Chapter

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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