The evolution of proton beam therapy: Current and future status (Review)

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Abstract. Proton beam therapy (PBT) has been increasingly used in a variety of cancers due to its excellent physical properties and superior dosimetric parameters. PBT may improve patient survival by improving the local tumor treatment rate while reducing injury to normal organs, which may result in fewer radiation-induced adverse effects. However, the significant cost of establishing and maintaining proton facilities cannot be overlooked. In addition, there has been significant controversy regarding routine application of this treatment in certain types of cancer. The challenges of PBT in the future mainly include the lack of basic clinical trials, unclear biological effects, immature imaging technology and miniaturization of imaging guidance. Overcoming these limitations may promote the rapid development of PBT. We herein provide an overview of the existing literature on the efficacy and toxicity of common oncological applications of proton beam therapy.

Contents

1. Introduction

Proton beam therapy (PBT) is a type of radiation therapy (RT). The appropriate application of PBT has led to fewer adverse effects and higher therapeutic efficacy compared with conventional RT using X-ray beams. Thus, facilities for PBT are being built worldwide, despite the requirement for costly equipment.

PBT was first proposed by Wilson (1) in 1946. After 12 years, the first PBT patient series was published (2) by researchers at the Lawrence-Berkeley National Laboratory. Over the next decades, several other proton treatment centers emerged worldwide and, thus far, PBT has used in the clinical setting for ~60 years, and has been applied to tens of thousands of patients with different types of cancer. PBT patient statistics by the end of 2015 are presented in Table I.

Over the past decades, with an increasing number of PBT applications worldwide, the number of new programs under development is growing. The reason for this is that the proton dose distribution that may be achieved is generally superior to the dose distribution of conventional photon RT. PBT may improve the survival rate of patients by improving the local tumor treatment rate, while reducing injury to normal organs, resulting in fewer radiation-induced adverse effects. Compared with conventional photon RT, the heavier subatomic particles are able to deliver their energy more precisely to the tumor, with less scattering to surrounding tissues. The clinical benefits of PBT have been acknowledged in terms of fewer side effects compared with photon therapy. However, the role of PBT remains controversial, due to the high treatment costs associated with the cost of proton facility building and maintenance. This increased cost, however, may be outweighed by effectiveness, compared with photon therapy, improved quality of life, and reduced costs associated with treatment of advanced disease. Further clinical research is required to determine which patients will benefit from PBT.

Further studies and discussions are required to address the use of PBT in several types of cancer, and for maintaining the quality of life of patients while achieving a high cure rate. The aim of this review was to report the characteristics and current developments in PBT (Table I).

2. Physical aspects of PBT

Protons are heavy charged particles, ~800 times the mass of electrons. The large mass and acceleration applied gives each proton a specific momentum that is mostly dissipated after traveling a defined distance, and then slowed down

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by interactions with the target, which causes a sharp rise in energy deposition at the end of the path of the proton, followed by no further dose delivery, which is referred to as the Bragg peak (3). This individual physical property provides superior dosimetric advantages over photons or electrons. Therefore, rather than traversing the target, protons are stopped at an energy-dependent depth in the target and have no exit dose, which completely spares the downstream normal tissue. Proton beams are generated by a cyclotron or synchrotron, and then accelerated to the desired target. Fig. 1 depicts the percentage depth-dose distribution curves of the proton vs. the photon beam, demonstrating that, at the prescribed depth, the proton beam does not deliver a dose, whereas the photon beam does.

3. Biological aspects of PBT

In RT, the proton dose is presented as Gy, which is determined from multiplying the physical dose by the relative biological effectiveness (RBE). Therefore, the clinical and biological effect may differ when the physical dose remains constant and the radiation quality changes. The RBE is used to link the biological effect to a reference radiation (^{60}Co). For external beam RT, which uses photons and electrons, the RBE is generally to be considered 1 (4,5).

Protons have completely different dose distribution properties compared with photons, and have the potential to avoid most of the extra-target radiation, imparted by the acceleration system that gives protons a specific momentum that carries them into a body. After traveling a specified distance, the velocity is slowed by interactions associated with their mass and charge, and then stopped abruptly at a specific depth. This is the point at which the proton will interact with surrounding electrons, delivering its energy and causing ionization of molecules and radiation damage in the DNA of the target cell.

Protons are characterized by low linear energy transfer radiation, and tissue damage is caused by single-strand DNA breaks, with sublethal radiation damage and potential radiation damage repair. The biological effect depends on the dose per treatment, which is slightly higher compared with that of ^{60}Co and high-energy X-rays. The RBE of the proton beam is generally considered to be 1.1 (6). However, near the end of the proton range, the stopping power increases, resulting in an increase in RBE. If a uniform RBE of 1.1 is used in proton planning, the varying RBE at the end of the range is not clearly accounted for. Due to these uncertainties, proton beam angles with critical organs at risk directly distal to the tumor are generally not used, and multiple beams are used to spread out the end of range uncertainty. With pencil beam scanning, the interaction of dynamic delivery with a moving target must be evaluated and minimized. Overall, at the biological level, there remain several uncertainties in our understanding of the interaction between protons and human tissues.

4. PBT for different cancers

Head and neck tumors. Previous studies (7-10) suggested that patients with head and neck cancer may benefit from PBT. PBT may decrease the recurrence risk by increasing the dose to the tumor and, due to the small dose to the mandible, salivary glands and maxilla, it may reduce the risk of xerostomia, dental extractions, dental caries and osteoradionecrosis.

For sinonasal mucosal malignant melanoma, there is evidence that hypofractionated high-dose PBT may improve the local control rate. Compared with surgery in patients with sinonasal mucosal malignant melanoma, the continuous control of the primary lesions may achieve a higher survival rate (11).

Considering intraocular melanoma, currently available data indicate that surgical removal is the optimal approach; however, sensitivity analyses indicated that both PBT and plaque brachytherapy may be considered effective (12). Compared with radioactive plaques, PBT has a number of advantages, including that surgery is not required, medical workers are not exposed to radiation and there is no need for hospital stay, while treatment is performed in 5 working days. Due to these advantages, an increasing number of patients opt for PBT rather than radioactive plaques.

PBT for uveal melanoma and other malignant and benign ocular tumors has been associated with major developments and success over the past four decades. PBT is associated with the lowest overall risk of local tumor recurrence in uveal melanoma, compared with other eye-preserving forms of primary treatment. PBT is also utilized for other malignant and benign tumors as primary, salvage, or adjuvant treatment with combined modality therapy. The physical characteristics of proton therapy allows for uniform dose distribution, minimal scatter, and sharp dose fall-off, making it an ideal therapy for ocular tumors in which critical structures lay in close proximity to the tumor. High radiation doses can be delivered to tumors with relative sparing of adjacent tissues from collateral damage. PBT for ocular tumors has resulted in overall excellent chances for tumor control, ocular conservation, and visual preservation. The treatment of uveal melanomas and other ocular tumors has been extensively evaluated for decades and PBT is considered the gold standard of care.

When considering skull base chordoma, previous results demonstrated that, by producing a greater probability of long-term tumor control, PBT is more effective compared with X-ray therapy, while causing no increasing risk of temporal lobe injury. A number of tumors encompassing regions of the skull base have demonstrated a proven benefit from PBT based on retrospective results. Studies into dose escalation and conformal treatment plans with PBT may further improve outcomes in these disease sites, without an increased risk of toxicity to normal structures (13).

PBT is also considered a standard treatment for nasal and paranasal lesions, as well as lesions at the base of the skull, as the radiation dose to critical organs, such as the eyes, optic nerves and central nervous system, may be reduced with PBT (14).

Chest tumors. Lung cancer is the most common type of cancer worldwide and RT is an important treatment mode. PBT is a type of RT that has the potential to reduce the toxicity of RT through its characteristic Bragg peak. In comparison with photons, PBT plans may deliver lower doses to the adjacent organs at risk, such as the esophagus, lungs and bone marrow, thus improving the therapeutic ratio (15). The early clinical

Table I. Proton beam therapy patient statistics until the end of 2015 (data collected by the Particle Therapy Cooperative Group).

Country, state	Site	Year of first treatment	Patient total	Date of last update
Belgium	Louvain-la-Neuve	1991	21	1993
Canada	Vancouver (TRIUMF)	1995	185	2015.12
Czech Republic	Prague (PTCCZ)	2012	780	2015.12
China	Wanjie (WPTC)	2004	1,078	2015.12
China	Shanghai (SPHIC)	2014	76	2015.12
England	Clatterbridge	1989	2,813	2015.12
France	Nice (CAL)	1991	5,478	2015.12
France	Orsay (CPO)	1991	7,560	2015.12
Germany	Berlin (HMI)	1998	2,750	2015.12
Germany	Munich (RPTC)	2009	2,725	2015.12
Germany	Heidelberg (HIT)	2009	1,187	2015.12
Germany	Essen (WPE)	2013	366	2015.12
Germany	Dresden (UPTD)	2014	106	2015.12
Italy	Catania (INFN-LNS)	2002	350	2015.12
Italy	Pavia (CNAO)	2011	195	2015.12
Italy	Trento (APSS)	2014	92	2015.12
Japan	Chiba	1979	145	2002
Japan	Tsukuba (PMRC, 1)	1983	700	2000
Japan	Chiba (HIMAC)	1994	138	2015.12
Japan	Kashiwa (NCC)	1998	1,560	2015.12
Japan	Hyogo (HIBMC)	2001	5,024	2015.12
Japan	Tsuruga (WERC)	2002	62	2009
Japan	Tsukuba (PMRC, 2)	2001	4,502	2015.12
Japan	Shizuoka (PTCC)	2003	1,873	2015.12
Japan	Koriyama (STPTC)	2008	2,797	2014.12
Japan	Ibusuki (MMRI)	2011	1654	2015.12
Japan	Fukui (Prefectural Hospital)	2011	646	2015.8
Japan	Nagoya (Nagoya PTC)	2013	1,095	2015.12
Japan	Nagano (Aizawa PTC)	2014	1	2014.9
Poland	Krakow (IFJ PAN)	2011	128	2015.12
Russia	Dubna (JINR, 1)	1967	124	1996
Russia	Moscow (ITEP)	1969	4,368	2015.12
Russia	St. Petersburg	1975	1,386	2012.12
Russia	Dubna (JINR, 2)	1999	1,122	2015.12
South Africa	Capetown (Themba LABS)	1993	524	2015.12
South Korea	Ilsan, Seoul (KNCC)	2007	1,781	2015.12
South Korea	Seoul (Samsung PTC)	2015	4	2015.12
Sweden	Uppsala (1)	1957	73	1976
Sweden	Uppsala (2)	1989	1,431	2014
Sweden	Uppsala (The Skandion Clinic)	2015	32	2015.12
Switzerland	Villigen PSI (OPTIS 1)	1984	5,458	2010
Switzerland	Villigen-PSI, incl OPTIS2	1996	2,242	2015.12
USA, CA	Berkeley 184	1954	30	1957
USA, MA	Harvard (HCL)	1961	9116	2002
USA, CA	Loma Linda (LLUMC)	1990	18,362	2014.12
USA, IN	Bloomington (MPRI, 1)	1993	34	1999
USA, CA	San Francisco (UCSF-NL)	1994	1,839	2015.12
USA, MA	Boston (NPTC)	2001	8,358	2015.12
USA, IN	Bloomington (IU Health PTC)	2004	2,200	2014
USA, TX	Houston (MD Anderson)	2006	6,631	2015.12
USA, FL	Jacksonville (UFPTI)	2006	6,107	2015.12
USA, OK	Oklahoma (ProCure PTC)	2009	2,079	2015.12

Table I. Continued.

Country, state	Site	Year of first treatment	Patient total	Date of last update
USA, PA	Philadelphia (UPenn)	2010	3,376	2015.12
USA, IL	CDH Warrenville	2010	2,316	2015.12
USA, VA	Hampton (HUPTI)	2010	1,399	2015.12
USA, NY	New Jersey (ProCure PTC)	2012	1,862	2015.12
USA, WA	Seattle (SCCA ProCure PTC)	2013	844	2015.12
USA, MO	St. Louis (S. Lee King PTC)	2013	270	2015.12
USA, TN	Knowville (Provision Center)	2014	856	2015.12
USA, CA	San Diego (Scripps PTC)	2014	400	2015.12
USA, LA	Shreveport (Willis Knighton)	2014	151	2015.12
USA, FL	Jacksonville (Ackerman CC)	2015	140	2015.12
USA, MN	Rochester (Mayo PBTC)	2015	186	2016.8
USA, NJ	Brunswick (Laurie PC)	2015	50	2015.12
USA, TX	Irving (Texas Center for PT)	2015	1	2015.12
USA, TN	Memphis (St. Jude PTC)	2015	1	2015.12
Total		1954	131,240	2015

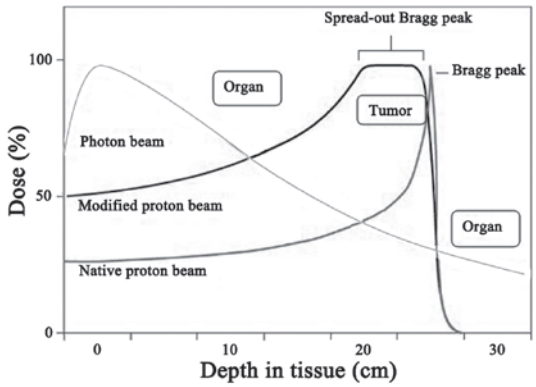

Figure 1. Percentage depth-dose distribution curves of proton beam vs. photon beam.

outcome of PBT in lung cancer patients (16-23) demonstrated that proton beam therapy combined with chemotherapy may relatively reduce the rates of toxicity and achieve a possible survival benefit compared with photon beam therapy and 3DCRT (24). Early results (25-29) suggested that PBT has the advantage of dose escalation, which may prolong patient survival, lower the risk of recurrence and severe toxicity, and intensify chemotherapy (15). For patients with stage III NSCLC, PBT may be an effective and safe treatment option. However, late toxicities remain unclear, and patients should continue to be followed up to determine these risks (30).

For esophageal and gastroesophageal junction cancers (31-35), the esophagus is a centrally located thoracic structure; thus, there is a more stringent requirement to balance the delivery of the proper high dose to the target, while decreasing the dose to adjacent critical tissues, due to the risk of clinically significant toxicities, including pericarditis, pneumonitis and myocardial infarction. Although technological advancements in photon RT delivery, such as intensity-modulated RT (IMRT), have reduced the risk of such toxicities, accumulating evidence indicates that further risk reductions are achieved with PBT (36-40). Since PBT has a zero exit dose, it is possible to further reduce the radiation exposure of normal tissue and provide clinically significant benefits to at least a proportion of patients with esophageal cancer. Furthermore, it may be possible to reduce cardiac-related complications and mortality by using proton beams to treat patients with esophageal cancer (41). High-dose PBT without chemotherapy was found to be efficacious and safe for the treatment of older patients with esophageal cancer (42).

In general, a growing body of evidence suggests that the dosimetric benefits of PBT may lead to a clinically significant reduction in treatment-related toxicities compared with conventional photon RT (43). RT and chemotherapy intensification, as well as re-irradiation, are promising future applications of PBT for esophageal cancer.

For breast cancer, it has been demonstrated that PBT was cost-effective, while standard photon radiation led to significant side effect in women at high risk of cardiac disease (44). Compared with conventional X-rays and electron beams, it was found that partial breast irradiation using PBT was safer, more effective and technically feasible; furthermore, it may provide satisfactory target coverage and improve normal tissue sparing. Moreover, compared with intracavitary and interstitial brachytherapy, PBT was found to be more cost-effective (45-54).

Abdominal and pelvic tumors. Although PBT has been used for several years to treat prostate cancer, this type of treatment remains controversial. Although the proton beam has unique physical properties and excellent dosimetric parameters, the currently available evidence suggests that the application of PBT in the treatment of prostate cancer offers no proven advantage over conventional IMRT. In addition, a number of the current treatment options, including brachytherapy, prostatectomy and IMRT, are more cost-effective compared with PBT. Thus, further research with adequate follow-up data is required to assess the clinical superiority of PBT in treating prostate cancer, in terms of improving the tumor control rate and reducing acute and long-term radiation toxicity. PBT is an important method of

RT due to its theoretical advantage over photon external beam RT. However, there is little consensus regarding whether significant toxicity or outcome benefits exist, and whether the benefits outweigh the cost of adopting an expensive new technology (55). Thus, long-term follow up is required to justify the increasing use of PBT for prostate cancer.

It has been demonstrated that PBT is a safe and effective method for patients with localized prostate cancer (56-59). However, it is necessary to further compare PBT with other treatment regimens for local prostate cancer to determine the optimal treatment regimen for different patients (60). Further comparative studies that address adverse effects, safety, patient quality of life and socioeconomic issues should be performed to determine the appropriate use of PBT for prostate cancer (13).

Pediatric cancers. Although there has been significant progress in RT technology (61), there remain concerns on treatment-related acute and long-term side effects. This problem is more pronounced in pediatric populations due to the development of organs and tissues and the longer life expectancy, which include the effect of radiation on growth, intellectual development, endocrine organ function and secondary cancer development; thus, the pediatric radiation dose to normal tissues should be reduced as much as possible (62-66). PBT has the advantage of reducing the dose exposure of normal tissue, which may lead to fewer adverse effects. For this reason, PBT may be useful for the treatment of pediatric cancer (13).

Dosimetric and clinical researches have demonstrated that, in the treatment of pediatric tumors, such as medulloblastoma, retinoblastoma, bone sarcoma, pelvic soft tissue sarcoma and orbital rhabdomyosarcoma, in terms of reducing dose and injury to healthy organs, PBT has a significant advantage compared with X-ray therapy (67,68). The risk of radiation-induced secondary cancer in children with cholangiocarcinoma treated with RT was also found to be the highest after X-ray therapy, and the lowest after intensive proton therapy (69). The increased risk of coronary artery disease and valvular dysfunction was found to be associated with cardiac irradiation during X-ray treatment of Hodgkin's lymphoma (70,71). Therefore, in order to reduce the morbidity, mortality, pain and health care costs of Hodgkin's lymphoma survivors, PBT may be a feasible option.

As the irradiation dose to normal tissue should particularly be reduced as much as possible in children, PBT has recently attracted worldwide attention as an RT modality for pediatric cancer (72).

Other cancers. PBT has potential advantages for the treatment of rectal and anal cancers due to the lower dose to the bladder, bowel and hip joints; it may also have potential advantages for pancreatic, gastric and hepatobiliary cancers, as it delivers a lower dose to the liver, small bowel, lungs, heart, spinal cord and kidneys, and may also be used for bone and soft tissue sarcomas. PBT may allow dose intensification of chemotherapy by improved hematological tolerance in gastrointestinal, thoracic, and other types of cancer (73).

5. Discussion

PBT has several potential advantages over photon therapy for the treatment of cancer. The entrance dose is low, the exit dose is almost zero, and most of the beam energy is delivered to a specified depth. However, given the persistent uncertainties regarding PBT planning and delivery, the lack of evidence supporting the use of protons over photons, the higher cost of proton therapy, and limited access and expertise with proton techniques, protons continue to lag behind contemporary photons.

PBT may offer a substantial potential benefit in special cases, particularly in terms of toxicity compared with photon treatments. Due to the lower cumulative doses to the sensitive organs, re-irradiation using PBT may be safer for patients with rectal, pancreatic, esophageal and lung cancer. In addition, for patients with Hodgkin's and non-Hodgkin lymphoma, it may be suitable to use PBT for consolidation following chemotherapy. With the technological improvements in proton therapy, by maintaining the benefits of RT while further minimizing the risks, the therapeutic ratio may be increased (74).

The physical properties of protons have been extensively investigated. Further research on the development of confined proton technology should focus on clinical trials investigating its biological effects and clinical applications.

The effectiveness of proton RT has not been supported by adequate patient data, and no large number of direct clinical trials have demonstrated that proton protection of normal tissue may prolong survival in cancer patients. In addition, data on the relative biological effect on different tumor cells and normal tissue cells under proton irradiation remain scarce.

Due to the position of the tumor patients, breathing movements, and other factors that may lead to uncertainties in proton RT, it is difficult to ensure that the beam may be delivered to the designated location with the utmost precision and, once a deviation occurs, the precise nature of the proton may become a disadvantage, inevitably leading to normal tissue irradiation whereas a part of the tumor will not be irradiated. If such problems occur, the advantages of proton RT are greatly reduced. In traditional photon RT, image-guided techniques may be used to reduce such uncertainties. However, proton RT using image guidance technology is immature, as the majority of the techniques remain at the two-dimensional stage.

6. Conclusion

PBT is the latest type of RT, which exerts a satisfactory curative effect, particularly in pediatric patients. In recent years, an increasing number of patients are treated with PBT worldwide. PBT can achieve a dose distribution that is generally superior to conventional external photon beam radiation. Compared with photon therapy, PBT is associated with obvious benefits, such as reducing the volume of irradiated normal tissue, improving the conformability and the quality of the target area. However, PBT is costlier compared with conventional X-ray therapy, although this increased cost may be outweighed by improving the quality of life of the patients and reducing the costs associated with treating late radiation-related adverse effects. However, the relative biological effect of PBT requires further investigation.

Future studies must integrate, evaluate and manage information associated with PBT, in order to provide patients with the optimal treatment while reducing injury to normal tissues and treatment costs, and to clearly determine which patients may benefit the most from PBT.

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