An evidence based review of proton beam therapy: The report of ASTRO’s emerging technology committee

Aaron M. Allen a,∗, Todd Pawlicki b, Lei Dong c, Eugene Fourkal d, Mark Buyyounouski d, Keith Cengel e, John Plastaras e, Mary K. Bucci c, Torunn I. Yock f, Luisa Bonilla a, Robert Price d, Eleanor E. Harris g, Andre A. Konski h

aDavidoff Center, Tel Aviv University, Israel; bUniversity of California, San Diego, La Jolla, USA; cM.D. Anderson Cancer Center, University of Texas, Houston, USA; dFox Chase Cancer Center, Philadelphia, USA; eUniversity of Pennsylvania, Philadelphia, USA; fMassachusetts General Hospital, Boston, USA; gH. Lee Moffit Cancer Center, Tampa, USA; hWayne State University Medical Center, Detroit, USA

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Abstract

Proton beam therapy (PBT) is a novel method for treating malignant disease with radiotherapy. The purpose of this work was to evaluate the state of the science of PBT and arrive at a recommendation for the use of PBT. The emerging technology committee of the American Society of Radiation Oncology (ASTRO) routinely evaluates new modalities in radiotherapy and assesses the published evidence to determine recommendations for the society as a whole. In 2007, a Proton Task Force was assembled to evaluate the state of the art of PBT. This report reflects evidence collected up to November 2009. Data was reviewed for PBT in central nervous system tumors, gastrointestinal malignancies, lung, head and neck, prostate, and pediatric tumors. Current data do not provide sufficient evidence to recommend PBT in lung cancer, head and neck cancer, GI malignancies, and pediatric non-CNS malignancies. In hepatocellular carcinoma and prostate cancer and there is evidence for the efficacy of PBT but no suggestion that it is superior to photon based approaches. In pediatric CNS malignancies PBT appears superior to photon approaches but more data is needed. In large ocular melanomas and chordomas, we believe that there is evidence for a benefit of PBT over photon approaches. PBT is an important new technology in radiotherapy. Current evidence provides a limited indication for PBT. More robust prospective clinical trials are needed to determine the appropriate clinical setting for PBT.

This report summarizes the past, present and future of proton beam therapy for malignant disease. Overall, hundreds of patients have been treated worldwide with proton therapy for a variety of different diseases. Two questions remain: Is proton therapy better than the current standard of care with photon treatment? Should it be adopted as the standard of care?

We are not the first to attempt to answer these important questions. In 2007, two systematic reviews of the literature were performed in Europe and published in Radiotherapy and Oncology. Olsen et al. summarized that in all disease sites including pediatric, ocular, GI, lung, base of skull that the evidence for the efficacy of proton therapy is low [1]. They did comment that there is more support for its use in prostate cancer as a method of dose escalation, but no conclusions could be drawn regarding the preference of protons over photons as a method of dose escalation. Lodge et al. similarly reviewed the literature in addition to studies of ion therapy. They concluded that there is no evidence for the use of protons in GI, pelvis, head and neck, lung, and sarcoma. They conclude that in prostate cancer, protons are an option but not superior to photons. In opposition to Olsen et al., they conclude that there is evidence for the use of protons in chordomas and large ocular tumors. They did not review the role of protons in pediatric patients [2]. Another review by Brada et al. published in 2007 concluded that there is insufficient evidence at the present to recommend the use of proton therapy in any of the disease sites [3]. This review focuses specifically on the use of PBT to treat CNS malignancies, lung cancer, gastrointestinal malignancies, ocular melanoma, prostate cancer, head and neck cancer, and pediatric malignancies.

Central nervous system

CNS tumors are treated with ionizing radiation in definitive, post-operative and palliative clinical settings. Unfortunately, the radiotherapy dose necessary to achieve long term local control of CNS tumors often exceeds the tolerance doses of critical structures, including the spinal cord, brain stem, optic nerves, pituitary gland, vertebral bodies, and eyes. As a result, difficult clinical choices
must be made between risking damage to these structures and failing to deliver sufficient radiotherapy doses to attain local control of the tumor. Even while maintaining dose constraints to critical structures, CNS radiotherapy can lead to undesirable neurocognitive deficits that may be either temporary or permanent in adults and are often permanent in children. Therefore, any advance in dose conformity to the target volume and avoidance of critical structures either with IMRT (photons) or PBT (scanning or scattered beam) or certainly IMPT is welcomed.

Planning studies that have compared conformal photon and PBT CNS radiotherapy techniques have, in general, found that the coverage of the PTV is either similar or slightly better with PBT, but that the avoidance of critical structures and the total integral dose were substantially improved with PBT [4]. One site where PBT has been extensively used is chordomas. In a number of studies the local control of chordomas has approached 80%, better than a series of treatment with conventional photon therapy [5–7]. Other centers using either combinations of photons with PBT or PBT alone have found similar results and attributed the success of this therapy to the increased ability to safely deliver higher doses of radiotherapy using PBT techniques as compared to photons [8–10]. In other series using PBT to treat meningiomas, 91.7–100% local control was achieved at 3 years with rates of grade 3 or greater toxicity of 0–12.5% [11,5].

PBT has multiple theoretical advantages over photon radiotherapy for CNS tumors due to the ability of PBT to deliver high dose radiotherapy with steeper dose gradients to proximal critical structures than can be achieved with photon radiotherapy. Clinical data from PBT or mixed photon/PBT for base of skull tumors appear superior to previously published series of conformal photon radiotherapy; however, stereotactic photon radiosurgery may provide a significant dosimetric and clinical advantage to standard conformal (3D or IMRT) radiotherapy techniques. Overall, more clinical data (published clinical trials) are needed to fully establish the role of PBT in CNS tumors.

**Lung**

The most lethal malignancy in the world today, lung cancer represents a very large group of patients treated each year with radiation therapy [12]. Radiation is used as a sole modality to treat stage I NSCLC in the medically inoperable settings. In stage III NSCLC radiation is used in combination with chemotherapy and sometimes surgery to provide definitive treatment. It is also used in limited stage SCLC in combination with systemic therapy and for palliation of obstructive disease in stage IV lung cancer. Major treatment related toxicities include pneumonitis and esophagitis. For stage III or higher lung cancers, PBT has unique advantages in sparing lung volumes from receiving low dose irradiations from the exiting photon beams. Contralateral lung volume may be completely spared with PBT.

PBT has been shown in a limited number of patients to produce 80–90% local control rate with hypofractionated radiation in early stage lung cancer [13–16]. However, a recent meta-analysis showed no difference between photon based SBRT to PBT [17]. Very little published data exists for locally advanced lung cancer.

It is important to note that for all moving tumors, certainly for lung cancer, challenges exist in the accuracy and planning of PBT. Because of organ motion as well as changes in lung density during respiration, PBT in the lung requires significantly more work in planning and dose verification.

PBT has been used in the treatment of stage I NSCLC although no clear clinical benefit over photon therapy has currently been shown. Data regarding the use of PBT in other clinical scenarios remain limited and do not provide sufficient evidence to recommend PBT for lung cancer outside of clinical trials. In addition, unlike in some other disease sites, the issue of organ motion in lung cancer is critical and adds an additional challenge to the use of PBT.

**Gastrointestinal**

Radiotherapy plays a role in two different settings in GI malignancies. For diseases in which surgery plays a primary role in the treatment (rectum, gastric, and esophagus), radiotherapy provides either neoadjuvant or an adjuvant role delivering moderate dose treatment (45 Gy) to a large volume to provide downstaging and microscopic coverage [18]. For other diseases in which radiation plays the primary role in therapy (hepatocellular, esophagus, and pancreas), dose escalation and normal tissue avoidance become more important and thus a role for PBT may be more relevant.

The only area where PBT has been extensively studied is HCC. In a number of studies from the Asia, fractionated PBT has been used in HCC with good success providing a local control rate of between 70% and 85% [19–28].

PBT is mostly untested in GI malignancies, and the number of patients with GI malignancies who are eligible for PBT will be very small until indications for its use become clearer. In rectal and gastric cancers there appears to be little role for PBT. In esophageal and pancreatic cancers there may be a rationale for PBT, as these are two sites often with localized unresectable disease near critical organs at risk, but almost no clinical data exist. In hepatocellular cancer there appears to be the most data and perhaps promise for PBT as an alternative to photon based approaches, but more rigorous study and prospective clinical trials are necessary to define the differences in toxicity and efficacy between protons and photons.

**Ocular melanoma**

Ocular melanoma can threaten vision and is potentially fatal when it disseminates [29]. Advances in the treatment of ocular melanoma have been aimed at preservation of the eye and ideally vision while maintaining high cure rates. Therapeutic options range from local ablative treatments to enucleation of the eye, depending on the size and location of the tumor.

PBT has been reported in the literature in thousands of cases for ocular melanoma. Combined results of leading centers in the U.S. and Europe have shown a 95% local control rate and a 90% eye retention rate [30–34]. This technique is especially useful in large and posteriorly located melanomas that are unapproachable by other techniques.

PBT has been shown to be effective in the treatment of large ocular melanomas not approachable via brachytherapy. In the group of intermediate tumors that has been well studied by the COMS (Collaborative Ocular Melanoma Study) group, there is evidence for efficacy of both PBT and brachytherapy. Further comparative studies will help select patients for the appropriate therapy.

**Prostate cancer**

In the U.S. in 2010 alone, there were 217,000 estimated new cases of prostate cancer, the most common malignancy (excluding skin cancer) in males [12]. IMRT produces excellent local control rates and genitourinary and gastrointestinal toxicity are present but manageable in most patients with low rates of long-term dysfunction. Therefore, the bar is set high for a new technique such as proton beam therapy (PBT) to deliver either improved tumor control or reduced toxicity over IMRT.

Approximately 2000 prostate cancer patients treated with proton therapy have been reported in the literature. Toxicity so
far has been acceptable while dose escalation utilizing a PBT boost has improved outcome. Preliminary results with PBT only therapy are also available and similar to proton/photon results. Dosimetric studies suggest the greatest benefit for conformal proton therapy is reducing the mean integral dose to normal tissue, which may translate into fewer secondary malignancies. Sparing of normal tissues in the low to moderate range (<60–70 Gy) is superior with conformal proton therapy compared to photon therapy. Normal tissue sparing of high doses appears possible with IMPBT.

Prostate cancer has the most patients treated with PBT (conformal proton therapy) of any other disease site. The outcome is similar to IMRT therapy however, with no clear advantage from clinical data for either technique in disease control or prevention of late toxicity. This is a site where further head to head clinical trials may be needed to determine the role of PBT. In addition, careful attention must be paid to the role of dosimetric issues including correction for organ motion in this disease. Based on current data, proton therapy is an option for prostate cancer, but no clear benefit over the existing therapy of IMRT photons has been demonstrated.

Head and neck

The term “head and neck cancer” encompasses a variety of carcinomas from multiple subites in the upper aerodigestive tract from the nasopharynx through the hypopharynx. Treatment outcomes often involve significant treatment-related morbidities from both radiation doses to delivered targeted tissue as well as from radiation entrance and exit doses unavoidably deposited in normal tissue. The majority of clinical experience in head and neck cancer is with a combination of traditional photon therapy and passive scatter PBT [35–39].

Despite monumental progress in treatment, many patients continue to experience acute- and late-term toxicities from radiation delivered to normal tissue, even with optimal IMRT plans. While PBT, even with passive scattering, decreases the volume of normal tissue receiving a low dose of radiation, the more complex issue in head and neck cancer is the very small volume of a critical structure, especially a serial structure such as an optic nerve or the spinal cord, receiving a high dose. A second complicating issue in head and neck cancer is the potentially magnified effect of interfraction or inter-field variation due to the effects of sinus filling and the use of modulated proton therapy (IMPBT).

PBT has been shown to be well suited to treat targets near critical structures, especially at the base of the skull. Data for sinonasal tumors specifically are encouraging, but further data are needed. However, until IMPBT is more fully developed and tested, it will be difficult to establish whether PBT may be equivalent to photon IMRT in treating full head and neck plans. At this time, further clinical data through prospective clinical trials are needed regarding cases in which the target is the primary volume located near critical structures. Currently, there are insufficient data to recommend PBT for routine head and neck radiation therapy outside of clinical trials.

Pediatrics

There are 8600 new cases of pediatric cancer each year [12]. Of these cases, many solid tumors are treated with radiation therapy for a portion of their management. However, radiotherapy causes a disproportionate share of the adverse late effects of treatment [40,41]. In addition to the same side effects that adults experience [42] radiotherapy in children impairs growth and development of soft tissue, bone, and nerve. Brain tumors account for over 50% of pediatric solid tumors. Radiotherapy has a profound effect on the developing brain with younger patients faring worse [43].

PBT has the ability to significantly limit the low dose radiation beyond the treatment target volume. There have been multiple dosimetric studies clearly demonstrating superior normal tissue sparing and decreased integral dose with protons [44–48]. In orbital rhabdomyosarcoma, MGH reported seven clinical cases with excellent outcome (85% local control) and sparing of both ipsilateral and contralateral optic structures when compared to the photon late effects of historical controls in the same population [49]. MacDonald et al. published a study showing excellent outcome in ependymomas with PBT while sparing cochlea, hypothalamus, and temporal lobes [50]. Second malignancies are a major source of morbidity and mortality in pediatric cancer survivors. Protons decrease the volume and dose to normal tissues compared with photon techniques. An early report from MGH described a cohort of 1450 adult patients (median age 56 years) treated with protons at their institution from 1974 to 2001. They found a 6.4% rate of second malignancy as compared with a matched cohort from a SEER database of 12%. Of the 15 pediatric patients in this cohort none developed second malignancies.

PBT has perhaps its most developed place in pediatric brain tumors. Although the clinical evidence is lacking, the rationale for using PBT in posterior fossa tumors, optic pathway tumors, and brainstem lesions is compelling. Future clinical studies reporting on the outcome of patients treated with protons will decide how widespread protons become for pediatric CNS tumors. There does not appear to be sufficient evidence at this time to recommend treatment with protons for non-CNS pediatric malignancies.

Conclusion

In our report, we feel that there is reason to be optimistic about the potential developments in proton therapy, especially as the delivery and planning techniques such as active scanning beams and IMPBT become more prevalent and the prospective research that is ongoing at centers worldwide. Current data do not provide sufficient evidence to recommend PBT outside of clinical trials in lung cancer, head and neck cancer, GI malignancies (with the exception of HCC) and pediatric non-CNS malignancies. In hepatocellular carcinoma and prostate cancer and there is evidence for the efficacy of PBT but no suggestion that it is superior to photon based approaches. In pediatric CNS malignancies there is a suggestion from the literature that PBT is superior to photon approaches but there is currently insufficient data to support a firm recommendation for PBT. In the setting of craniospinal irradiation for pediatric patients protons appear to offer a dosimetric benefit over photons but more clinical data are needed. In large ocular melanomas and chordomas, we believe that there is evidence for a benefit of PBT over photon approaches. In all fields, however, further clinical trials are needed and should be encouraged.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.radonc.2012.02.001.

References


