An Evaluation of Proton Beam Therapy
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Introduction

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.* [1] summarized that in all disease sites, including pediatric, ocular, gastrointestinal (GI), lung, and base of skull, the evidence for the efficacy of proton therapy is low. 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.* [2] 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 use of protons in chordomas, large ocular tumors. They did not review the role of protons in pediatric patients. Another review by Brada *et al.* [3] 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.

This review discusses the technical and operational aspects of proton beam therapy. Included is a summary of the physics of proton therapy, including dose deposition, conventional delivery approaches, spot scanning, dose calculation and treatment planning; immobilization and the need for accurate imaging; and the issues of neutron generation, risk of secondary cancers, and radiobiological effectiveness (RBE) of protons. The review then focuses specifically on the use of proton beam therapy (PBT) to treat central nervous system (CNS) malignancies, lung cancer, GI malignancies, ocular melanoma, prostate cancer, head and neck cancer and pediatric malignancies. In each section, the report discusses the problem definition, tumor localization and planning, future predictions and evaluation/summaries of existing studies.

History

In recent years, there has been a meteoric increase of interest in proton therapy. The physical advantage of proton dose deposition compared to photons and electrons is not in dispute. Marked by the publication of Robert Wilson's seminal paper suggesting the use of protons for radiotherapy, this advantage has been known for over 60 years; however, the advantage could not be fully exploited until the dawn of computed tomography (CT) scanners and 3-D treatment planning.

In 1930, Ernest Orlando Lawrence at the University of California at Berkeley, invented the Cyclotron, which was used to produce high speed protons [4]. Robert Wilson, a graduate student of Lawrence's who received his PhD degree in 1940, was a high-energy experimental physicist who oversaw the design of Fermilab in Bativa,

Illinois, serving as its director from 1967- 1978 (www.fnal.gov). In 1946, the same year he published his seminal paper on protons for radiotherapy, Wilson moved to Harvard as an associate professor and designed a 150 MeV cyclotron. Dr. Wilson's influence can be seen in the design of almost every major cyclotron or synchrotron implemented in the United States [5].

The first use of protons in patient treatment took place in the mid1950s at the University of California, Berkeley [6]. Larsson proposed the use of protons in radiosurgical techniques in 1958 [7]. In 1961, the Harvard Cyclotron Laboratory started treating intracranial lesions with protons [8]. At Harvard in the mid1970s, Suit and Goitein proposed and implemented a much broader use of proton beams in radiotherapy using conventional fractionation schemes and large fields [9]. This work was funded, in part, using a grant from the National Cancer Institute. An early review by Miller lists institutions to first use protons and numbers of patients treated while Smith provides an excellent recent review [10, 11].

The First Hospital System

Early applications of protons were in the area of cranial radiosurgery and delivered at laboratories designed and built for physics research. Loma Linda University Medical Center (LLUMC) developed the first hospital-based system and treated the first patient in 1990. Archambeau and Slater of LLUMC were considering proton therapy in the 1970s, but LLUMC did not have a cyclotron laboratory attached to it. Together with Suit and Goitein of Harvard, they started a consortium known as the Proton Therapy Cooperative Group (PTCOG), which continues to this day. In the process of starting a

proton therapy program from scratch, they developed many significant aspects of proton therapy, including a gantry system, beam transport system, room and site configuration, variable beam energy, and beam control for intensity, homogeneity, and beam size. The beam transport system magnets were designed at Fermilab. It was also decided to utilize a synchrotron rather than a cyclotron for proton acceleration. All aspects of the LLUMC facility startup and initial operation are described by Slater [12].

The Physics of Protons

It is worth noting that the same equation determines the absorbed dose for an electron beam as for a proton beam. The dosimetric difference between electrons and protons stems mainly from the difference in the local energy deposition, which is greatly influenced by the mass of the proton. Being almost 2000 times heavier than electrons, protons do not experience the same degree of angular scattering and traverse the medium with limited deflections. As a result, the local proton energy spectrum does not change dramatically from the initial quasi-monoenergetic distribution. The spectrum slightly widens with depth acquiring a non-Gaussian tail due to energy straggling effects. Since the stopping power significantly peaks in the region where the proton velocity is comparable to that of the atomic electrons, the absorbed dose also experiences a significant peak in this region, known as the Bragg peak. One should be aware that there is a beam size dependence of the Bragg peak: very small fields will result in a degradation of the Bragg peak. As protons travel through heterogeneous tissue, distal edge degradation of the Bragg peak can also occur.

Since protons stop at a specific depth in the patient, it is essential to know the anatomic details of the patient in three dimensions, including the density and composition of each tissue element. Many of the tools that we have come to expect in modern photon beam planning systems, such as the beam's eye view, dose volume histograms, and error analysis to account for motion and setup uncertainties, were originally developed for PBT planning [13-14].

The latest versions of proton dose calculation models are based on pencil beam algorithms [15]. Proton beam planning systems must compensate for the range of proton penetration to adapt for the patient's surface, tissue heterogeneities, and the shape of the distal target volume. Range compensation can be done by calculating a physical compensator or the energy of a scanning pencil beam.

Treatment planning for PBT is performed on a CT scan obtained with the patient in the treatment position. Correlation between the CT scanning system's Hounsfield Units (HU) and the proton relative linear stopping power (RLSP) must be established at each institution. The conversion of HU to RLSP allows the determination of the energy required of the proton beam. This differs from conventional photon treatment planning in which one needs the correspondence between CT/HU and the relative electron density. As a matter of quality assurance for PBT treatment planning, it is still essential to assess the accuracy of the CT/HU to RLSP conversion, assess the accuracy of the treatment planning algorithm and assess the adequacy of patient specific immobilization techniques.

It is difficult to evaluate a PBT plan using only the planning treatment volume (PTV) concept. The location of the tumor as well as the anatomy upstream along the beam path affects the range of the proton beam. Therefore, the single field PTV concept in PBT must be beam specific. One must incorporate the uncertainties in the distal and proximal range of the target volume. It cannot be simply assumed (as is done in photon therapy) that the entire target will receive the prescription dose as long as it remains laterally within the PTV. The concept of the PTV may need to be revised for PBT, especially when reviewing a PBT plan. In practice, range uncertainties caused by CT number conversion to RLSP, setup error and organ motion are typically incorporated in a proton beam design. Non-uniform proton dose distributions thus generated in a treatment plan may anticipate such uncertainties to happen. Hot and cold spots in a treatment plan may not completely reflect the reality on a static CT image. Thus, it is difficult to evaluate a PBT plan, compared to a photon plan, using only the PTV concept.

Double scattering systems that use an aperture and a range compensator are currently the most common way to deliver PBT. However, one needs a machine shop on site or to rely on a commercial company to manufacture apertures and range compensators. The treatment planning system must design the compensators, and a physicist must verify the manufacture of each compensator. For patient specific quality assurance (QA), one may measure the depth dose distribution for each treatment field and compensator combination. The range compensators compensate for the patient's surface, inhomogeneities, and distal tumor surface. One must compensate to the most distal part of the tumor, which is equivalent to "blocking" tissues distal to the target from receiving dose. The use of scatterers to create a wide beam is an inefficient way to

create a clinical proton beam as only about 40 percent of the beam is utilized. In proton beam planning, one can typically use a fewer number of beams than photons; however, one may end up with more beams if field-patching is necessary. For example, there can be 14 fields used to obtain a good PBT plan for some nasopharynx cases. An issue in plan delivery is that one should change match and patch locations to wash out uncertainties such as hot and cold spots as is done with matching fields in photon cranialspinal treatments.

Proton treatment plans can be improved using multi-field intensity-modulated proton therapy (IMPBT). Compared to passive scattering systems with apertures, spot scanning without apertures allows for increased dose conformation and reduction of neutrons. An air gap between the aperture and the patient's surface will widen the lateral penumbra of the clinical proton beam [16].

For moving targets, gating can be used for both scattered and scanned beam systems. In beam scanning, there is usually no physical compensator. Both beam intensity and energy (which is equivalent to the depth of penetration) will have to be synchronized with patient's anatomy and the gating signal. An active area of research is to incorporate treatment uncertainties in IMPBT design [17]. IMPBT allows for different intensity and energy in the beam's eye view (BEV) of the target. In this way, one can treat very complicated targets with a limited number of fields, but this method tends to be sensitive to range uncertainties in PBT.

Challenges in Patient Positioning

As with any radiotherapy treatment, the issue of accurate and reproducible patient positioning is of the utmost importance. From the outset, the approach to PBT planning was similar to that of photon treatments. As previously mentioned, many of the planning techniques developed for PBT served as precursors for photon treatments. Immobilization has been investigated with an emphasis on PBT, and it was found that typical immobilization devices can reproduce the mean patient position to within 3 mm [18]. For protons, another dimension of accuracy to be concerned with is the depth in the BEV direction. Moving tumors as well as normal tissues in the path of the beam present a special problem for proton therapy compared to photon treatments. This is particularly true where the density of the tumor can be significantly different from that of the surrounding tissue such as in radiotherapy of the lung.

Unlike photon therapy, in-room X-ray imaging for patient setup was required for PBT even in early systems.This is due, in part, to the fact that the proton portal images are not physically possible for protons [10]. Since protons stop in the patient, there is nothing to image on the beam exit side of the patient. These early in-room X-ray systems served as precursors to the in-room X-ray systems currently being used for photon therapy.

Proton treatments can be more resource intensive because of the setup accuracy needed. Most institutions have implemented procedures to not only image the patient prior to every *fraction* but prior to every *field* in each fraction [18]. Special immobilization for special treatments such as eye therapy can be quite extensive with specially designed chairs and restraint devices similar in idea to what is found in frame-based photon beam cranial radiosurgery treatments. Treatment tables with six degrees

of freedom have been developed for the purpose of accurate and efficient patient setup. This is partly the result of using fixed-gantry systems and the need to have additional options of different beam directions.

In general, one always wants to maximize use of available treatment beam time. In this regard, PBT differs from photon treatments in which each radiation delivery device is its own entity. Currently, all treatment rooms for PBT are operationally connected since a single cyclotron or synchrotron provides the proton treatment beam for all treatment rooms. Some have investigated and adopted a remote patient positioning method in which the patients are set up and imaged using a CT scanner outside the treatment room [19]. The patients are then moved into the treatment room and rapidly positioned under the beam for treatment. Bolsi *et al.* [19] found that patient motion between imaging and treatment was not significant and that positioning errors below 2.5 mm are achievable.

Operational Issues

The implementation of a PBT program is a technical challenge that requires extensive resources in finance, staffing and operation. In general, the process of and quality assurance for PBT are similar to any other radiotherapy treatment modality. However, due to the precise nature of PBT and system complexity, additional efforts in both maintenance and quality assurance are necessary. Quality assurance of pencil beams, for example, requires verification of the energy and range as well as spot size and shape, which requires rapid collection of large amounts of data and real-time beam

information. Significant staffing and time are required as compared to conventional treatment delivery systems.

Aspects of a proton therapy program that must be specified prior to start-up include the following: the baseline configuration, system accelerator and beam transport system, beam delivery systems and gantries, treatment control system, treatment planning and information system (or appropriate connectivity to an existing information system), patient positioning systems, accelerator control system, system operation and maintenance and other general requirements. Even though there are several manufacturers of PBT equipment, the equipment can still be configured with a large degree of flexibility. Some of these choices can have a significant effect on the overall cost of a system. For example, if one requires a fast beam switching time between rooms (e.g., less than 30 seconds), then the accelerator cost and operating costs can rise.

The Risk of Secondary Cancers and Neutron Production

It is clear that the integral dose is lower for PBT compared to intensity-modulated radiation therapy (IMRT) photon treatments, but the out-of-field dose equivalent is a concern and perhaps controversial for PBT. It has been asserted that neutrons produced by passively scattered proton beams result in an unwanted effective dose to the patient that is higher than for IMRT treatments [20]. This conclusion is primarily due to the neutron dose being a total body dose [21] and that neutrons have a much higher quality factor. The significance of the deleterious effect of neutrons in proton beams is a topic of debate in the field. In PBT, neutrons are generated inside the patient and in the

beam line of the treatment machine. Neutrons generated in the beam line of the machine depend on many factors such as beam-shaping, field size and the energy of the proton beam. The scattering mechanism used to generate a broad proton beam is the primary culprit in generating neutrons. Most would agree that this issue of secondary neutron dose will be significantly decreased for active scanning systems. More recent research has determined that for passive scattering prostate treatments, neutrons created in the nozzle predominated effective dose, though neutrons created in the patient contributed substantially to the equivalent dose in organs near the proton field. It has been shown that the neutron dose in PBT may be equal to or lower than that for IMRT [22]. For pediatric cases, it has been argued that secondary cancers can be reduced by using PBT compared to IMRT [23, 24]. A significant issue in this debate is the uncertain value for the quality factor of the neutrons. The range for neutron quality factors is anywhere from 5 to 20. The true biological effective dose due to neutrons is still a question and should be investigated.

The concern for secondary cancers is not specific to PBT as this is a concern in all treatment types, including IMRT. Despite many debates and theoretical estimations of the risk of secondary cancers in PBT, there has been no clinical report thus far to indicate that PBT produced more secondary cancers than photon treatments.

Radiobiological Effectiveness of Protons (RBE)

PBT was initially contemplated in part because of protons' advantageous physical property to stop at a desired location and because protons have a biological effectiveness very similar to conventional photons. It has been shown that there is still

too much uncertainty in RBE values to propose specific RBE values for tissue, dose fractionation, or proton energy [22]. Furthermore, Paganetti *et al.* [25] also suggested that there is a region of dose deposition where the RBE of protons may increase to the point that it should be considered in treatment planning systems. Clinically, however, the RBE of proton beams should still be considered 1.1 until further research warrants a change [25, 26]. RBE is a function of linear energy transfer (LET), cell type and fractionation scheme. One must use caution at the distal end of the target and near critical structures. There is a consensus of a 2 percent RBE effect at typical doses and fractionation schemes [27]. Currently, the uncertainty in proton RBE does not appear to be taken into account by clinicians using proton therapy.

Evaluation

I. Central Nervous System

Problem Definition

In the United States, approximately 42,000 benign and malignant primary central nervous system (CNS) tumors were diagnosed in 2007, with approximately 3300 of these diagnosed in patients younger than 20 years of age [28]. The treatment of these tumors with ionizing radiation is performed 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 is welcomed.

Future Prediction Based on Technology Development

Technological development in CNS PBT is currently focused in two broad areas. The first area of major innovation concerns tumor localization and patient immobilization. New techniques developed for photon-based image guided therapy are quickly being adapted for use at major PBT centers. The other major area of innovation is in the delivery of PBT itself. Currently, most PBT centers use passively scattered proton beams to treat CNS patients. However, in the near future, these centers will also have the ability to use energy-modulated, intensity-varying proton beams with scanning techniques and inverse planning optimization methods. However, at this time there are limited data on the scanning technique.

Evaluation/Summary of Results of Existing Studies

Planning studies comparing conformal photon and PBT CNS radiotherapy techniques have found, in general, that the coverage of the PTV is either similar or slightly better with PBT and that the avoidance of critical structures and the total integral dose were substantially improved with PBT [29, 30].

One site where PBT has been extensively used is chordomas. Patients with partially resected base of skull or cervical spine chordomas and chondrosarcomas who were treated at Massachusetts General Hospital (MGH) with combined photons and PBT showed a 5-year actuarial local control of 82 percent and disease-free survival of 78 percent [31]. In a series of postoperative PBT for pediatric base of skull chordomas and chondrosarcomas, 5-year progression free survival was 100 percent and 77 percent for chondrosarcomas and chordomas, respectively [32]. 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 [32-35]. Of note, these results are often compared to conformal photon radiotherapy, and results in some series for stereotactic radiosurgery compare more favorably with PBT results [36, 37]. Overall, there are limited data on the toxicity of these PBT-based chordoma treatment regimens, and it is difficult to make meaningful comparisons among the toxicity results of the available small trials of protons, protons/photons, or photons.

Only two published series address the treatment of malignant brain tumors in adults using PBT. In one series of 20 patients, patients with grade 2 and 3 gliomas were treated post-operatively to 68.2 cobalt gray equivalent (CGE) and 79.7 CGE, respectively, and the long term local control and survival rates were not found to be greater than historical controls treated with photons alone [38]. In another series of 23 patients, patients with grade 4 astrocytomas (glioblastoma) treated following resection with 90 CGE using PBT and photons were found to have a median survival of 20 months, which is greater than expected for photon radiotherapy alone [39]. Treatment

failures predominantly occurred in the areas that received 60-70 CGE, but the authors thought that extending the 90 CGE coverage to these areas would have led to unacceptable toxicity levels. In a trial of combined photon and PBT for atypical or malignant meningiomas after surgical resection, Boskos and colleagues [40] recently reported a local control, 2-year overall survival, and 5-year overall survival of 61.3 percent, 95.5 percent, and 53.2 percent, respectively. Thus, while PBT may allow for dose escalation with sparing of normal tissues, there is certainly a limit to the clinical benefit attainable by this approach. Finally, the treatment of olfactory neuroblastomas with PBT has recently been reported, and in this series, high dose PBT (65 CGE in 2.5 CGE fractions) was delivered and resulted in 84 percent progression free survival at five years without any grade 3 or greater acute or late toxicities [41].

Due to the increased ability of PBT to spare normal CNS tissues, there has long been a strong interest in using PBT to treat benign brain tumors. An early study of PBT for secreting pituitary macroadenomas showed similar rates of hormone normalization with higher rates of pituitary deficiency and oculomotor deficits in patients receiving PBT [42]. However, more recent series have found high rates of improvement in presenting symptoms, hormone secretion, and resolution of mass effects, with the majority of patients having no new visual field or hormone deficits [43]. In other series using PBT to treat meningiomas, 91.7-100 percent local control was achieved at three years with rates of grade 3 or greater toxicity of 0-12.5 percent [44, 45].

Summary

In the treatment of skull base and cervical spine chordomas and chondrosarcomas, the use of conformal photon based radiotherapy leads to decreased local control and increased disease progression [46]. However, most photon-based treatments have used lower doses than similar attempts with PBT [47]. In contrast, stereotactic photon radiosurgery series have achieved more comparable results to PBT [36, 37]; therefore, the absolute clinical benefit for PBT is less clear for lesions in which the dosimetry of photon radiosurgery provides for adequate sparing of normal tissues. In patients with glioblastoma, one trial of combined photon/proton radiotherapy yielded improvement in local control as compared to trials of conformal or stereotactic radiotherapy alone [39], although high dose PBT has yet to be combined with temozolomide. For the majority of CNS malignancies, however, the potential benefit of using PBT remains theoretical and deserving of further study.

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 are needed to fully establish the role of PBT in CNS tumors.

II. Lung Cancer

Problem Definition

The most lethal malignancy in the world today, lung cancer represents a very large group of patients treated each year with radiation therapy [48]. Radiation is used as a sole modality to treat stage I non-small cell lung cancer (NSCLC) in the medically inoperable setting. 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 small cell lung cancer (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.

Tumor Localization and Planning

Planning for lung cancer is generally quite sophisticated. Both 3-D combined chemo-radiotherapy (CRT) and IMRT approaches have been used [49]. Planning must take into account margins or corrections for organ motion which can complicate the IMRT plans used because of concern for leaf interplay effects [50]. Mobile lung tumors are difficult to localize; traditional planning has relied on safety margins to account for this uncertainty. Recently, with the use of implantable fiducial markers and cone beam CT, the localization can be achieved more accurately [51, 52].

Future Prediction Based on Technology Development

As a result of the organ motion issues in lung cancer, PBT in lung malignancies requires complex planning to avoid normal tissues. Developments in tracking and gating now being applied to photon therapy would have a dramatic effect if also applicable to PBT in the future. In addition, the development of a robust algorithm for IMPT to be used in stereotactic treatments with PBT could produce even further gains in the new area of lung stereotactic radiation therapy, especially for centrally located lesions.

Evaluation/Summary of Results of Existing Studies

Radiotherapy is used in lung cancer for definitive therapy in stage I and III NSCLC, yet the success of radiation has been variable. Two factors limit its effectiveness: the limitation of dose escalation because of concern for normal tissue toxicity and the radioresistence of certain lung cancers. It is possible that proton technology could contribute to solving one or both of these problems.

Treatment of stage I medically inoperable NSCLC has changed significantly over the past five years. The emergence of stereotactic body radiotherapy (SBRT) has revolutionized the treatment of these lesions with local control results of over 90 percent with T1 and T2 tumors [53]. PBT has also been used in this setting with good results. Hata *et al.* [54] showed that using 5-6 Gray (Gy) in 10 fractions with PBT could produce a 95 percent local control rate. Another Japanese experience delivered 3-4 Gy fractions to a total dose of 70-94 Gy with 80 percentlocal control [55]. Finally, in the series with the longest follow-up, Bush *et al.* [56, 57] from Loma Linda showed a 74 percent local control rate at three years with 5 Gy x 10 fractions. More recently, a meta-analysis

published from Europe compared 3-D CRT to SBRT to carbon ion therapy, showing an improvement in overall survival for both SBRT and ion therapy over 3-D CRT but no difference between SBRT and ion therapy [58]. Weighing these data against the current results from the U.S. and Japan with stereotactic photon therapy, the data appear equivalent in terms of local control with the photon treatment having a slight advantage. However, the biologic effective dose that has been delivered with photons > 100 Gy exceeds that currently being reported with PBT. Therefore, no definitive conclusions can be made in regards to the benefit of one approach over the other.

There is one scenario, however, in which PBT may pose a therapeutic advantage. In central tumors within 2 cm of the mediastinum, investigators have shown that classic SBRT fractionation (20 Gy x3) is not possible with photon therapy due to excessive toxicity [59], although some have used a lower dose per fraction regimen to good effect and without significant toxicity [60]. It might be feasible to treat these tumors with protons without the same toxicity; however, this has not yet been tested.

In stage III NSCLC there is also room for improvement in the outcome after radiation. These patients are often treated with concurrent chemotherapy and radiation and have a local control rate of 30-40 percent [61]. Both esophageal and pulmonary toxicity can limit the dose of radiation that can be delivered [62, 63]. The theoretical advantages of PBT at sparing normal tissues could be quite useful in this area as well; however, almost no data exist in the literature describing clinical experience with protons for this disease. Recently, some preliminary data has been presented in stage III NSCLC. Treating stage III patients with chemotherapy and concurrent proton beam therapy decreased toxicity when compared with IMRT [64]. Significantly less fatigue

has been observed in patients treated with protons when all grades of fatigue were compared ($p = 0.04$). This data and other ongoing studies may contribute to improvements in the treatment of locally advanced NSCLC, but the role of protons in stage III NSCLC is still untested and remains limited to clinical trials.

Thoracic tumors present one other unique consideration for PBT. Unless patients are treated with breath holding techniques, the respiratory motion that occurs during thoracic radiation can significantly alter the dose deposition in the lungs with PBT as opposed to photons. Proton dose distribution is dependent on density at depth. Since the expansion of the lungs with air can change that density, significant corrections need to be done to accurately estimate the dose [65]. Some groups have investigated 4-D CT-based planning for PBT and have shown success when correcting for these density changes in treatment planning exercises [66-68]. Such studies are essential to advancing this technology; however, current data is insufficient to recommend PBT outside of clinical trials.

No current data exists for treatment of SCLC or preoperative NSCLC with protons.

Summary

PBT has been used in the treatment of stage I NSCLC although no clear clinical benefit has been shown to date. Data regarding the use of PBT in other clinical scenarios remains limited and does not provide sufficient evidence to recommend PBT for lung cancer outside of clinical trials. Unlike in some other disease sites, the issue of

organ motion in lung cancer is critical and adds an additional challenge in the use of PBT.

III. Gastrointestinal Malignancies

Problem Definition

Radiotherapy plays a role in two different settings in GI malignancies, which represent a very large portion of oncology cases treated each year in the United States. For diseases in which surgery plays a primary role in the treatment (rectum, gastric, 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. 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.

Tumor Localization and Planning

The tumor is generally localized by CT, MRI, or PET scan. Once the gross tumor volume (GTV) and clinical target volume (CTV) are defined, creating the PTV involves identification of the setup uncertainty and particularly the organ motion involved. In some diseases (pancreas and liver), organ motion is a critical element of the localization process; whereas, in the post-operative setting (gastric, rectum), it becomes less important.

Planning for GI malignancies can be quite varied. In some simpler post operative or neoadjuvant cases, a standard 3-D CRT approach is taken while other more complicated cases require the use of IMRT and stereotactic treatment approaches.

Future Prediction Based on Technology Development

Three developments will enhance and create opportunities for the use of PBT in GI malignancies: the IMPBT technique, the ability to use 4-D or other motion correction technology, and the development of stereotactic body treatments with PBT.

Evaluation/Summary of Results of Existing Studies

In the most prominent sites for radiotherapy in GI malignancies, such as rectal and esophago/gastric, treatment is delivered in combination with surgery. As such, the fields tend to be large and standardized and the dose low, so the need for PBT has been limited. As in other malignancies, PBT's main advantage is in reducing doses to normal tissues [69], thereby decreasing early and late radiation sequelae to these organs as compared to photon therapy [70, 71].

Esophageal Carcinoma

A small number of studies include the use of PBT for treatment of esophageal cancer. The largest trial, performed in Japan, included 46 patients with localized esophageal cancer who were treated between 1985 and 1998 using PBT alone (mean dose 82 CGE) or in combination with conventional photon radiotherapy (mean dose 76 Gy). The 5-year disease specific survival rate was 67 percent for all patients (95 percent for T1 tumors; 33 percent for T2-T4 tumors). In another trial evaluating 30

patients with esophageal carcinoma (13 superficial, 17 advanced), patients were treated with PBT alone or with photon therapy followed by PBT. Mean total doses of the irradiation were 77.7 Gy in superficial carcinoma and 80.7 Gy in advanced carcinoma. Five- and 10-year local control and disease-specific survival rates were better with higher radiation doses. The main toxicity was radiation-induced esophageal ulcer without injury of adjacent organs, reported in 66.7 percent of the patients [72]. None of the studies above used chemoradiotherapy, which is the standard treatment for esophageal cancer. However, in a recent planning study from MD Anderson, IMRT used with protons can lead to improved dosimetric outcomes with reduced lung volumes [73]. Overall, the data is too early and limited to draw substantive conclusions on the applicability of these results.

Gastric Carcinoma

As in esophageal cancer treatment, radiation in gastric cancer plays a crucial role, mainly in the adjuvant setting [74]. As a result, the data on PBT in the adjuvant setting are very limited. Two cases reported in Japan evaluate the use of definitive PBT for medically inoperable early gastric cancer patients. The patients received 86 Gy and 83 Gy, respectively. In both cases, after two years of follow up, no local or other recurrences were detected, although a persistent ulceration of the primary tumor site was present [75].

Pancreatic and Billiary Carcinomas

Treatment of pancreatic cancer, especially in the unresectable setting, is limited by the presence of radiosensitive adjacent organs (duodenum, liver, stomach, kidneys),

and radioresistance of these tumors with traditional photon treatment has been a concern. Little experience exists in the use of PBT in these tumors, but it presents an intriguing area for the applicability of protons. Kozak *et al.* [76] performed a planning study to deliver 5 CGE for 5 fractions for neoadjuvant treatment in preparation for an institutional phase I trial. They showed an improvement in normal organ doses to the kidney, liver, and small bowel over conventionally fractionated IMRT (1.8 Gy for 28 fractions). A parallel study done at the University of Pennsylvania demonstrated dosimetric superiority of PBT to 3-D photon plans [77]. Unfortunately, no current data is available to answer the clinical question of whether or not these dosimetric differences will lead to improved outcome or reduced toxicity in practice.

Hepatocellular Carcinoma

Multiple treatment options can be offered according to the specific stage and characteristics of hepatocellular carcinoma (HCC). The use of radiotherapy in HCC has been somewhat limited because of concerns over radiation induced liver disease (RILD). The mainstay of therapy has been in the unresectable setting or for larger lesions not amenable to radiofrequency ablation. Recently, the institution of SBRT has opened a new area of radiotherapeutic management of both primary and metastatic liver tumors.

Compared to other GI tumors, HCC treatment has more experience with PBT. In 1994, Matsuzaki *et al.* [78] reported the usefulness and safety of PBT in 32 patients with unresectable HCC. Delivered as monotherapy or in combination with lipiodol targeted chemotherapy with a mean does of of 76.6 Gy +/- 9.5 Gy, the treatment achieved a 92%

and 100% tumor size reduction for each study arm in the first year after treatment without any serious adverse effect. In 1997, Ohara *et al.* [79] described that radiation tolerance during PBT in patients with cirrhotic livers and HCC is related to the preserved functional capacity of the untreated liver volume as it is in surgical treatment. In 2004, a phase II trial of high dose PBT in unresectable HCC patients achieved a 75% local control rate and an overall survival rate of 55% at two years. The total dose administered was 63 cGE. Reduction in alpha-fetoprotein was documented in 85% of the patients. Six patients underwent liver transplantation between 6 and 16 months after completion of radiotherapy with 2 showing no evidence of residual carcinoma within the explanted liver. Therapy was well tolerated [80]. In a series of studies from Japan, patients with poor performance status, multiple medical co-morbidities, and unresectable disease from HCC were treated with single doses of 24 Gy and fractionated doses of 63-84 Gy in 3 Gy fractions. Response rates approached 80% with some patients having disease control for longer than 3 years [81-83]. Recently, these data have been updated and report 5-year local control at 88% and 5-year overall survival rate of 38.7% (n = 51) [84]. A recent report from Japan on large tumors (> 10 cm) showed good local control (87%) but modest 2-year survival (36%) [85] while another summarizing 300 patients gave an overall 3-year survival of 64% [86]. These data appear promising, but further prospective data is needed.

Rectal Carcinoma

Used as either neoadjuvant or adjuvant treatment, radiotherapy in rectal cancer is known to improve local control and may impact on survival when combined with systemic therapy [87-90]. In this setting, the role for PBT has not been extensively

evaluated, and only a few reports of PBT in rectal carcinoma are found in the literature. When Tatsuzaki *et al.* [91] evaluated the potential usefulness of PBT in rectal cancer patients by comparing 3D treatment planning of protons and photons, dose distribution analysis showed greater small bowel sparing with PBT although the difference was not statistically significant. A later study in 6 patients from Sweden also showed improvement in dose to small bowel with conventional planning of PBT versus photons. Predominately, there was a difference in the low dose volume to small bowel with photons delivering between 20-30 Gy to 50% of small bowel and PBT delivering < 10 Gy to this same percentage of tissue [92]. Whether these dosimetric differences would lead to any clinical benefit is unknown and has not been studied.

Summary

Although GI malignancies form an extremely large group of patients treated with radiotherapy, the number eligible for PBT is very small until the indications for its use in this setting become clearer. PBT is mostly untested in GI malignancies. In rectal and gastric cancer there appears to be little role for PBT. In esophageal and pancreatic cancer there may be a rationale for PBT but almost no clinical data exists. 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.

IV. Ocular Melanoma

Problem Definition

Ocular (uveal) melanoma is a rare cancer with an annual incidence in the United States of 6 cases per 1 million persons (~ 1500 new diagnoses per year) [93]. Ocular melanoma can threaten vision and is potentially fatal when it disseminates. Loss of local control may cause uveitis, astigmatism, cataracts, exudative retinal detachment, neovascular glaucoma, and secondary glaucoma from trabecular invasion [94]. Due to its rarity, ocular melanoma causes relatively few cancer deaths; however, about one quarter of ocular melanoma patients will die from metastatic disease [95]. Poor prognostic characteristics are associated with worse outcomes [96]. 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.

Tumor Localization, Planning, and Treatment

In order to localize the tumor, the ophthalmologist can use transillumination and/or indirect ophthalmoscopy during surgery. The tumor is demarcated by suturing 4 fiducials (tantalum rings) to the sclera at the margins. For ciliary body and peripheral choroid tumors, transillumination can be used instead of surgery to demarcate melanomas in relation to the iris and cornea, which serve as natural anatomic fiducials. Illustrations of the tumor dimensions, shape, and relation to the fiducials are required for computer assisted treatment planning.

Simulation uses a treatment planning program to create a customized proton radiation therapy plan. Three-dimensional planning is used to determine all treatment

parameters, including the fixation angle, the proton range modulation, the shape of the field-defining aperture, and the relative positions of the tumor-defining rings and beam aperture. At the time of simulation, treatment position radiographs are used to confirm the position of the fiducials. These radiographs, the ophthalmologists' illustrations, and ultrasonographic findings (axial eye length and tumor height) determined at the diagnostic examination are used to create a 3-D model of the melanoma that is superimposed on a custom-scaled model of an eye. Using the treatment planning program, a proton therapy plan is developed that ideally delivers high dose to the entire tumor while sparing normal tissues.

Patients sit in a specialized chair placed in the axis of a lateral proton beam. The head is immobilized, and the patient is instructed to fix his gaze in order to recreate the proper position of the eye based on the plan. The eye is monitored in real time during the entire procedure with high-magnification videography. The position of the tumor relative to the proton beam axis is confirmed by fluoroscopy, which also serves to monitor proper immobilization. A beam simulation field light is used to confirm adequate position and fixation within the treatment field before treatment commences. A 1.5 mm margin is included in the treatment field to allow for setup error, possible microscopic extension, and motion during treatment.

Typically, treatment is fractionated over 5 fractions of 14 CGE for 7 to 10 days to a total dose of 70 CGE. Other dosing schemes have been used, such as 4 fractions of 15 CGE to a total dose of 60 CGE [97].

Future Prediction Based on Technology Development

Improvements in PBT are needed, specifically strategies to reduce the cytotoxic effects of radiation on normal tissues of the eye. This collateral damage can lead to unwanted functional loss and enucleation. Some possible methods may be to increase the fractionation scheme or to treat with a combination of radiation and transpupillary thermotherapy. Other strategies employing biologic agents such as angiogenesis inhibitors may also be useful.

Some technical modifications of techniques over time may improve the therapeutic ratio of PBT [98]. Treating the tumor through the closed upper eyelid to avoid irradiating the lid margin may help avoid palpebral conjunctival keratinization and corneal damage. Juxtapapillary tumors can be treated with a "notched" beam to prevent optic neuropathy.

Ultimately more important than technology development is the development of effective ways to address both potential and known metastases, especially since the local control rates achieved with PBT and other types of radiotherapy are quite good. Evaluation of new potential molecular targets includes genes involved in the cancer process, proteins that may be prognostic or predictive biomarkers, and immune system factors.

Evaluation/Summary of Results of Existing Studies

Several large single-institution experiences treating uveal melanoma with PBT have been reported. At the Harvard Cyclotron, excellent local control and eye retention rates were described in 1006 adult patients with uveal melanoma treated with PBT between 1975 and 1986 [99, 100]. Updated to include over 3000 patients treated over

three decades [101], this series suggested that proton radiation therapy (PRT) was particularly useful in patients with large and/or posterior tumors, for which other modalities may be difficult or have increased risk for toxicity. Similar results have been reported by other institutions. From 1998 to 2003, 245 patients with uveal melanoma were treated with 60 CGE in 4 fractions at the Hahn-Meitner Institute in Berlin with a 96.4% local control at a median follow-up of 18.4 months and 95.5% at 3 years [102]. Eye retention rates were 92.6% at 20 months median follow-up and 87.5% at 3 years. PRT was used to treat 1406 patients using the same fractionation schedule at the Orsay Center [103]. At 5 years, local control was 96% and overall survival was 79% with a 7.7% complication-related enucleation rate. At the Biomedical Cyclotron Centre in Nice, France, 538 patients with uveal melanoma were treated with PBT [104, 105]. At 5 years the study reported a CSS of 86%, enucleation-free survival rate of 88%, and local failure rate of 4.5%. A randomized controlled trial of 151 patients demonstrated a significant decrease in the secondary enucleation rate in patients treated with proton radiotherapy followed by transpupillary thermotherapy [106]. In sum, these data show that PBT for uveal melanoma can provide excellent local control and good rates of eye preservation with minimal late side effects.

In addition to enucleation, alternates to PBT include brachytherapy, stereotactic irradiation [107], trans-scleral local resection, transretinal resection, and diode laser phototherapy. Compared with PBT, however, these alternatives appear to have a lower chance of achieving local control [98]. The most commonly used treatment is brachytherapy, usually with I-125 or Ruthenium-106, but this modality can only be used to treat tumors 8-10 mm thick due to the penetration of the isotopes. Compared to

treatment with I-125 brachytherapy, PBT was associated with fewer late local recurrences (more than 5 years) [108]. Of the 996 patients compared in this study, I-125 brachytherapy was used to treat all 11 of the patients with late recurrences. "Non-double scattered" PBT delivers the lowest dose to normal tissues, including the unaffected eye and distant sites, when compared to highly conformal external beam radiotherapy [109, 110].

There are potential late toxicities of PRT for uveal melanomas that may necessitate enucleation, including development of a tumor scar exudate and glaucoma. As described above, a randomized controlled trial of proton radiotherapy followed by transpupillary thermotherapy showed a decreased rate of enucleation for late toxicity ($p=0.02$) [106]. There are few data regarding concurrently administered systemic treatments.

In the event of a local recurrence, enucleation has been the standard salvage treatment. A small trial of organ preservation with PBT re-irradiation has been reported [111]. Local control was achieved in 20 out of 31 patients re-irradiated with PBT, most frequently with 70 CGE, with a 55% eye retention rate at 5 years.

Summary

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

VII. Prostate Cancer

Problem Definition

Prostate cancer is the most common malignancy in males (excluding skin cancer) with 186,000 new cases in the U.S. in 2008 alone [48]. Patients with low risk disease as well as those with non-metastatic but high-risk disease are offered external beam radiotherapy. Radiotherapy for prostate cancer in the U.S. is delivered mostly through IMRT with 75-88% control rate depending on stage at presentation [113]. In most patients, genitourinary and gastrointestinal toxicity are present but manageable with low rates of long-term dysfunction. Therefore, the bar is set high for a new technique such as PBT to deliver either improved tumor control or reduced toxicity over IMRT.

Tumor Localization and Planning

The implications of PBT for treatment margins [114], anatomic motion [115], and use of fiducial markers [116] have been studied. Several dosimetric comparisons between photons and protons have been performed [117-121].

To emphasize the dependence of treatment planning margin expansions on the therapy used, Thomas [114] compared margins between typical prostate plans using conformal photon and PBT based on the British Institute of Radiology report on *Geometric Uncertainties in Radiotherapy* [122]. Three beam geometries were used: a single field, a parallel opposed, and a 4-field arrangement. Margins for expansions from clinical target volume to planning target volume were compared between protons and

PBT, assuming identical geometrical uncertainties for each modality. Comparing PBT to photon beams, a smaller margin was deemed necessary to achieve tumor coverage from 11 mm to 7 mm in favor of PBT. Furthermore, the planning organ at risk margin (as recommended by ICRU 62 [123]) in the axial direction reduced from 7 mm to 4 mm also in favor of PBT. Thomas concluded that there are many clinical cases in which good dose distributions can be obtained with 1 or 2 fields, which results in smaller margins for the planning target volume and planning organ at risk volume with PBT. However, reductions were not seen on the other axes, or for any axis of the 4-field plans. Larger margins were necessary in the 4-field PBT plan. This was attributed to the narrower penumbra of protons, which gives a larger margin for random errors. In the direction perpendicular to the beam axis, the margins for the PBT plans are nearly independent of beam arrangement and are slightly larger than the photon beam.

Inspired by concern over the increased susceptibility of PBT to tissue density uncertainties related to target intrafraction motion [124], Zhang *et al.* [115] investigated the effect of anatomic motion on PBT dose distributions. For each of the 10 patients studied, 8 computed tomography scans were selected from sets of daily setup computed tomography images obtained with a computed tomography-on-rails system. The effect of daily motion was assessed using two different methods. First, standard PBT and intensity-modulated photon plans were designed for each patient using standard modality specific methods. The images, the PBT plan, and the intensity-modulated photon plan were then aligned to the 8 computed tomography images based on *skin marks*. The doses were recalculated on these 8 computed tomography images using beams from the standard plans. Then the plans were redesigned and evaluated

assuming a smaller clinical target volume to planning target volume margin (3 mm). The images and the corresponding plans were then realigned based on the *center of volume* of the prostate. Once again, dose distributions were evaluated using isodose displays, dose-volume histograms, and target coverage.

Intensity-modulated photon plans used 8 coplanar 6 MV beams, and PBT plans used parallel-opposed lateral beams similar to those used at Loma Linda Proton Treatment and Research Center. When aligning on skin marks, 4 of the 10 intensity-modulated photon plans were deficient; whereas, 3 of 10 proton plans were deficient in achieving adequate tumor coverage. When aligning on the center of volume of the prostate, the PBT plan for only 1 patient was deficient; whereas, 3 of the 10 intensity-modulated photon plans were deficient. The authors concluded that the dosimetric impact of interfractional anatomic motions was similar for both modalities.

The placement of radiopaque fiducial markers is one method for correcting for interfraction motion. Newhauser *et al.* [116] performed analyses testing gold seed, stainless steel, and titanium markers. They investigated the influence of marker size and material on radiographic visibility and on dose perturbations using Monte Carlo simulations of a conformal, parallel opposed lateral proton beam arrangement. Two commonly used commercially available fiducial sizes—a ‘small’ fiducial (0.9 mm in diameter and 3.1 mm long) and a ‘large’ fiducial (1.25 mm in diameter and 3.0 mm long)—were studied in order to assess the influence of the marker dimensions on the dose shadows. The kilovoltage radiographs revealed that both sizes of gold and stainless steel markers were readily visible in both the lateral and anterior–posterior

views. The titanium markers provided sufficient contrast resolution in the anterior–posterior view but not in the lateral view, which is required for patient alignment.

The Monte Carlo simulations revealed that titanium and stainless steel markers minimally perturbed the proton beam, but gold markers cast unacceptably large dose shadows. The simulations revealed that the magnitude of the fiducial perturbation depended strongly on both the spatial implantation depth and orientation with respect to the beam direction. The largest shadows were produced in the cases where the fiducial marker was implanted very near to the end of the proton beam range. The parallel orientation with the proton beam resulted in more pronounced dose shadows. It was concluded that a 0.9 mm diameter, 3.1 mm long cylindrical stainless steel marker provided better radiographic visibility than titanium while perturbing the proton dose distribution in the prostate by less than 8% (goal < 10%; better than gold and slightly more than titanium). Stainless steel markers best fulfilled the clinical requirements.

Evaluation/Summary of Results of Existing Studies

Planning Studies

Mock *et al.* [119] compared dose distributions from a Loma Linda-type conformal PBT (opposed lateral beams) with 3D conformal (4-field box) and intensity-modulated (7 fields at gantry angles of 0, 52, 104, 154, 208, 256, and 308 degrees) photon radiotherapy. For each of 5 patients, different target volumes (clinical target volumes) were defined according to early, intermediate, and advanced stages of disease: clinical target volume I consisted of the prostate gland; clinical target volume II encompassed prostate and base of seminal vesicles; and clinical target volume III, the prostate and

seminal vesicles. The planning target volume included a uniform 5 mm volume expansion of the corresponding clinical target volume. Dose-volume histograms were analyzed for rectal wall, bladder, and both femoral heads for each of the three scenarios. With photon- and proton-based radiotherapy techniques, similar mean and maximum planning target volume doses were achieved with similar conformality. Conformity indices varied from 1.4 to 1.5 for the photon techniques while PBT values ranged from 1.1 to 1.4. The greatest benefit seen for PBT was sparing of bladder and rectum in low to medium dose ranges (< 70% prescription dose). Reductions in dose for these structures ranged from 40 to 80%. For example, the mean dose to the rectal wall was 34 Gy for intensity modulated photons compared to 20 Gy for PBT when the prostate alone was treated. As the planning target volume grew larger to include all of the seminal vesicles, the sparing was greater (42 Gy vs. 23 Gy, respectively). The femoral heads were better spared with the 7-field intensity-modulated photon technique compared to the opposed lateral PBT. The authors concluded that a rather simple 2-field PBT-based treatment technique further reduced doses to organs at risk compared to photon beam radiotherapy.

Conformal photon and PBT plans for prostate cancer have also been compared by Lee *et al.* [120] with emphasis on locally advanced cases. Again, a parallel-opposed Loma Linda-type proton therapy (gantry angles of 90 and 270 degrees) was compared to 3-field (gantry angles of 0, 105 and 255 degrees similar to that used at the Royal Marsden Hospital) and 6-field (gantry angles of 45, 90, 135, 225, 270, and 315 degrees similar to that used at the University of Michigan) photon plans for 20 T3 prostate patients. The planning target volume was defined as the prostate and seminal vesicles

with a margin of 1 to 1.5 cm. Dose distributions were analyzed in terms of dose-volume histograms. Tumor control probability and normal tissue complication probability were used to determine which plan resulted in the best dose distribution. On average, the PBT technique resulted in the best dose distribution in terms of rectal complication probability. The 3-field photon plans were more effective than the 6-field photon technique in sparing the rectum. At 5% rectal normal tissue complication probability, the predicted PBT average tumor control probability for the 20 patients is 2% (in absolute terms) greater than that obtained using 3-field photon therapy. For 7 of the patients, the gain in tumor control probability is more than 3%. In comparison with the 6-field plan, the use of PBT increased the mean tumor control probability between 4.2% and 7.6% within the range of the volume-effect parameter (n) studied. For the same rectal normal tissue complication probability as the 3-field photon plan with a 64 Gy mean target dose, the use of PBT increases the tumor control probability by 2% on average. For 5 of the patients, the increases are greater than 4%. A few cases benefited more from the 3-field photon plan because dose inhomogeneity at the prostate-rectum interface resulted in slightly lower rectal dose compared to the opposed lateral technique. The authors concluded that in general PBT was beneficial but a few patients were better treated with photons.

A third comparison of a Loma Linda-type proton therapy to photon therapy treatment was recently reported by Trofimov *et al.* [121]. Their comparison focused on treatment of early stage prostate cancer with either intensity-modulated photon therapy or 3D conformal PBT. Ten patients were planned with 2 parallel-opposed lateral proton fields or 2 intensity-modulated photon fields (seven equally spaced coplanar fields).

When prescribing 79.2 Gray equivalents (GyE) to the prostate, photon plans yielded better dose conformity to the target; whereas, PBT plans achieved higher dose homogeneity and better sparing of rectum and bladder in the range below 30 GyE. Bladder volumes receiving more than 70 GyE (V70) were reduced, on average, by 34% with photons versus PBT, but treatment of rectal V70 was equivalent. However, the authors were able to show the doses to the rectum in the higher dose range (70 Gy) were reduced by up to 35% with photons compared with the standard lateral configuration. The authors concluded that for doses higher than 60 GyE, intensity modulated photons achieved significantly better sparing of the bladder while rectal sparing was similar with proton and photon therapy. Dose to healthy tissues in the range lower than 50% of the target prescription was substantially lower with PBT.

Investigators from the University of Florida Proton Therapy Institute have published a dose-volume comparison of proton and intensity-modulated photon therapy [125]. The data from the first 10 patients treated on a Phase II PBT trial for low risk prostate cancer were analyzed. All patients were simulated with CT and MRI and immobilized in a vacuum-lock bag. The prostate defined the clinical target volume. The seminal vesicles were not included. The planning target volume included the clinical target volume with a 5 mm axial margin and 8 mm craniocaudal margin. PBT was delivered with opposed lateral fields optimized to maximize planning target volume coverage while sparing the rectum. Intensity-modulated photon therapy was designed with 5 equally spaced fields. Both photon and PBT plans were designed for each patient to deliver 78 GyE (relative biologic effectiveness = 1.1) in 39 fractions. Both treatments were able to fulfill the target conformality (V100 = 95%) and dose

homogeneity constraints (max dose < 108%) used. However, the mean and maximum dose to the planning target volume was higher with photons. Mean doses to the rectum (sigmoid flexure to ischial tuberosities; 14.2 vs. 34.8 GyE) and rectal wall (3 mm inner wall; 16.5 vs. 33.2 GyE) were significantly lower with PBT. Through the dose range, PBT offered greater sparing than the photon plans. For the bladder, there was greater sparing with PBT for doses less than 60 GyE. The benefit diminished as the dose escalated. The mean bladder (18.4 vs 28.9 GyE) and bladder wall (18.4 GyE vs. 28.9 GyE) doses were lower with PBT.

Intensity-Modulated Proton Beam Therapy (IMPBT)

Intensity modulation for PBT has been compared to conformal PBT as well as conformal and intensity-modulated photon therapies. Motivated by benefits of inverse planning and intensity modulation of photon therapy, Cella *et al.* [117] performed a comparative planning exercise between intensity modulated photons and protons for a case of prostate cancer. While both intensity modulated photons and protons achieved equally homogenous coverage of the target volume and predicted normal tissue complication probabilities, IMPBT offered reduced low to medium dose to the organs at risk and a lesser integral non-target mean dose compared to photons.

Cella *et al.* [118] performed a more thorough analysis of the potential role for IMPBT and assessed the implication of reduced dose to normal tissues with intensity modulated photons for dose escalation. Four treatment plans were compared in a prostate cancer patient with the aim of delivering 81 Gy to the target: 1) conformal 18 MV photons, 6-fields (Gantry angels 45, 90 135, 225, 270 and 315 degrees, modeled after the technique used at the University Hospital of Geneva); 2) 214 MeV protons, 2-

fields (gantry angles 90 and 270 degrees, Loma Linda style); 3) intensity modulated 15 MV photons, 5-fields (gantry angles 45, 105, 180, 255 and 315 degrees, modeled after the technique used at Memorial Sloan Kettering Cancer Center); and 4) 177-200 MeV intensity modulated protons, 5-fields as in Plan 3. In addition, intensity-modulated proton methods were used to further escalate the tumor dose to 99 GyE. The clinical target volume was the prostate and seminal vesicles. A 1 cm margin expansion was used for the planning target volume except posteriorly where 6 mm was used. Dose-volume histograms were used to physically compare the treatment plans. Dose-volume histogram data were also used to obtain normal tissue complication probabilities for the rectum, bladder, femoral heads, and tumor control probabilities. The planning target volume dose distribution was satisfactory with the four treatment plans. Target homogeneity was less with photon, both in conformal and intensity-modulated techniques. The IMPBT plan showed superior rectal sparing for doses less than 64.8 GyE compared to intensity modulated photons. The parallel-opposed lateral field conformal proton technique (*i.e.* Loma Linda style) spared more rectum of lower doses below about 60 GyE than the intensity-modulated photon plan. The integral non-target dose was reduced with PBT plans: 3.1 times less than conformal photons, 1.3 times less than conformal PBT, and 1.7 times less than intensity modulated photons. For a prescribed dose of 81 GyE, only the intensity-modulated photon and IMPBT plans succeeded in predicting an acceptably low normal tissue complication probability for the rectum (< 5%, grade 3). When escalating the dose to 99 GyE, no additional improvement between IMPBT and intensity modulated photon beams was observed. Both intensity-modulated photon and proton therapies were able to optimize the dose

distribution and comply with the goal of delivering the highest dose to the target while reducing the risk of severe morbidity to acceptable levels. The main advantages of IMPBT compared to intensity modulated photons were the ability to significantly reduce low-to-medium dose to the nontarget tissues and a small improvement in planning target volume dose heterogeneity.

In summary, several authors have compared photon and PBT dosimetry. While the techniques have varied (e.g conventional, conformal, or intensity modulated), PBT generally can reduce the low (< 30 GyE) and medium dose (< 60-70 GyE) regions of the bladder and rectum. Sparing in the high dose region ≥ 70 GyE is comparable between photon and protons when intensity modulation is used. Dose escalation up to 99 GyE has not identified a clear advantage to protons vs. photons when intensity modulation is used. Conventional PBT results in comparatively higher femoral head doses compared to photon therapy (whether conventional, conformal, or intensity modulated is used). The anatomy of the prostate-rectal interface in some patients is not well suited for conventional, parallel-opposed proton therapy because dose inhomogeneity with protons can be high in this region, resulting in hotspots.

Existing Clinical Data

Dr. William Shipley of the Massachusetts General Hospital (MGH) in a 1979 manuscript entitled "*Proton radiation as boost therapy for localized prostatic carcinoma*" [126] presented toxicity results of the first 17 men to receive PBT for prostate cancer. The 160-MeV Harvard Cyclotron was modified to treat patients utilizing a 2000 to 2500 rad perineal "boost". After 12-27 months of observation, there were no noteworthy rectal complications and only 2 easily managed urethral strictures. This technique was

the subject of subsequent randomized Phase I/II [127] and Phase III dose escalation trials conducted at MGH [128]. Since 1991, more than 1200 patients have received PBT alone or in combination with photon therapy at Loma Linda University Medical Center (LLUMC) [129-135]. After Loma Linda and MGH combined resources in 1996 to form the Proton Therapy Oncology Group (PROG), they completed the second Phase III randomized trial for prostate cancer utilizing a proton "boost" [136].

In Japan, the Hyogo Ion Beam Medical Center (HIBMC) implemented PBT for prostate cancer in 2001 and conducted a Phase I/II clinical trial through 2002 [137]. HIBMC adopted an exclusive PBT to treat clinically localized prostate cancer. Acute toxicity results are available for their experience, now including approximately 300 patients [138]. The University of Florida closed three Institutional Review Board (IRB) approved prostate trials for low, intermediate, and high risk prostate cancer [139]. At MGH, a Phase I/II trial investigating 82 GyE for low risk disease enrolled 85 men with morbidity results expected in 2008 [140]. Accrual to a similar Phase I/II trial for intermediate and high risk patients that will treat to 82 GyE with a proton boost is expected to begin soon. Meanwhile, all proton patients treated off of these two protocols are treated to 78 GyE at MGH and are followed on a detailed quality of life protocol. Presently, the M.D. Anderson Cancer Center is accruing patients to a similar observational trial that also prospectively evaluates the quality of life after proton therapy for prostate cancer [141, 142]. Requests for further information from Loma Linda and Indiana were not returned [143, 144].

Clinical Trials

In North America, there have been one phase I/II [127] and two phase III randomized clinical trials [128, 136, 145] investigating PBT for prostate cancer. Together, they included 676 patients, 560 of which were treated with PBT. Sixty-four patients were treated with combined pelvic photon therapy plus a perineal proton beam boost in the early MGH phase I/II trial [127], 103 men received a 25.2 GyE boost on the phase III MGH trial [128], and 393 were randomized to receive either a 19.8 GyE or 28.8 GyE on the PROG trial [136]. All three trials were designed to test dose escalation using a proton “boost”.

The pilot study conducted at MGH from 1976 to 1979 assigned 64 patients with clinically localized prostate cancer to external beam photon radiotherapy and a perineal proton beam boost [127]. The results were compared to a non-randomized control group of 116 patients treated with external beam photon radiotherapy from 1978 to 1993. Patients included were T1-4, NX/0/+, M0 (AJCC 1978), and there was no obvious imbalance between the two groups. Estrogens, orchiectomy, or combined estrogen administration and orchiectomy were permitted.

All patients were simulated with computed tomography (CT), and radiation dose was prescribed to the isocenter (100%). Photon therapy was delivered with a 10 MV linear accelerator or 42 MV betatron. Initial fields consisted of 50 Gy in 5.5 weeks to the pelvis using a 4-field box technique (anterior-posterior, posterior-anterior, right and left laterals) with corner blocks to spare normal soft tissue. The top border included the bifurcation of the common iliac vessels. For surgically staged node negative patients, smaller fields including only the prostate and immediately adjacent periprostatic tissues

were used. A boost to the tumor volume delivered a total minimum tumor dose of 68 Gy in 7.5 weeks. The mean minimal prostate dose was 67 Gy (range: 60 to 68.4 Gy).

Treatment planning for the proton boost was performed using CT with the patient in the lithotomy position. The proton boost group received the same initial pelvic treatment; then the prostate was boosted to a dose of approximately 74 GyE (radiobiologic effectiveness = 1.1). A rectal probe technique was used to assist in the accurate alignment, and a rectal balloon was inflated to displace the posterior rectal wall and any ampullary gas out of the treatment beam [126]. The mean minimal tumor dose in the proton boost group was 74 GyE (range: 70-76.5 GyE).

Overall and disease-free survival results were related to more advanced (T3-4) and poorly differentiated tumors but not to the addition of proton beam therapy. There was no statistical difference in survival or disease-free survival between the patients treated with or without hormonal therapy. Local control was assessed by digital rectal examination, and an enlarging nodule was evidence of a local recurrence. There were 3 (5%) local recurrences (all T3) in the combined group (n = 64) while there were 13 (11%) in the photon only group (n = 116). A statistical comparison between groups was not performed. Patients treated with hormonal therapy were more likely to experience a local recurrence, which may be related to selection bias. Thirty-nine men in the photon group and 10 in the combined group received hormonal therapy prior to or concomitant with RT.

There were no significant differences in toxicity between photon versus PBT “boost” groups in terms of mild dysuria/increased urinary frequency (10% vs. 11%),

hematuria (10% vs. 8%), and benign stricture (4% vs. 5%). There were also no significant differences between groups in terms of mild proctitis (occasional diarrhea or rectal urgency not requiring medication, 11% vs. 8%); moderate proctitis (including patients with rectal symptoms which required medication, 5% vs. 13%), or severe proctitis (defined as rectal problems requiring surgery; 1% vs. 0%). Only 1 patient, who was treated in the photon only group, required a colostomy for chronic painful tenesmus. Because of the minimal complications observed in the proton group despite a 10% increase in dose, a randomized phase III clinical trial comparing these two treatment techniques was devised.

From 1982 to 1992, the first phase III clinical trial using proton therapy for prostate cancer randomly assigned patients with locally advanced T3-4 (T4 - 5%) NX/0-2 M0 prostate cancer to conventional photon therapy (50.4 Gy in 1.8 Gy fractions) followed by a photon boost (16.8 Gy in 2.1 Gy fractions five days a week) or a proton boost (25.2 GyE in 2.1 GyE fractions four days a week; radiobiologic effectiveness ratio of 1.1) [128, 145]. The total combined dose was 67.2 Gy for the photon group and 75.5 GyE for the combined photon and PBT group. Eligibility criteria included a performance status of 2 or less, a normal serum acid phosphatase level, no evidence of metastasis on bone scan or retroperitoneal lymph nodes at or above the bifurcation of the common iliac vessels computed tomography or lymphadenectomy. Patients were stratified by stage (T3 or T4), histopathologic differentiation (Gleason grade 1-2, grade 3 or grade 4–5 [this group would have included Gleason score 7 or higher]), and lymph node status (NX, N0, N1-2). The study was designed and initiated prior to the routine use of prostate specific antigen (PSA); therefore, PSA was not used as a stratification criterion.

As PSA became available, however, it was used and biochemical outcomes were reported.

Both arms were initially treated using conventional pelvic radiotherapy. Conventional photon therapy (4-field technique) was delivered using 10 to 25 MV photons. Custom blocking to the prostate and pelvic lymph nodes below the bifurcation of the common iliac vessels (typical fields were: AP/PA, 15 cm by 16 cm; lateral 15 cm by 11.5 cm). The photon boost utilized opposed lateral fields. After 1984, a beam-width improving device was used to modify a 10 or 25 MV photon beam for each individual patient that reduced the volume of rectum raised to high dose by 40-50% [146]. Patients were resimulated with rectal contrast for design of the beam-width improving device lateral fields. The photon boost doses were usually prescribed to the 98% isodose line that allowed for a 5 mm minimum margin beyond the tumor volume.

For patients receiving a PBT boost, a 7-10 day break was permitted to allow for sufficient healing of any acute proctitis so that the patient could tolerate the daily insertion of a Lucite probe to assure correct positioning of the tumor volume relative to the horizontal proton beam [126]. The proton beam was designed with a 5 mm margin between the target volume and 90% isodose line. The planning used pelvic CT with the patient in the lithotomy position with contouring so as to spare the posterior rectum, and all but the anterior proximal anus defined the target volume [145]. The perineal field was aligned with the aid of a gold seed inserted at the prostate apex.

Endpoints of the study included biochemical failure, local recurrence, distant metastasis, and total recurrence-free survival. Biochemical failure was defined as a PSA value of 4 ng/mL or more, or if the serum PSA level increased by more than 10%

compared with a previous value obtained less than 2 years following treatment. Clinical failure was defined by a palpable regrowth on digital rectal exam, genitourinary symptoms requiring a transurethral resection of tissue harboring cancer, or a positive rebiopsy in an otherwise asymptomatic patient with a non-suspicious digital rectal exam. Prostate rebiopsy was indicated 24 months after treatment if no evidence of clinical local failure was evident and no salvage hormonal therapy was used. Rebiopsy was encouraged but not required. A positive biopsy was defined by architectural criteria [147]. No attempt to grade the tumor or establish viability was made. Distant metastasis was defined by radiographic evaluation, primarily bone scan. Bone scans were performed at the discretion of the physician if patients developed symptoms suspicious for metastatic disease or when the prostate acid phosphatase or prostate specific antigen level (since 1988) increased on successive visits. Total recurrence-free survival was defined as no evidence of biochemical failure and a negative prostate biopsy if done.

Two hundred and two patients were randomized. All pretreatment characteristics were well balanced. Overall compliance with assigned treatment was 93.6%: 90.3% for low dose and 97% for high. There was no difference in biochemical failure, local recurrence, distant metastasis, or total tumor-free survival between the two groups. There was a trend toward improvement in freedom from local or symptomatic regrowth of tumor and a lower positive rebiopsy rate 2 or more years after treatment in men with a normal digital rectal exam. Actuarial local recurrence rates were 22% for low dose and 12% high dose (p = 0.2). Gleason score 7-10 patients were found to benefit from higher dose in terms of local control (8-year rate: 84% vs. 19%, p = 0.0014) in subgroup

analysis. Cox regression identified a strong quantitative interaction ($p < 0.0001$) between dose and Gleason grade for local control, although neither separately was statistically significant. This did not translate to a benefit in terms of tumor-free survival, disease-specific survival, or overall survival. There was a non-statistically significant difference in the positive rebiopsy rate at 24 months in men without evidence of recurrence between the low and high dose groups (45% vs. 28%, respectively).

Toxicity was scored using the Radiation Therapy Oncology Group (RTOG) Common Toxicity Criteria [148]. There were no grade 3, 4, or 5 toxicities during treatment. The most severe gastrointestinal toxicity was one patient in the high dose group who developed grade 4 toxicity 7 years following treatment with progressive grade 3 rectal and bladder bleeding requiring surgical diversions. The actuarial rates of rectal bleeding at 8 years were significantly higher in the high dose arm (32%) than in the low dose arm (12%) with a median follow-up of 61 months ($p = 0.002$). In the high dose group, rectal bleeding persisted in 8 of 25 patients. In the low dose arm, bleeding persisted in 2 of 9 patients. Thirty-one of 34 patients with rectal bleeding were grade 2 or less.

Genitourinary toxicity included an 8-year actuarial incidence of urethral stricture of 19% in the high dose arm and 8% in the low dose arm ($p = 0.07$). In the high dose arm, 12 patients required a minor surgical procedure for urethral stricture, which was corrected in 8 patients for a persistence rate of 4.3%. In the lower dose arm, successful surgical correction of their urethral stricture was accomplished in 3 of 5 patients, for a persistence rate of 2.1%. The 8-year actuarial rate of gross hematuria was 14% in the high dose group and 8% in the low dose group ($p = 0.25$). This was managed

conservatively and/or by fulguration in 11 of 13 patients in the high dose arm and 4 of 6 patients in the low dose arm. Urinary incontinence was reported in 1 patient in the high dose arm treated successfully with an artificial sphincter and in 1 patient in the low dose arm who developed a local recurrence. Impotence rates were also reported although impotence was not defined. There were 78 potent men prior to treatment of which 24 (60%) in the high dose group and 24 (62%) in the low dose group became impotent.

The authors concluded that further dose escalation with a similarly conformal technique using PBT was feasible. Based on the apparent benefit in local control with the higher dose in the favorable group, further dose escalation would be tested for early stage patients in the subsequent trial.

The PROG trial followed the MGH trial and was a combined effort of MGH and Loma Linda from 1996 to 1999 [136]. The hypothesis of this trial was that increasing radiation dose delivered to men with early stage prostate cancer improves disease outcome. Patients with T1b through T2b disease were eligible, and pretreatment PSA was required to be 15 ng/mL or less. Patients were stratified for serum PSA (< 4 ng/mL vs. 4 to 15 ng/mL) and nodal status (NX or NO; only 2 patients underwent formal lymph node sampling). A combination of conformal photon and proton beams were used. Patients were randomly assigned to receive conformal photon therapy (50.5 Gy in 28 fractions) followed by either a 19.8 GyE or 28.8 GyE proton “boost” in 1.8 GyE fractions (radiobiologic effectiveness ratio of 1.1). The total combined external beam radiation dose was 70.2 GyE or 79.2 GyE. Androgen deprivation therapy was not used.

Treatment planning was CT-based. Immobilization included casts of thermal-setting plastic or body foam. The photon therapy technique was universal and used a

4-field box technique (anterior, posterior, and right and left lateral) with 10 to 23 MV photons. The clinical target volume was the prostate with a 5 mm margin. The planning target volume was dependent on the boost technique used, and an additional 7-10 mm margin was added to the clinical target volume based on the technical requirements of each institution.

Patient positioning for PBT was variable based upon the treating institution. Patients treated at MGH received a single anterior proton field with 160 MV protons in the lithotomy position while patients treated at Loma Linda received parallel-opposed lateral fields (gantry angles 90 and 270 degrees) with 250 MV protons in the supine position. A rectal balloon technique was used. A round Lucite probe was inserted 12-15 cm into the rectum and inflated with 25 to 50 mL of saline to immobilize the prostate and displace the posterior rectal wall from the path of the proton beam. Weekly images during photon therapy and daily portal images during PBT therapy were used.

Three hundred and ninety three patients were enrolled: 197 were randomized to 70.2 GyE and 195 to 79.2 GyE. Two hundred and ninety two patients were available for analysis. Compliance with assigned dose was 91.9% for 70.2 GyE and 88.2% for 79.2 GyE. There were no obvious imbalances between the two groups in terms of well established risk factors.

Biochemical failure was defined according to the 1997 American Society for Therapeutic Radiology and Oncology (ASTRO) consensus panel recommendations (three consecutive rises with backdating) [149]. With a median follow-up of 5.5 years, the 5-year freedom from biochemical failure rate was 61.4% for the low dose group and 80.4% for the high dose group ($p < 0.001$). This represents a 49% reduction in the risk

of failure at 5 years. An unplanned analysis of biochemical failure by risk group was performed [150]. There was a benefit for higher dose seen in the low risk group (60.1% vs. 80.5%; $p < 0.001$) and intermediate risk group (62.7% vs. 81%, $p = 0.02$) but not in the high-risk group ($n = 33$). These results were not altered when the analysis was repeated without backdating of biochemical failure.

Clinical outcome was also analyzed. Local recurrence was defined as a positive rebiopsy of the prostate. Rebiopsy was indicated if the post treatment PSA level did not decrease to 1 ng/mL by 2 years or if the PSA subsequently increased above that level. A PSA level less than 1 ng/mL was used based on evidence that less than 6% of men are expected to have a positive rebiopsy [151, 152]. If these criteria were met, a biopsy was not performed, and the patient was judged as a local failure in the absence of distant metastasis. Of those scored as local failure, 24% were biopsy confirmed. Local control was 47.6% in the low dose group and 67.2% in the high dose group ($p < 0.001$). Overall survival was 97% in the low dose group and 96% in the high dose group. There were 18 deaths (10 low dose, 8 high dose) and 2 prostate cancer-related deaths (both low dose).

Morbidity was determined according to the RTOG Common Toxicity Criteria [148]. Severe grade 3 or higher gastrointestinal or genitourinary toxicity was rare (1-2%). For genitourinary toxicity, there was no significant difference in grade 2 acute morbidity (42% vs. 49%) or late morbidity (18% vs. 20%). There was significantly higher grade 2 acute gastrointestinal morbidity (41% vs. 57%, $p = 0.004$) and late gastrointestinal morbidity (8% vs. 17%, $p = 0.005$) for the high dose arm.

The authors' primary conclusion was that high dose conformal radiotherapy was beneficial for men with localized prostate cancer versus standard dose. They further concluded that this trial validated the use of PBT, but it did not test whether this modality was more or less effective.

Non-randomized Trials

The preliminary report of morbidity and tumor control for patients treated at Loma Linda was published in 1997 [135]. From December 1991 to April 1993, 106 patients with clinically localized prostate cancer were treated with conventional photon radiotherapy to the pelvis (45 Gy in 1.8 fractions) followed by a conformal PBT boost (30 GyE in 2 GyE 15 fractions; RBE = 1.1) to the prostate and seminal vesicles with a 7 mm margin prescribed to the 90% isodose line. With a median follow-up of 20.2 months (range: 10-30), there was no grade 3 or 4 gastrointestinal or genitourinary morbidity (RTOG Common Toxicity Criteria). The incidence of grade 2 gastrointestinal toxicity was 3.8% and genitourinary was 3.8%. The rate of PSA normalization was high, 96% at 2 years, and was related to initial PSA level. Local failure was defined as progression in the primary tumor, as evidenced by reappearance or increasing size of the tumor mass or nodule with respect to pretreatment examination, or a continued abnormal prostate with rising PSA. Local failure was found in 3 patients (2.8%). Distant failure was defined as evidence of metastasis outside the primary site or regional lymph nodes and was found in 8 patients (7.5%).

This experience was later expanded and reported by Slater *et al.* [132-134] in a series of manuscripts. From October 1991 to December 1997, 1961 patients with localized prostate cancer were treated with combination proton and photon beam

radiation therapy or PBT alone. Early in their experience, combined photon and PBT treatment was used. The whole pelvis was treated using 4 fields with 18-23 MeV photons to a dose of 45 Gy in 1.8 Gy fractions (prescribed to the 100% isodose line). The PBT boost targeted the prostate and seminal vesicles with a 1.2 cm margin using opposed lateral fields and 225 to 250 MeV protons to deliver 30 GyE in 2 GyE fractions (RBE = 1.1; prescribed to the 100% isodose line). PBT was delivered before photons were used. Patients were treated in the supine position with a water balloon inserted into the rectum. The balloon consisted of a condom over a pediatric enema tip that was inserted into the rectum prior to each treatment and filled with 120 mL of water to distend the posterior rectal wall, both to remove it from the planned treatment field and to minimize the volume of air in the rectum. This technique was shown to be well tolerated [153]. Patient alignment was verified with digitally reconstructed radiographs weekly for photon therapy and daily for proton treatment. Later in their experience, patients with a risk of pelvic lymph node involvement of 15% or greater according to the Partin nomogram [154] received combined treatment to incorporate the pelvis while more favorable patients were treated with PBT alone. In favorable patients, lateral opposed proton fields were used to deliver 74 GyE in 2 GyE fractions to the prostate and seminal vesicles.

The most current report from Loma Linda was published in 2004 [132]. The study included 1255 men who received no prior surgery or hormonal therapy prior to treatment for clinically localized prostate cancer. The patients were largely favorable to intermediate risk. The proportion of men with T3 disease was 4% (T4 = 0%), initial PSA > 20 ng/mL was 11%, and Gleason score 8-10 was 7%. With a median follow-up of 62

months (range: 1-132), the overall 8-year actuarial biochemical disease-free survival was 73% [149]. Multivariate analysis identified initial PSA ($p = 0.0001$), Gleason score ($p = 0.001$), and PSA nadir ($p = 0.0001$) as independent predictors of biochemical disease-free survival.

Grade 3 or higher acute genitourinary or gastrointestinal toxicity (RTOG Common Toxicity Criteria) was < 1%. Late grade 3 was seen in 1% and grade 4 in 4.2%. Late gastrointestinal toxicity includes grade 3 bleeding and pain. A bowel obstruction requiring colostomy was seen in 1 patient. All severe gastrointestinal toxicity was seen in the first 2.5 years following treatment. Late genitourinary morbidity was seen more commonly than gastrointestinal. Grade 3 late toxicity included 8 urethral strictures and hematuria in 4 patients. Dysuria was seen in 2 patients. There was no difference in toxicity seen between patients treated with combined photons/protons versus protons alone.

The authors concluded that conformal proton beam radiotherapy at the reported dose levels (74 to 75 GyE) achieved equivalent freedom from biochemical failure rates to other reported series with radical prostatectomy [155] and photon radiotherapy [156].

In Japan, Hyogo Ion Beam Medical Center (HIBMC) conducted a phase I-II clinical trial for PBT in 2001 and 2002 [157]. Sixteen prostate cancer patients from this early experience were reported in 2004 [137]. Patient characteristics included T1-T2b (UICC TNM), Gleason score 6-9, and range of PSA from 0.2 ng/mL to 23.0 ng/mL. Androgen deprivation therapy was permitted. Their technique delivered 74 GyE (in 37 fractions; RBE 1.1) with opposed lateral fields. Patients were immobilized in a custom-shaped foam cast, and a rectal balloon was inserted before each treatment to distend

the posterior rectal wall. Computed tomography was used for treatment planning (FOCUS-M; Computerized Medical Systems, Inc., Toyoko, Japan and Mitsubishi, Kobe, Japan) [158].

Toxicity was assessed at mean follow-up of 11.9 months (range: 7.9 to 14.5 months) using the National Cancer Institute Common Toxicity Criteria Grading System (version 2.0, April 1999) and RTOG late morbidity criteria [148]. There were no grade 3 or 4 toxicities. All patients showed grade I skin toxicity. Genitourinary grade I toxicity was 69% and grade II, 6%. Two patients reported rectal bleeding and none developed anal pain or diarrhea. Based on normalization of PSA, PSA response was reported as 100%. With magnetic resonance imaging (MRI) used to assess tumor response, tumors were observed in 9 of 16 (56%), and a partial response was seen in 6 of 9 (67%). No tumor growth was seen.

By December 2003, 136 patients were treated with proton therapy at HIBMC. A total of 287 patients with Stage T1-4 N0 M0 (UICC 1997 TNM) prostate cancer were treated with 190 –230 MeV PBT between 2003 and 2004. Acute morbidity for these patients will be reported in 2007 [138]. Patients with prior history of transurethral resection of the prostate (TURP), radical prostatectomy, urinary retention, pelvic irradiation, or resection of rectal cancer were excluded. Androgen deprivation therapy was used for men with Stage T2b-T3b or baseline PSA 20-50 ng/mL or percentage of positive biopsy cores > 50% and for men with Stage T4 or PSA >/= 50 ng/mL. Neoadjvant androgen suppression therapy consisted of a combination of luteinizing hormone–releasing hormone agonist and antiandrogen. Patients with T4 or PSA ≥ 50

ng/mL were required to continue androgen suppression for > 12 months. Patients otherwise receiving androgen suppression prior to radiotherapy were permitted.

Fused CT-MRI was used for simulation, and CT-based dose calculation was routine. The clinical target volume was defined as the prostate and base of the seminal vesicles (unless seminal vesicle invasion was suspected, in which case the entire seminal vesicles were included). The planning target volume was defined as the clinical target volume plus 1 cm. An additional 0.5 cm was added to the planning target volume for penumbra. A 3.75 mm multileaf collimator was used for collimation.

An opposed lateral technique was used to deliver 3 GyE prescribed at isocenter. Patients were immobilized in a thermoplastic cast. Orthogonal digitally reconstructed radiographs were used for daily patient setup to align the bony anatomy. Patients initially received 60 GyE. At 50 GyE, a secondary computed tomography simulation was performed. The secondary planning target volume was defined as the clinical target volume plus 1 cm except posterior where 3 mm were used. The planning target volume with 5 mm for penumbra was prescribed to a dose of 14 GyE (74 GyE total). Typically, the distance from the clinical target volume to the edge of the MLC was set to 15 mm in the initial fields and 8 mm in the boost fields. The external rectal wall was contoured from 1.5 cm below to 1.5 cm above the clinical target volume, and the entire external bladder was contoured. Doses were calculated using a pencil beam algorithm. Surrounding critical structures, including the rectum, bladder and femoral heads, were also delineated. Dose-volume histograms were used to evaluate plans, but composite dose volume histograms were not used due to limitations of the treatment planning software.

Acute effects were defined as newly diagnosed symptoms or clinical findings within 90 days from the initiation of PBT. Genitourinary and GI morbidity was evaluated with the National Cancer Institute Common Toxicity Criteria (NCI CTC v2). Patients were evaluated twice weekly during PBT. A follow-up evaluation was performed 1 month after completion of treatment and every 3 months thereafter. Acute rectal radiation mucositis was evaluated in 178 patients before and immediately upon completion of treatment between April 2002 and March 2003.

Acute GI morbidity was rare. There were no grade 2 or higher toxicities. Five patients experienced mild rectal discomfort not requiring medication (i.e. grade 1). Thirteen of 178 patients (7%) who were evaluated after treatment with endoscopies were found to have erythema of the anterior rectal wall.

Assessment of acute genitourinary morbidity revealed no grade 4 morbidity and 4 patients with grade 3 (1%). All 4 grade 3 toxicities were in men with T3-4 tumors. Grade 1 was most common (54%) followed by grade 2 (39%). Dysuria (91%) was the most common grade 2 toxicity followed by frequency (32%), hesitancy (8%), and hematuria (8%). Genitourinary symptoms were relieved in 89% with 0.2 to 0.4mg of tamsulosin. There were no predictors for acute grade 2-3 genitourinary toxicity among various bladder dose-volume histogram parameters (e.g. V30, V50, V70, V90, V95 for initial and boost phases). Univariate analysis identified clinical target volume ($p = 0.01$) and older age ($p = 0.03$) as predictors of grade 2 or greater acute genitourinary morbidity. The use of androgen suppression therapy was marginally statistically significant ($p = 0.05$). Diabetes mellitus, PSA level, and T-stage were not. On multivariate analysis, larger clinical target volume ($p = 0.001$) and androgen suppression

therapy (p = 0.017) were independent factors for predicting acute grade 2 or higher genitourinary toxicity in a model with age and diabetes mellitus. Patients with larger clinical target volume receiving androgen suppression were approximately twice as likely to have acute grade 2-3 toxicity.

Late Effects

The risk of rectal bleeding and its relationship to radiotherapy dose was established in part due to the experience at MGH treating T3 and T4 tumors with a PBT "boost" [145]. Between 1976 and 1992, 167 men with stages T3 to T4 prostate cancer were treated at MGH. Of the surviving 42 men, 39 were interviewed with a median follow-up of 13.1 years (range 7 to 23) [o124]. The actuarial incidence of grade 2 or greater genitourinary morbidity (RTOG Common Toxicity Criteria) was 59% at 15 years. The actuarial incidence of grade 2 or greater hematuria was 21% at 5 years and 47% at 15. For grade 3 or greater hematuria, the risk was 3% and 8% at 5 and 15 years, respectively. No patient required cystectomy, but one required diversion for morbidity. Urethral stricture and urinary incontinence with pads needed developed in 4 and 3 men, respectively. This particular morbidity was strongly associated with previous or subsequent prostate surgery. The actuarial incidence of grade 2 or greater gastrointestinal morbidity was 13% at 5 and 15 years, while grade 1 rectal bleeding occurred in another 41%.

Second Malignancy

To estimate the impact of intensity-modulated photon therapy and conformal proton radiotherapy on secondary cancer incidence, Schneider *et al.* [159] used the organ equivalent dose model to assess dose distributions of 30 patients who received

radiation therapy for prostate cancer. The organ equivalent dose concept (utilizing both plateau and linear dose-response models) was applied to 11 patients treated with 3D conformal photons, 11 patients receiving intensity modulated photons, and 8 patients receiving conformal PBT (Loma Linda style). The photon plans were calculated with 6 MV, 15 MV, and 18 MV beam energies. Compared to conventional 4-field planning with 15 MV photons, a modest increase of 15% radiation-induced cancer results from 6 MV intensity modulated photons. The probability to develop a secondary cancer increases with intensity modulated photons of higher energies by 20% for 15 MV and 60% for 18 MV. The use of conformal PBT was found to reduce secondary cancer incidence as much as 50% as compared to IMRT. The resulting increase in risk for secondary cancer using modern treatment techniques such as intensity modulated photons was not as dramatic as expected. By using 6 MV photons, only a moderate risk increase is expected. The authors concluded that conformal PBT is the treatment of choice in regard to secondary cancer incidence [159, 160].

To estimate the impact of dose escalation on the secondary cancer risk as it relates to photon and proton therapy, Schneider *et al.* [159] again used an organ equivalent dose model for 3-D conformal photon, intensity-modulated photon, and conformal PBT (Loma Linda style) treatment plans. The purpose was to determine the level of risk for further dose escalation with target doses ranging from 70 GyE to 100 GyE. The organ equivalent dose concept (utilizing both plateau and linear dose-response models) was applied to the dose distributions of 23 patients: conformal RT was used in 7 patients, 8 patients received intensity-modulated photon therapy with 6 MV and 15 MV photons, and 8 patients were treated with spot-scanned PBT. Cancer

risk was estimated as a function of target dose and tumor control probability. At a 100-GyE target dose, the secondary cancer risk relative to the 3-D treatment planning at 70 GyE was +18.4% for the 6 MV intensity modulated photons, +25.3% for the 15 MV intensity modulated photons, and -40.7% for the conformal PBT (Loma Linda style). The increasing risk of developing a radiation-associated malignancy after radiotherapy with increasing dose was balanced by the enhanced cure rates at a larger dose. Once again, the authors concluded that conformal PBT is the treatment of choice for dose escalation because this therapy can halve the risk of secondary cancers. Recently, a study done by Fontenot *et al.* [160] compared a PBT plan to IMRT 6-MV plan with respect to second malignancy. Following a calculation based on Monte Carlo simulation, PBT reduced the risk of second malignancy from 39% with IMRT to 26% with PBT.

Cost Effectiveness

Because new treatments are introduced routinely into clinical practice without rigorous economic analysis, Konski *et al.* [161] examined the cost effectiveness of proton beam radiation compared with intensity-modulated photon therapy using a Markov model. The model was informed by cost, freedom from biochemical failure, and utility data obtained from the literature and from patient interviews, and it compared the cost effectiveness of 91.8 GyE delivered with proton beams versus 81 GyE delivered with intensity-modulated radiation therapy. The authors assumed a 10 GyE dose escalation would be possible without increased toxicity. The 5-year freedom from biochemical failure probability was estimated to be 83% for patients treated with intensity modulated photons and 93% for protons. The expected mean cost of proton

beam therapy at 15 years for a 70 year old was $63,511 and $36,808 for a 60 year old. For intensity modulated photons, the expected mean cost for a 70 year old was $64,989 and $39,355 for a 60 year old. The quality-adjusted survival for the 70 year old was 8.54 years for photons and 9.91 years for protons. The quality-adjusted survival for the 60 year old was 8.12 years for photons and 9.45 years for protons. The incremental cost effectiveness ratio was calculated to be $63,578 per quality-adjusted life year for a 70-year-old man and $55,726 per quality-adjusted life year for a 60-year-old man. A 10 GyE escalation of prostate dose compared with intensity modulated photons did not satisfy the commonly accepted standard of $50,000 per quality-adjusted life year requirement for cost effectiveness. In an editorial comment, Zeitman [162] indicated that both changes in treatment reimbursement with time and data regarding the additional toxicity related to dose escalation, such as erectile dysfunction, may alter the balance in the future.

Summary

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 second 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 with no clear advantage from clinical data for either technique either in disease control or prevention of late toxicity. Further head to head clinical trials may be needed to determine the role of PBT in treating prostrate cancer. In addition, careful attention must be paid to the role of dosimetric issues, including correction for organ motion in this disease. Based on the current data, proton therapy is an option for prostate cancer, but no clear benefit exists over the existing therapy of IMRT photons.

V. Head and Neck Cancer

Problem Definition

The term “head and neck cancer” encompasses a variety of carcinomas from multiple subsites in the upper aerodigestive tract from the nasopharynx through the hypopharynx. The majority of these are squamous cell cancers, and standard treatment includes a combination of surgery, radiation, and/or chemoradiation, depending on stage and tumor subsite. Organ preservation approaches over the past two decades have trended toward an increase in the use of chemoradiation as the preferred treatment for a number of subsites for locally advanced disease. Treatment outcomes often involve significant treatment-related morbidities from radiation dose to delivered targeted tissue as well as from radiation entrance and exit dose unavoidably deposited in normal tissue.

The advent of IMRT in the 1990s was a major step forward for the field of radiation oncology in general and for the area of head and neck in particular due to the close proximity of the target to critical structures. In a frequent scenario in head and neck cancer, a critical structure has a maximum tolerated dose less than the dose required for tumor control, which results in an increased volume of normal tissue receiving a low dose of radiation. Due to sharp dose fall-off, IMRT delivers two major benefits: a full prescription dose to an irregularly shaped tumor in close proximity to a critical structure (example, the nasopharynx) and a decrease in radiation–related morbidity by specifically sparing structures (example, decreased xerostomia by parotid-sparing). The majority of clinical experience in head and neck cancer is with a combination of traditional photon therapy and passive scatter PBT [163-166].

Despite monumental gains, further improvements are still needed. Any dose delivered outside of the target represents an area of potential morbidity. Many patients continue to experience acute- and late-term toxicities from radiation delivered to normal tissue, even with optimal IMRT plans.

The ability to further improve head and neck treatment with PBT depends on the type of planning and delivery used for the PBT and the goals of the treatment. There is little debate that PBT, even with passive scattering, decreases the volume of normal tissue receiving a low dose of radiation, or the total area under the curve on a dose-volume histogram. 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 inter-fraction or inter-field variation due to the effects of sinus filling and the use of IMPBT.

Tumor Localization and Planning

In the same manner as for photon therapy, patients undergo CT simulation with emphasis placed on adequate immobilization and without the traditional metal radio-opaque BBs, which could perturb the beam. Adequate patient immobilization is vital to minimize inter-fraction and intra-fraction motion. Techniques used include aquaplast mask, bite-blocks, and stereotactic head frame for hypo-fractionated treatment. The planning CT images are transferred to a treatment planning system and fused with the diagnostic images, typically either a contrast-enhanced CT, MRI, or both depending on tumor site. GTV and CTV definitions are the same as for photon planning; however, the concept of PTV doesn't translate, given the exquisite sensitivity of PBT to tissue density and the dosimetric variation produced by shifting tissues of different densities through a calculated PBT field. In a passively scattered beam, a setup margin can be accounted for in the compensator and collimator. This is not the case in IMPBT because each field is not optimized individually. For passive scatter PBT, multi-beam field-patching technique is commonly used for H&N planning to provide conformal avoidance of normal structures.

Patient position is verified daily with some form of image guidance, typically orthogonal kilovoltage X-rays. Alternatively, CT scanning with treatment couch docking may be used. No treatment center in the U.S. currently has in-room 3D imaging for PBT.

Radiation prescription doses are the same as those used in traditional radiotherapy and range from 54 (typical post-operative dose) to 70 Gy or higher delivered in 2 – 2.2 Gy fractions (higher daily fractions used with dose painting techniques; example: 66 Gy in 2.2 Gy fractions to GTV, or 70 Gy in 2.12 Gy fractions to GTV). Multiple altered fractionation schemes have been used in head and neck cancer and are beyond the scope of this review.

Future Prediction Based on Technology Development

As IMPBT becomes clinically available, PBT will likely be used more frequently than it is currently to treat head and neck cancers. Further planning and clinical outcome studies are critical to study dosimetric uncertainties in this site. Areas for further study include planning studies to evaluate the inter-fraction and inter-field effects of patient's anatomy variations on daily or repeated patient CTs over time (rather than on the same CT, shifted) to identify true changes in patient geometry, position, and the dosimetric consequences (e.g., sinus filling for base of skull and sinus tumors, weight loss and non-rigidity for more inferior targets). Morbidity and quality of life need to continue to be outcome measures for clinical studies.

Evaluation/Summary of Results of Existing Studies

Planning studies

Recent PBT planning studies focused on comparing the best available photon plans (IMRT) with the best available PBT planning techniques. Multiple studies have shown decreased dose to surrounding structures receiving low doses of radiation with IMRT while preserving dose heterogeneity to the target [167-170].

Dose verification studies

An issue for all sites treated with proton therapy, dosimetric uncertainty is an increased concern for IMPBT and H&N cancer due to the close proximity of critical structures to targets and the complex geometry of the sinuses (large air cavities lined with bone). It is a particular concern for IMPBT over other types of PBT because dose optimization is done for the plan as a whole rather than for each single beam. Several studies have addressed this issue: one planning study of the effect of possible patient motion [171] and one study of dose verification in treated patients using PET, with radiated tissue as the photon source for the scan [172].

Lomax *et al.* [171] applied an IMPBT plan optimized in two different ways to a single patient's CT with the CT shifted 5 mm either for the whole plan or between fields. The resulting dose varied as much as 10-15% for small areas, depending on the original optimization of the plan. The CT shift did not include rotation or a change in the filling of the sinuses; an additional study might use two different CTs from the same patient.

Parodi *et al.* [172] show the feasibility post-treatment PET/CT for in-vivo dose verification. Measured PET values were compared to expected PET values from CT-based Monte Carlo complemented by functional information (delivered dose, tissue composition). The resulting comparisons were within the range of statistical variation and have prompted a larger, ongoing study to continue to evaluate this method of verification of delivered dose.

Clinical studies

The largest clinical experience in H&N cancer is from the Francis H. Burr Proton Therapy Center at the Massachusetts General Hospital. Chan *et al.* have reported the results on over 120 patients treated with a combination of photons and PBT for cancers of the nasopharynx cavities [164] and sinonasal cavities [173], with visual outcomes reported for 36 sinus patients [174]. For 102 sinonasal patients with mixed histologies, 5-year actuarial local control (with 6.6-year median follow up) of 86% compares favorably to that seen in the literature with modern photon planning techniques; however, patient groups may not have been comparable between series. Of the 36 patients with reported visual outcomes, toxicities included LENT/CTC grade 1 (n = 5), grade 2 (n = 6), and grade 3 (n = 2), including a grade 3 cataract and lacrimal stenosis [175].

Loma Linda University Medical Center reported results on 29 patients with oropharynx cancer treated with a combination of photons and PBT using a concomitant boost fractionation scheme to 75.9 Gy/45 fractions over 5.5 weeks [163]. Photon fields were 2D and 3D, and PBT boost fields were passive scatter single beams. There were 26 Stage III-IV patients. The study inception predated the use of concurrent chemotherapy, which was not used. Median follow up is 36 months. The 5-year local control rate, excluding 4 stage 1 patients, is 92%, with 88% loco-regional control and 65% disease-free survival. Three late RTOG grade 3 toxicities include 1 vocal cord paralysis, 1 subcutaneous fibrosis, and 1 trismus and tooth decay. Photon beam arrangement precluded bilateral parotid sparing, and xerostomia was not reported.

The University of Tsukuba Proton Research Medical Center reported results on 33 H&N patients treated from 1983 to 2000 [166]. Sites included oral cavity (n = 4),

unspecified tongue (n = 4), hypopharynx and larynx (n = 4), base of tongue (n = 1), nasopharynx (n = 4), nasal cavity (n = 4), paranasal sinuses (n = 8), parotid gland (n = 4), and middle ear (n = 1). Sixteen patients received a combination of photons and PBT, and 17 patients received PBT alone. PBT fractionation varied from 1.5 Gy to 6.0 Gy per fraction. Patients who received PBT alone received a median dose of 75 Gy (range, 42/6.0 Gy fractions – 99/3.3 Gy fractions). One patient with a parotid tumor had been previously irradiated and was excluded from toxicity analysis. Four oral cavity patients had verrucous type low-grade lesions. For the 23 patients with Stage III-IV disease, 5-year local control and survival were 74% and 41%, respectively. Acute and late toxicities included osteoradionecrosis (n = 2), esophageal stenosis (n = 1), mucosal ulceration (n = 3), and skin ulceration (n = 1). Because of the heterogeneity of the patient population and dose fractionation schedule, these results are difficult to compare to others in the literature.

Summary

Head and neck cancer combines the need to radiate tumors near critical structures as well as complex and often large subclinical target volumes. IMRT has been extremely successful in addressing the combination of these two challenges. PBT has been shown to be well suited to accomplish the first of these goals by treating targets near critical structures, especially at the base of skull. Data for sinonasal tumors specifically is encouraging, but further data is needed. Daily variation in sinus filling may significantly perturb PBT dosimetry when the sinuses are in the beam path. Daily planning studies are needed to evaluate this effect to possibly exclude patients with critical structures at dose tolerance near the sinuses.

While there is consistent support in the existing planning literature for IMPBT, this technique is not yet clinically available. There are significant planning challenges and dosimetric uncertainties for tumors of each subsite, all of which deserve further study. Targets in close proximity to critical serial structures that require a prescription dose which exceeds the critical structure tolerance should be approached with the utmost caution. The clearest benefit from IMPBT over the best available photon therapy in existing planning studies is in decreasing the areas of low dose delivered to large volumes of normal tissue. The benefit to very small volumes of high dose delivered to normal tissue in close proximity to target volumes is less clear. Identifying which group of head and neck patients fall into each category is crucial for selecting which patients will clearly benefit from PBT. Tumors that are good candidates for PBT at this time include those for which the prescription dose does not exceed the tolerance of surrounding critical structures and the goal of treatment is to decrease the dose-volume effect to structures receiving a lower dose.

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, it appears that it would be most beneficial to obtain further clinical data regarding cases in which the primary volume located near critical structures is the primary target. Currently, there is insufficient data to recommend PBT for routine head and neck radiation therapy outside of clinical trials.

VI.PEDIATRICS

Problem Definition

There are 8600 new cases of pediatric cancer each year [48]. Of these cases, many solid tumors are treated with radiation therapy for a portion of their management. The variety of sites is quite varied from pelvic sarcomas to CNS malignancies. Fortunately, cure rates for pediatric malignancies are now 80% due to dramatic improvements in surgery, chemotherapy, and radiotherapy [105, 176]. Radiotherapy, however, causes a disproportionate share of the adverse late effects of treatment, which are now being well documented in the literature [177, 178]. In addition to all of the same side effects that adults experience [179], radiotherapy in children impairs growth and development of soft tissue, bone, and nerve. Regarding the negative effects of radiotherapy, there is a positive correlation between dose and volume of normal tissue irradiated, and it is inversely correlated with age at irradiation. When certain parts of the body are irradiated and fail to keep pace with the growth of other parts of the body, cosmetic and functional outcomes will result. For example, a limb length discrepancy resulting from ipsilateral radiotherapy for a pelvic Ewings sarcoma can lead to back pain and scoliosis requiring treatment over a lifetime. The late effects depend on the site of the body treated and vary dramatically. It is clear, however, that these childhood cancer survivors are more likely to have treatment-related chronic conditions, require more medical care and services, and score lower on measures of quality of life [180-182].

Brain tumors account for over 50% of pediatric solid tumors. Because many require radiotherapy, the effects of radiotherapy on the developing brain are addressed in greater detail. It is clearly documented that radiotherapy has a profound effect on the

developing brain with younger patients faring worse [183]. Deficits in neurocognitive function become more pronounced with time from treatment [184]. While these children do not lose previously acquired information and skills, they are unable to acquire new skills and information at a rate comparable to their healthy same-age peers [185]. Whole brain radiotherapy is worse than partial brain radiotherapy; higher radiation dose and the addition of chemotherapy exacerbates the effect [186]. Merchant *et al.* [187, 188] demonstrates with math models that the adverse effects of radiotherapy to the brain on neurocognition are directly correlated to dose and volume in a continuous fashion. Although these data raise the issue that large amounts of low dose radiotherapy may have adverse effects of neurotoxicity, this is as of yet unproven in a prospective fashion.

Tumor Localization and Planning

Pediatric radiotherapy involves much of the same planning and techniques as adult radiotherapy for the same sites, such as immobilization of the torso or pelvis for tumors in that region and use of head masks and/or stereotactic immobilization for CNS tumors. Both 3D conformal (CRT) and IMRT are used routinely in pediatric radiotherapy. Craniospinal radiation is used routinely in a number of pediatric malignancies; whereas, its use in adult tumors is much more limited. Avoidance of low dose radiation to the gonads and other organs including bone (not often an avoidance structure in the adult population) to prevent late toxicity is another special challenge in pediatric radiation therapy as has been mentioned previously. Therefore, more effort is required to reduce these low dose areas in pediatric RT.

Future Prediction Based on Technology Development

While PBT techniques for pediatric patients are improving, a major concern is the risk of second malignancy. This risk is always present in all radiotherapy of children; however, it has been suggested that the risk is larger with scattered PBT than with conventional radiotherapy [21]. Use of scanning beam proton therapy may provide a reduction in second malignancies [21, 189]. Interestingly, two recent studies which examined scatter dose with protons as compared to photon treatment found no significant increase even with scattered protons [190, 191]. Further clinical data in this area is needed to make definitive conclusions.

Another potential advance in pediatric PBT is the development of IMPBT, which could further the gains of conventional PBT; however, these data are preliminary [192].

Evaluation/Summary of Results of Existing Studies

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 [193-200]. For a given proton beam path, the exit dose to normal tissues is eliminated, and in many circumstances (i.e., deep tumors), the entrance dose is also reduced [201]. Until recently, however, there were only two proton centers in the U.S. capable of treating large fields and only a handful around the world. Thus, there are few studies reporting the reduced late effects in the pediatric population due to the small numbers of

patients who have been treated with enough follow up and the need for a good photon comparison group.

The two major areas in which PBT has been tested or examined are in CNS tumors and in craniospinal irradiation to spare visceral organs. In orbital rhabdomyosarcoma, MGH reported 7 clinical cases with excellent outcomes (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 [200]. The sparing of normal tissues with PBT was also seen in dose to the lens and normal brain where low dose radiotherapy can have important adverse effects. Other planning studies have shown the ability to spare optic structures with PBT as compared to photon radiotherapy [194].

Radiation therapy has played an important role in craniopharyngiomas, especially when a complete resection cannot be achieved [202]. Despite overall good outcomes, concern for long term effects of photon radiation on the brain, brain stem, and optic structures have made this a site for investigation of PBT. In a series of 16 patients, Luu *et al.* [203] achieved a 94% local control rate with limited long term complications. Results reported by Fitzek *et al.* [204] with long term results from MGH showed similar control rates and limited long term toxicity.

Perhaps the area considered to have the most potential benefit from PBT in the pediatric population is tumors of the posterior fossa. Early dosimetric studies comparing traditional techniques to PBT showed reduction of overall brain dose [205]. Further dosimetric studies comparing both 3D CRT and IMRT to PBT showed significant

sparing of the cochlea and hypothalamus with PBT [25, 27, 34]. The first study, published by MacDonald *et al.* [206], showed excellent outcome in ependymomas with PBT while sparing cochlea, hypothalamus and temporal lobes. A summary of a portion of the important studies on PBT in children is compiled in Table 1.

While PBT appears to be dosimetrically superior to external beam photon radiotherapy techniques in certain anatomical regions, particularly with respect to normal tissue doses, the sparing of normal tissues may not reach the threshold of clinically relevant measurability, especially in the era of modern imaging, targeting, and IMRT. More time and experience with PBT is needed in the pediatric population to answer these questions. However, given the improvements in dose distribution and the well-established negative effects of dose in normal tissues in children, a randomized trial may not be practically or ethically feasible. The National Institutes of Health (NIH) has encouraged randomized trials comparing PBT and photons in the pediatric populations because of the likelihood of improved late toxicity profiles (Tom DeLaney, Director of Northeast Proton Center MGH, personal communication, 2007).

Second malignancies are a major source of morbidity and mortality in pediatric cancer survivors. IMRT affords great conformality to the target volume at high doses, but due to the increased volume of tissue receiving lower doses, IMRT may nearly double the risk of second malignancy compared with 3D conformal techniques [207]. The second malignancy rates in children from incidental normal tissue dose are on the order of 2-10% by 15-20 years after radiotherapy [208-210]. Mirabell *et al.* [23] demonstrates expected second malignancy risks in a mathematical modeling study comparing proton and photon techniques and found the expected risks for second

malignancy using PBT to be significantly less by a factor of 2 to 15 depending on the case and the photon technique. An early report from MGH [211] described a cohort of 1450 adult patients (median age of 56 years) treated with protons 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. Further study and follow-up will determine the strength and importance of these results.

Hall *et al.* [20] proposed that neutron scatter from currently treating clinical proton facilities may obviate the benefit of PBT in the pediatric population. However, this proposal only considers the scatter dose outside of the field paths for IMRT, 3D conformal photons, and PBT. It does not take into account the entrance and exit dose to normal tissues that may increase the second malignancy risk in these tissues. Such an omission leaves out the largest source of risk for second malignancies. Furthermore, data used in the study to generate the scatter neutron dose with PBT were experimental data that overestimated neutron production and are two orders of magnitude higher than what is actually produced clinically [212]. Therefore, the probability remains likely that PBT will reduce the risk of second malignancies in the pediatric population compared with external photon beam techniques, even when considering neutron scatter inherent in the passive scattering techniques currently employed by most proton centers.

Proton scanning techniques could possibly lead to a further reduction in second malignancies because of the following factors: greater conformality (proximal and distal tumor shaping to the target); less neutron scatter; and, in many cases, fewer beams

needed to achieve conformality [213, 214]. Such a scanning technique is currently employed at only one institution—Paul Scherrer Institute—and is under development at other proton centers.

The costs of proton radiotherapy are higher than photon techniques [215]. One cost-benefit study from Sweden, however, found proton radiotherapy to be a cost-effective treatment for a 5 year old medulloblastoma patient when the reduction of late effects and the costs associated with managing those effects were considered [216]. Further studies in this area will be needed.

In at least one pediatric study, a reduction in radiation dose to normal tissue has been shown to reduce the late effects of treatment compared to historical controls [200]. A reduction in late effects could be possible for many solid tumors of childhood based on improvements seen in dosimetric studies and what is known about the toxicity of proton radiotherapy on developing tissues.

Summary

The pediatric solid tumor population potentially has the most to gain from more widespread use of PBT because of the potentially devastating side effects of impaired growth and function, the increased risk of second malignancies, and the high likelihood of cure. The greatest burden of late effects from treatment in the pediatric population are from radiotherapy [177, 178], and protons are a viable modality with potential to decrease these late effects.

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 determine how widespread protons become for pediatric CNS tumors. There does not appear to be sufficient evidence at this time to recommend non-CNS pediatric malignancies for treatment with protons.

Table 1. A Summary of Clinical Studies of Protons in Pediatric Patients

Publication	Disease Site	Number of Patients	Type of work (Prospective, retrospective)	Benefit for Disease Control with Protons	Decrease in Late Effects?
Merchant TE *et al.* 08' [217]	Pediatric Brain Tumors		Planning Study		Decreased dose to the hypothalamus and cochlea with all sites in apparently clinically significant manner
Yuh GE *et al.* 04' [218]	Craniospinal for medulloblastoma	3	Retrospective		Excellent sparing of bowel, esophagus,heart and bone marrow (no change in WBC as a result of treatment
St. Clair WH *et al.* 04' [219]	Craniospinaland Posterior fossa for medulloblastoma		Planning Study		Substantial sparing of cochlea, hypothalamus in brain with protons over IMRT. Also sparing of esophagus, lung, heart and kidney on CSI.
Hug EB *et al.* 02' [220]	Base of Skull Tumors (sarcomas)	20	Clinical Retrospective	60% (6/10) chordomas; 4/4 LC rhabdomyosarcomas; 3/3 chondrosarcomas; 2/3 other sarcomas	Late effects limited to 7%

CONCLUSION

In our report as of October 2009, we feel that there is reason to be optimistic about the potential developments in proton therapy 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, there is evidence of 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 occular melanomas and chordomas, we believe that there is evidence for a benefit of PBT over photon approaches. In all fields, however, further clinical research is need and should be encouraged.

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