the equipment. It is likely that adding many of the current areas of flexibility now used with routine for photon care including optical tracking, intensity modulation, and image guidance will increase cost for the next iterative application of proton care. Proton care will need to continue to work on cost and the current belief is cost will decrease with volume-based adjustments. Specifically, once proton units become more numerous and populated worldwide, cost may decrease over time as expenses can be modified based on the redundancy of production. This will require further miniaturization of the proton footprint in a manner similar to the photon footprint including the computer operations. Couch function for proton care will likewise need to adjust to the flexibility of protons including further improvements in the precision of proton care delivery. This has begun with the introduction of multi-leaf collimation. Photon multi-leaf collimation has provided field size adjustment with significant precision and efforts to apply this technology will further support proton care in ultra-small targets identical to photons. The stereotactic body radiosurgery tools have been well developed for photons. Given the improved radiation therapy dose distribution for protons, applying radiosurgery techniques for protons in the similar manner used for photon care will improve patient outcome including the capacity for motion management.

Continued miniaturization and re-modeling of existing technology for the generation of protons will continue to decrease cost with smaller footprints and more limited shielding. This will continue to make proton care more affordable. One of the smallest footprints is generated by a high-energy superconducting synchrocyclotron which eliminates the need for complex magnet-guided beam-lines. This also serves to optimize power consumption further reducing cost of maintenance. Designs facilitating upgrades of hardware are important to limit future costs. Technologies including dielectric wall accelerator units and proton plasma acceleration may pivot the strategy for the infrastructure for these units and promote further change in cost and footprint. Of equal importance, protons are now being used to treat malignancies of all cell types and tissues of origin. Independent of cell type and body site of disease, dose distribution is simply better with protons and the improvements can be applied across all epithelial and liquid disease sites. The challenge has uniformly been in proof of principle. Although dose to normal tissue can be titrated with protons in nearly all body areas, demonstrating with statistical significance the benefit of dose reduction is not a simple or straightforward task as scoring a null event for significance requires large cohorts of patients with decades of follow up. This creates a challenge to score tissues of limited self-renewal capacity such as heart and lung for late effects. While many feel the advantage or proton dosimetry is self-evident, it remains to be proven to payers that the improvements provide the efficacy to balance the cost. Both areas require process improvements as we are obliged to provide effective and safe care

with proton manufacturers remaining responsible for cost reduction to promote its application at an enterprise level [28–38].

6. Summary

Since its inception, proton care has been an important component of radiation therapy. Because of the challenges of size and infrastructure, centers of operation were few and application of proton care remained eclectic as photon therapy matured at a rapid rate with significant process improvements for treatment delivery and validation. Proton centers became more numerous during the past two decades in the United States and with the development of single gantry systems, smaller units became commercially available at a more affordable cost that could be reached by health care institutions and private oncology systems. The number of centers has significantly increased over the past decade and protons are now used with more routine in multiple disease sites worldwide. In selected clinical protocols, twenty-five percent of pediatric patients treated with radiation therapy are treated with protons. Proton dosimetry has provided decrease dose to normal tissue in all disease sites with therapeutic advantages in all body areas. At one level, if cost can be contained and hybrid workflow strategies can be developed, one can envision proton care as an equal partner to photon care for the next generation of radiation oncologists [34, 35].

Conflict of interest

The authors declare no conflict of interest.

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Over the past twenty-five years, proton therapy has become more prominent worldwide. It is an important component of clinical radiation therapy for both adult and pediatric clinical care. Due to the inherent ability of protons to spare normal tissue, protons will continue to develop and become increasingly important in radiation oncology. As such, *Proton Therapy - Current Status and Future Directions* reviews many aspects of proton care including the application of protons in modern clinical trials. It also reviews problems associated with the migration of proton care worldwide and examines the future direction of proton care. This project was created by colleagues at IntechOpen and was carefully managed by Romina Rovan. It has been a privilege to help coordinate the text and chapters designed to acknowledge the history, footprint, and growing interest of proton care worldwide. Proton management is now embedded in the clinical trials process. In pediatric care, proton delivery is embedded with photons for the management of pediatric malignancies and adult groups have initiated proton-specific clinical trials. A proton registry has been established and outcomes are under evaluation. Due to the inherent ability of protons to spare normal tissue, protons will continue to develop and become increasingly important in radiation oncology.

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