INVITED PAPER

A REVIEW OF PROTON RADIATION THERAPY AND THE PATH TO WIDESPREAD CLINICAL ADOPTION

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Abstract— **After many years of development, proton therapy is finally reaching the point of mass adoption in clinical practice. Advances in particle accelerator technology and improved dose delivery techniques have provided strong driving forces for expanded use. Pencil beam scanning (PBS) is the generic name for radiation dose delivery to a target volume using individually controlled small pencil beams of accelerated protons. The first proton beam patients were treated with PBS at the PSI facility in Switzerland in 1996, but it took many years for PBS to become available at more facilities. Today, PBS is in routine clinical use in the majority of proton therapy facilities. PBS has truly revolutionized proton therapy, offering increased flexibility in dose shaping and improved dose conformality. Large and non-contiguous targets benefit especially from pencil beam scanning proton therapy, and general utilization has now expanded to almost all sites in the body. The traditional limitations related to range uncertainty have been further reduced with PBS through robust optimization. Treatment plans are now calculated with advanced optimization strategies and dose algorithms, which account for perceived uncertainties. PBS treatment plan deliveries are now robust against changes and uncertainties throughout the entire treatment process. We can now talk about the certainties of PBS proton therapy rather than traditional uncertainties. This certainty provides physicians with vastly improved confidence in the dose delivered to the target. Pencil beam scanning is enabling another paradigm shift, i.e. that we now face the question of which targets will not benefit from proton therapy, rather than the inverse.**

Keywords- **Proton, Radiation Therapy, Pencil Beam Scanning, IMRT, Multi Field Optimization.**

I. INTRODUCTION

After many years of development, proton therapy is finally reaching the point of mass adoption in clinical practice worldwide. This is mainly due to two contributing factors: advances in accelerating technology and advances in delivery techniques. First, technological developments have made proton therapy systems commercially available and allowed these systems to become more compact and less expensive. Second, the clinical realization of pencil beam scanning (PBS) has allowed proton therapy to be more in-line with modern day state-of-the-art intensity modulated x-ray radiation therapy (IMRT) treatments. PBS is the generic name for delivering radiation dose to a target using individually controlled pencil beams of accelerated protons to cover a target in 3 dimensions. The first proton patients were treated with PBS at the Paul Scherrer Institute in Switzerland in 1996, but it took the industry many years to commercialize the system and make it available at more facilities. Today, PBS is in routine clinical use in a majority of proton therapy facilities across the globe. The increased flexibility in dose shaping has enabled improved dose conformation, especially to large and non-contiguous targets, and truly revolutionized proton therapy in the last few years. The general utilization of proton therapy has been expanded to almost all sites in the body, and with robust optimization, which is a practical solution only with PBS, the traditional problems with range uncertainties have been addressed to a greater extent. Using intelligent optimization strategies and computer algorithms, treatment plans are now optimized with the perceived uncertainties in mind, rendering the delivered plans robust against changes and uncertainties in the entire treatment process. We can now talk about the certainties, rather than uncertainties, in PBS proton beam delivery, which provides physicians with vastly improved confidence in the delivered target dose. The largest paradigm shift caused by PBS is that we now are faced with the question of which targets, from a treatment planning perspective, will not benefit from proton therapy, rather than the traditional inverse question.

This review will walk the reader through a brief history of technological developments in radiation therapy, since the first patients were treated with radiation. We will also discuss the latest developments in the clinical utilization of protons and the projected impact

these developments will have on future patients treated with protons.

II. RADIATION THERAPY

In order to understand proton therapy and the way protons are used in clinical practice, a brief summary of external beam radiation therapy, also referred to as tele-radiation therapy, is required. The goal of radiation therapy, since the beginning, was always to increase the therapeutic ratio, which is defined as the ratio between tumor control and normal tissue complications. This means that if we increase tumor control while reducing treatment related complications, we increase the therapeutic ratio. The primary means of reducing complications is to reduce the dose outside the target volume. This is why external beam radiation therapy technology improvements, reviewed in the next section, always aimed at getting a higher dose at depth. The x-ray or gamma beam fluence is attenuated exponentially with depth, which means that the dose delivered by such beams will decrease exponentially with depth. By intersecting several x-ray beams through the target volume, the target will be struck by the radiation beam several times while the healthy tissues are traversed less than the target volume. This results in a higher dose in the target volume relative to the healthy tissues. Protons are used in a similar fashion, except that with proton beams, the radiation stops at the distal end of the target area, so for a specific beam, no dose is delivered beyond the target. In addition, when proton beams of decreasing energy are stacked on top of each other, the primary pristine Bragg peaks are spread out in the beam direction, forming the Spread Out Bragg Peak (SOBP), which has a higher dose at depth than at the entrance, illustrated in figure 1.

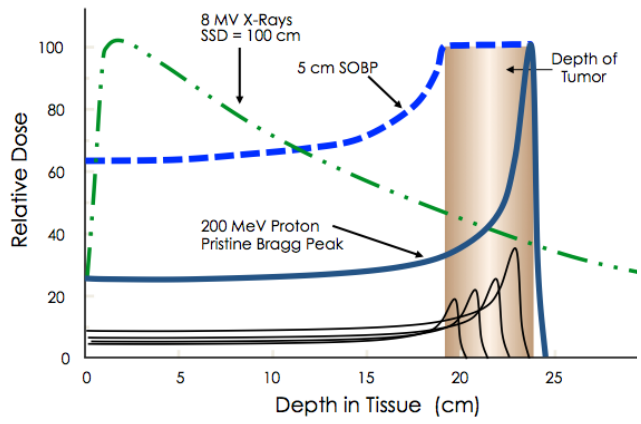

Figure 1. Depth dose curves for an 8 MV x-ray beam (Dash-dot-dot line) and a 200 MeV proton beam (solid lines). The thinner solid lines show Bragg peaks for proximal energy layers stacked onto the deepest energy layer to constitute the Spread Out Bragg Peak (Dashed line) required to cover the target area (shaded).

III. HISTORY OF RADIATION THERAPY

Shortly after the radiation physics discoveries made by Roentgen, Becquerel, and Curie in the early 20th century, the medical and scientific world was quick to adapt radiation for cancer therapy. These early discoveries were low energy radiation, which resulted in high skin dose and the inability to treat deep-seated tumors. In 1913, the only x-ray tube that could penetrate beyond 1 centimeter was the 140 kV 'hot cathode' manufactured by G.E. [1]. At the time, the knowledge of penetration depth of radiation was still in its infancy, and the unit of dose was not officially defined until 1954 [1]. Due to severe skin reactions from these low energy x-rays, Roentgenologists in the 1920's were viewed with skepticism until higher energy x-ray and gamma ray therapies became available [1]. Although radium tele-therapy (gamma radiation, around 1 MeV, from radioactive radium sources) offered increased dose at greater depths, its disadvantages included the large cost of radium, excess exposure to operators, and low dose rate compared to x-ray modalities. Despite the disadvantages, many clinicians were acutely aware of the differences in side effects between low energy x-rays and higher energy tele-therapy gamma rays [1].

Before the onset of the atomic age during World War II, the search for higher energy radiation that could spare more skin and treat greater depths began with the invention of various particle accelerators. Scientists such as Van de Graaff, EO Lawrence, and Coolidge ultimately produced the machines that revolutionized radiation therapy. For example, Coolidge sold his 750 kV 'cascade tube' to various hospitals starting in 1933 [1]. In 1930, Lawrence invented the cyclotron and was awarded the Nobel Prize for his invention. This led to the discovery of the neutron by Chadwick in 1932, when he observed very penetrating radiation produced by the interaction of alpha particles with a Be target [2]. In 1937, not long after the discovery of the neutron, the first neutrons for therapeutic use were produced by bombarding a Be target with 8 MeV deuterons from the cyclotron at the Lawrence Berkeley Laboratory in California [3]. In 1939, the clinical program was transferred to the new dedicated Crocker Medical cyclotron, which could accelerate deuterons to an energy of 16 MeV [4].

Also in 1939, the first cancer patient was treated with 1 MV x-rays using a Van de Graaff generator in Boston [1]. The tubeless betatron followed ten years later, to treat patients with 20-22 MV photons. Higher energy modalities were being developed that ultimately improved skin sparing, depth dose, and dose rate. In the decades to come, cobalt and linear accelerators dominated the market worldwide for therapy units. The Lawrence Berkeley Laboratory (LBL) soon became a large producer of cobalt-60, which would be a source of 1.25 MeV gamma rays for tele-therapy and a reliable dosimetric calibration standard. Higher energy clinical linear

accelerators (LINACs), which could treat up to 8 MV by 1953, and cobalt-60 tele-therapy units proved more clinically advantageous than their kilo-voltage and tele-radium predecessors [1]. At the time of their release, all of these new developments were opposed by their predecessors and often regarded as unnecessary. The General Electric marketing team predicted that only 10 Cobalt units would be sold in the fifties and that 250 KV x-ray units would never be replaced [1].

In 1946, Bob Wilson (a graduate student of Lawrence) published a paper in which he claimed that the properties of fast proton beams made it "possible to irradiate intensely a strictly localized region within the body, with but little skin dose" [5]. In addition, he also claimed that "it will be possible to treat a volume as small as 1.0 cc anywhere in the body and to give that volume several times the dose of any of the neighboring tissue" [5]. These claims and ideas, although many years ahead of the technology in the 1940's, have proven tremendously influential to charged particle therapy.

In 1954, Berkeley treated the first cancer patient with a proton beam. Shortly after, in 1957, Uppsala University built a cyclotron that could produce 185 MeV protons and subsequently treated a patient with their cyclotron [6]. The development of proton therapy gained slow momentum during the sixties and seventies, with pioneering work done primarily at the Harvard Cyclotron laboratory in Cambridge, Massachusetts (USA) and at LBL. In July of 1972, Koehler and Preston stated that "the use of high-energy protons or other heavy charged particles makes possible substantially improved control of the geometric distribution of therapeutic radiations over that obtainable with super-voltage x-rays or electrons" [7]. In these early days, the only way to spread the small proton beam extracted from the accelerator was by means of inserting scatterers in the beam, so the beams were referred to as passively scattered. This technique is essentially three dimensional (3D) proton therapy. This includes other proton modalities, such as double scattering (DS) and uniform scanning (US) systems, which are further explained in section IV. Although passive scatter techniques decreased the integral dose, i.e. the dose outside the target, dramatically, they still suffered from inadequate dose conformality, secondary dose from neutrons, and heavy apertures and compensators that remained problematic. Pencil beam scanning (PBS), first proposed by Kanai in 1980 [8], made it into clinical practice when the first proton patients were treated with PBS at the Paul Scherer institute in Switzerland in 1996. This technique utilizes scanning magnets to steer the beam, along with changing the energy, to deliver individual "spots" of dose at depth.

During the early nineties, a new player emerged in the photon world that would change the face of radiation therapy over the next decade. Intensity Modulated Radiation Therapy (IMRT) was first delivered in 1993 using the NOMOS Peacock MIMiC system utilizing a binary multileaf collimator that could be mounted on a traditional rotating gantry [9]. This technology, termed serial tomotherapy, was adaptable to most commercial linear accelerators. It enabled a relatively easy and low cost transition from 3-dimensional conformal radiation therapy (3DCRT) to a form of intensity modulated therapy. Several treatment machines were developed specifically for IMRT deliveries, such as the helical tomotherapy system which was initially described by Mackie in 1993 [10]. Arc therapy capabilities, first proposed by Yu in 1995 [11], were added to regular IMRT LINACs, to enhance the delivery of x-rays (e.g. VMAT and Rapid Arc) to all kinds of tumors. This resulted in extremely optimized x-ray treatment plans where the high isodose lines are very conformal to the target volumes. The clinical outcomes of patients treated with these new technologies increased dramatically, mainly due to inverse planning techniques and greater conformality, which offered superior normal tissue sparing and the opportunity for dose escalation.

Similar to this x-ray therapy evolution, intensity modulated proton therapy (IMPT) using PBS offered treatment improvements over 3D proton therapy. IMPT has become a clinical reality in many more treatment centers since 2010, when the Hitachi system at MD Anderson, and the IBA system at U-Penn started treating patients with PBS. PBS offers much lower integral dose than traditional x-ray therapy and often more conformal dose distributions for a myriad of cancer types, when compared to x-rays and even 3D proton therapy. The quest for further technological developments is therefore fully supported by the cancer therapy technological advances over the past century.

IV. TECHNOLOGY DEVELOPMENTS

Recent advances in the proton therapy industry are changing the way the technology is used. New techniques in beam delivery, treatment planning, and image guidance are improving the quality of treatments for current treatment sites and opening the door for sites not previously treated with protons. As stated before, the most significant advancement in recent years has been the widespread adoption of PBS delivery techniques. Whereas early proton treatment systems relied on spreading the beam and then shaping it through the use of patient specific apertures and compensators, PBS actively controls a thin pencil beam, steering it to deliver dose in discrete "spots".

Early proton beam delivery methods used double scattering (DS) or "uniform" magnetic scanning (US) to spread the beam over a larger area than necessary and required apertures and compensators to shape the beam laterally and distally. The only beam parameters that could be adjusted were the range and modulation, or width, of the SOBP. Effectively, one could choose how

deep to deliver the beam, conform the distal end to the target with a compensator, and decide how far to pull back the high dose region. By necessity, the shape of the proximal high-dose region would mimic the shape of the distal end, since the dose could only be uniformly modulated, or pulled back. The physics thus give rise to unintended proximal high dose areas outside the target for each individual beam. This effect is mitigated through the use of multiple beams, similar to 3D photon-based techniques.

Likewise, there is no freedom to adjust the width of the beam at different depths since the aperture, which cannot change for a given beam, provides all lateral shaping. These previous delivery techniques did benefit from the physics of protons, which include reduced entrance dose and no exit dose, but were severely limited by lack of freedom in shaping the dose distribution within the patient. Figure 2 illustrates the beam design for traditional proton therapy.

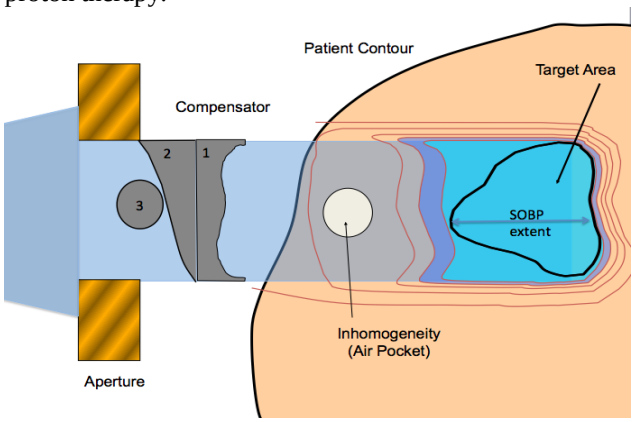

Figure 2. An illustration of traditional proton therapy using DS or US, where the beam is shaped with an aperture and the distal dose is conformed to the target with a compensator that corrects for the distal shape of the target (1), the oblique incidence of the beam (2) and inhomogeneities (3) in the beam path.

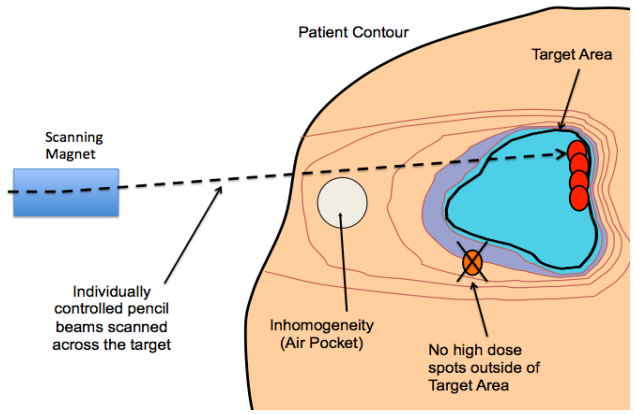

Figure 3. An illustration of the PBS technique. PBS is uses individually controlled small pencil beams of accelerated protons to cover a target in 3 dimensions. The individual pencil beams are scanned off-axis with a fast scanning electro magnet. The beam is stationary at a spot until the desired dose for each spot is delivered.

The advent of pencil beam scanning delivery techniques has overcome these disadvantages. In PBS, the beam is actively steered to deliver dose in discrete "spots" at given depths and lateral offsets. This is illustrated in figure 3.

PBS therefore gives the treatment planner full control over how and where dose is deposited from each beam. Choosing the spot locations allows for changing the beam width with each energy layer. Using this technique, the high dose can conform to both the distal and proximal ends of the target or create a concave shape on the lateral edge of the beam. Compared to 3D proton therapy, PBS allows for improved proximal sparing and does not require apertures and compensators. The only side effect that PBS cannot avoid is that each spot must still deposit its entrance dose. An advantageous clinical application of the proximal sparing of PBS is in the treatment of breast cancer discussed in section VI. A simple single beam comparison between a DS/US and a PBS beam for a target in the brain is shown in figure 4.

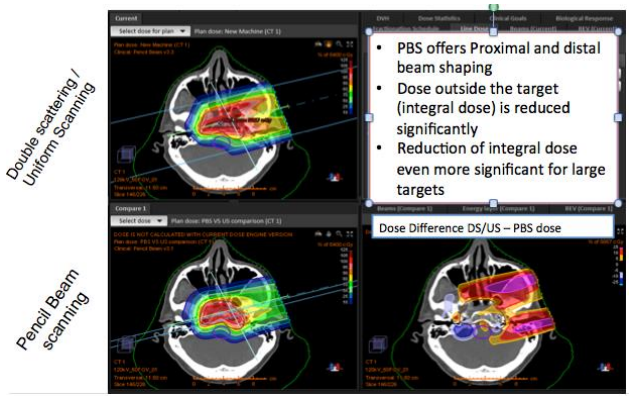

Figure 4. The difference in dose between a single proton beam delivered with DS/US and with PBS. The bottom right panel shows the unnecessary dose delivered outside the target area with US/DS.

The freedom and flexibility provided by PBS opens the door to other advanced planning techniques. In earlier delivery methods, each beam could only deliver a nominally uniform dose, with unintended hot and cold spots resulting from scattering in the patient's anatomy or compensator. With PBS, it is possible, and often sufficient, to mimic this technique, with each field giving a uniform dose to the target; however, this is no longer a requirement. If desired, each beam can be optimized to deliver dose to the target, based on that particular beam's eye view. For example, if a clinical target volume (CTV) wraps around an organ-at-risk (OAR), a right lateral beam may deliver more dose to the near (right hand) side of the CTV, and less dose to the far side, which would require passing through the OAR. The severity of this biasing can be adjusted to any degree the planner prefers.

In addition to new beam delivery technologies, proton treatment planning techniques are progressing. Monte Carlo based dose calculation will soon become

mainstream, allowing more accurate dose calculations for difficult geometries and providing additional information to the treatment planner. Pencil beam dose calculation algorithms for protons have always struggled to model upstream scatter, such as through a thick compensator. With PBS, the problem becomes the range shifter. For most proton therapy systems, there exists a lower energy limit – typically 75 MeV, or approximately 4 cm range in water. Outputting energies lower than this limit would require too much degrader material in the beam path, which would reduce the dose rate and increase the spot size. To mitigate this issue, a range shifter is utilized, as needed. A range shifter is a piece of acrylic placed in the beam, near the patient, that can further degrade the beam to energies low enough for shallow targets, such as breast treatments. The range shifter is positioned outside of the vacuum in the delivery system, so the protons will scatter in air. The air gap is defined as the distance between the range shifter and the patient, and a shorter air gap will scatter the beam less. For large air gaps with a thick range shifter, the algorithm may overestimate the shallow dose. Monte Carlo calculation will greatly improve the accuracy of the dose calculation with upstream scatterers, as well as in the presence of heterogeneities such as air pockets, lung, and metal implants.

One widespread unknown in proton therapy is the relative biological effectiveness (RBE) of protons relative to photons. It has become standard to use a factor of 1.1 [12], so that everyone will be "equally wrong". However, we know that RBE is tied to the Linear Energy Transfer (LET) of the protons at any point in their slowing down process, and the LET varies with energy. It is this variation of LET with energy that actually produces the Bragg peak. With Monte Carlo dose calculations, we can view LET-weighted dose distributions to evaluate what areas might be at risk of elevated biological doses, and hopefully minimize this effect, or at least ensure that it does not occur in sensitive critical structures. Once LET-to-RBE relationships are better established, biologically optimized plans should become possible.

Despite the advanced nature of proton therapy, it has historically trailed the photon world in the development of imaging and patient setup techniques. Respiratory gating is a good example of a technique that is common in photon therapy, but has not yet found widespread use in proton clinics. Cone-beam Computed Tomography (CBCT) is another such technology, but it is now commercially available on all new proton systems and may soon be retrofitted in existing proton treatment rooms. Multiple vendors are now offering CBCT as either an option, or the main imaging modality in the upcoming iterations of their treatment systems. The current industry standard imaging method, 2D orthogonal x-ray images, is largely limited to setup based on bony anatomy and fiducial markers. CBCT is a desirable option, since it can provide improved localization based on the patient surface or soft tissue. Improved confidence in target localization and patient setup may allow target volume margins to be reduced, enabling improved sparing of organs-at-risk.

Another interesting application of periodic CBCT images is the ability to calculate the treatment plan dose on the patient's anatomy in a verified treatment position. Quality assurance CT scans are commonly performed in proton therapy, but currently they require moving the patient to the axial CT scanner and performing a separate setup in the treatment position, without the benefit of image guidance. If the dose could be calculated on the CBCT image acquired in the treatment room, it would increase confidence in the results, as well as avoid additional imaging dose to the patient [13]. The information gained from treatment room CBCT imaging is a valuable tool for physicians in deciding if and when adaptive planning might be required. A further refinement of the process would be real time adaptive planning. This would use deformable registrations and fast treatment planning optimizations to adjust the plan each day for optimal coverage and OAR sparing. At present, however, clinical implementation of this idea in proton therapy is likely years in the future.

In addition to its role in patient setup, imaging technologies may also be applied to verification of delivered dose distribution in the patient. When protons interact with the nuclei of organic molecules in the patient's body, they undergo nuclear interactions and create positron-emitting nuclides, including C-11 and O-15 [14]. If a positron emission tomography (PET) scan is performed on a patient immediately after proton treatment, a PET signal can be seen in the tissue traversed by the proton beam. Converting the PET signal to a meaningful dose estimate is challenging, but useful information can be derived in terms of the beam trajectory and where the beam stopped. Research is ongoing, but this technique already presents an interesting opportunity for in-vivo quality assurance of proton beams.

Another technique that is in the process of being implemented in proton therapy is the detection of prompt gamma rays. Instantaneous discrete energy gamma rays are emitted during proton nuclear interactions with the nuclei in the patient body. Prompt gamma imaging was first mentioned for proton range verification in the medical setting by Jongen and Stichelbaut [15].

Proton radiography is another promising development in proton therapy. X-ray imaging utilizes attenuation information of photons passing through tissue to obtain an x-ray image. A multitude of such x-ray images at known angles with respect to each other is used to reconstruct a 3D CT image. In a similar manner, a series of proton radiographs can be used to reconstruct a proton-computed tomograph (PCT) [16]. The PCT will depict the relative stopping powers of each voxel, and hence of the different tissue types, in the patient's body. An accurate map of the proton stopping powers in the patient's body

is what is missing today to calculate the proton range in the accurately [17].

V. ADVANCES AND EFFICIENCIES IN PBS TREATMENT PLANNING

Traditional treatment planning in proton therapy requires the use of apertures and compensators. Apertures are typically made of brass and are used to limit the field size for each beam. Compensators are made of Lucite or wax and provide distal range conformation for each beam. This range conformation accounts for tissue compensation, as well as distal organ-at-risk (OAR) sparing.

Treatment planning using apertures and compensators is very similar to 3D conventional photon planning. A target is contoured on several slices in the CT scan and beams are chosen to reduce uncertainties and spare normal tissues. Typically, 1-3 beams are sufficient for most proton targets, regardless of the proton modality. Beam angle uncertainties can include immobilization device uncertainty, patient inhomogeneity uncertainty, and target motion uncertainty. These uncertainties must be considered, even in more modern PBS treatment planning. For each beam in a DS or US plan, an aperture is developed by adding a lateral margin around the target. If aggressive sparing is required from a certain beam angle, the aperture can exclude a portion of the target. Margins must also be added proximally and distally to the target, essentially widening the SOBP. This accounts for uncertainties both in the HU-to-stopping-power conversion as well as uncertainties in the compensator design [18, 19]. A beam specific compensator is developed to account for tissue compensation in order to conform the dose to the distal end of the target and for distal OAR sparing. Robust evaluation of a plan is performed, determining if coverage is sufficient if the patient shifts or if the HU-to-stopping-power conversion is slightly off. This includes shifting the isocenter in 6 directions and evaluating a denser and less dense CT. This concept of robust evaluation technically obviates the need for a Planning Target Volume (PTV). In photon therapy, a PTV is typically a uniform margin around the Clinical Target Volume (CTV), to account for patient set up variations. In proton therapy, a beam specific PTV, which includes lateral, distal, and proximal margins, is required. However since each beam will be treated with different energies, the distal and proximal margins will vary per beam, hence a beam specific PTV. The catch 22 situation is that you don't know the beam angles until you do the plan but you need the PTV before you start the plan. This problem is now mitigated with PBS robust optimization, as we will discuss later.

After the plan is approved, the design for each aperture and compensator can be manufactured on or off site. Quality Assurance (QA) should then be performed on each aperture and compensator, prior to treatment. For each patient, there is typically one aperture and compensator pair per beam. If a cone down or an adaptive plan is necessary, new apertures and compensators may need to be designed and manufactured.

With the development of PBS, the need for apertures and compensators practically vanished. PBS offers the ability to place spots precisely within the target for each energy layer, negating the need for an aperture to define the field size (see figure 3 above). Additionally, since each layer can be optimized, there is no need for a compensator. This leads to a very different type of treatment planning for proton therapy that is very similar to IMRT treatment planning i.e. an inverse optimization technique, referred to as inverse planning. The treatment planner instructs the optimizer what targets to treat and what OARs to spare, and the optimizer will choose the number of layers and location and intensity of each spot per layer. What has remained very similar to 3D proton planning is the need for stable and well-characterized immobilization and the need for well thought out beam angles.

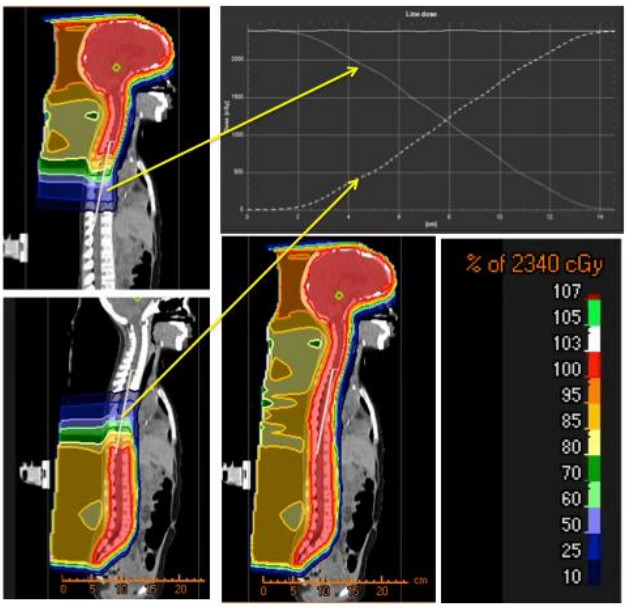

Figure 5. An illustration of the spine junction between two PBS fields for a CSI treatment. The dose gradients for the upper and lower fields, shown in the upper right panel, are tailored to about 1 % per mm, which makes the dose in the junction very insensitive to setup errors.

One of the most advantageous and publicized treatment sites for proton therapy is Cranial Spinal Irradiation (CSI), particularly in pediatrics [20, 21]. One of the challenges of a CSI treatment is accounting for the necessary match line within the treatment field. CSI treatments require match lines due to the large field sizes when treating the brain and entire spine. Another treatment site requiring match lines is head and neck treatments, due to the need for ideal beam angles to avoid

uncertainties and healthy tissues. In 3D proton planning, as in 3D photon planning, match lines require the use of feathering. With the sharp beam edge defined by an aperture, a very precise gap must be left between the beams, causing a significant cold or hot spots in the junction if the gap is not reproduced accurately during treatment. The usual mitigation for this effect is to shift the beam junction, a tedious process requiring at least a second set of fields (and apertures). A further downside is that this tactic leads to extreme sensitivity in the shifting of the patient from one isocenter to the next. Shifting too far could greatly increase the cold spot in the junction, and shifting too little could create a severe hotspot. With the use of PBS treatment planning, a gradient can be developed between abutting fields that can step up and down the dose for each field [22] over a larger distance. This gradient can be made shallow, such as 1% per mm, which will negate the need for a feathering technique and create a more robust treatment, as shown in figure 5. In this treatment, if the patient set-up on a single fraction caused abutting beams to be as much as1 cm closer together than planned, there would be only a 10% hotspot at a point.

In 3D proton planning, weighting can be adjusted between beams; each beam typically treats the entire target. There are more advanced planning techniques, such as Match-Patch and others, which are described well in various texts [23, 6]. This same 3D methodology can be applied in PBS, known as single field optimization (SFO). This means that each beam is optimized as if it were a single field treatment i.e. each beam covers the target with a uniform dose. Another method is multiple field optimization (MFO), which is similar to IMRT in that each beam in the treatment relies on every other beam, i.e. only the sum of all beams will result in uniform target coverage. MFO allows the treatment to better spare OARs, because each field does not have to treat the entire target. Robust planning, explained below, in combination with MFO, can reduce the target dose cloud and improve OAR sparing. One of the most dramatic improvements over 3D proton planning and photon planning is head and neck treatment. MFO PBS can significantly reduce posterior neck and oral cavity low dose irradiation, improve parotid sparing, and maintain robust target coverage, particularly in the match line region in the neck [24].

With some treatment planning systems, we now have the option to plan PBS treatments robustly referred to as robust optimization. This means that the optimizer will evaluate, for each iteration, the effect of an isocenter shift and/or a change in stopping power. The user can designate what robust situations should be considered in the optimization. Ideally, each spot will be positioned to provide the most robust treatment plan. Before robust planning, the method to create a robust plan typically meant treating to a larger target volume (by creating beam specific PTVs), to allow the coverage to drop during a robust evaluation, but still meet the physician's requirements. By optimizing robustly, we can ideally reduce the excess dose cloud on the nominal plan while maintaining robust coverage [25].

As PBS becomes more readily available, it is crucial to ensure the treatment planning process is as efficient as possible. Robust treatment planning improves the robust evaluation process by ensuring that the plan is more likely to pass on all perturbations. Robust treatment planning does not guarantee a robust plan, but if planned properly, can improve plan quality. In proton planning, fewer beams are desirable and it is important that the patient set up and immobilization devices allow for ideal beam angles.

Because protons are more sensitive to changes in patient anatomy and set up, adaptive plans are becoming more and more prevalent in proton therapy. Without the need for apertures and compensators, PBS treatment planning offers the flexibility to create and implement adaptive plans more efficiently. With some treatment planning systems, plans can easily be visualized on a new patient CT to identify the change in dose distribution. Contours can be deformed on to the new CT and an adaptive plan can either be made from scratch or using a template from the original plan. Adaptive plans are conveniently fitted into the workflow for physics and dosimetry, without stressing the system.

Scripting can also provide a measure of efficiency and is offered by many treatment planning software. Treatment sites, such as prostate, are commonly treated with the same opposed lateral beam set up to very similar targets. Treatment planners can initiate a script to create a plan with pre-loaded beams and optimization parameters, significantly reducing time spent on relatively simple plans. This allows the planner to invest more time in high-complexity plans, such as head and neck treatment plans.

Through the progression of treatment planning, from 3D photons to IMRT to 3D protons to PBS, lessons have been learned and passed along the path. For example, the same treatment planning techniques used in IMRT are currently utilized in PBS, and the same patient setup and beam angle considerations used in 3D proton planning are used in PBS today. These insights have led to creating robust PBS treatment plans with stable target coverage and improved OAR sparing, compared to previous methodologies.

VI. CLINICAL ASPECTS

Prior to the clinical realization of pencil beam scanning, the dose from an individual proton beam was conformed to the target by means of apertures and compensators. This limited the utilization of proton breams to small, contiguous targets. Large and non-contiguous targets have been treated in the past, but with

great difficulty and great expense, since manufacturing these large apertures and compensators was expensive and time consuming. Also, by nature of the fixed extent of the SOBP for a specific beam, the high dose volume often extended outside the target area, which in turn increased the integral dose significantly (see figure 2). With PBS, this problem is mitigated since it is now possible to limit the high dose region to the target volume (see figure 3), i.e. not placing spots outside the target volume, and treat large and non-contiguous targets while minimizing the dose outside the target volume. Such targets include, but are not limited to, treatment sites including lymph nodes, such as advanced breast cancers, head and neck cancers and high-risk prostate cancers.

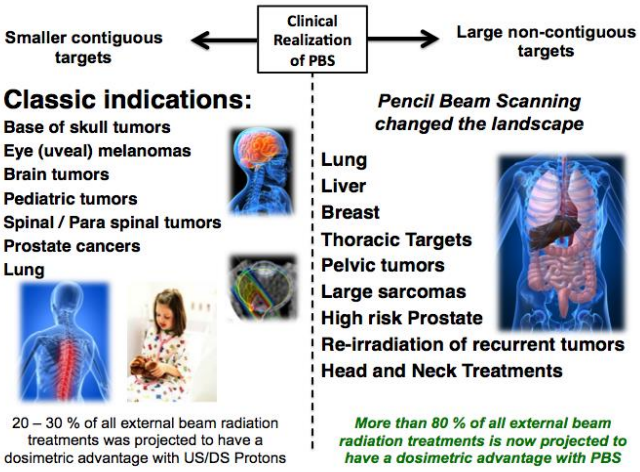

Figure 6. An illustration of the change in the clinical landscape as a result of PBS. It is projected that, with PBS, many more patients will have a dosimetric advantage because large and non-contiguous targets are now added to the list of cancers treated with proton beams.

Figure 6 illustrates the change in the therapeutic landscape with the clinical realization of PBS. On the left side of the dashed line, we list the tumors treated traditionally with 3D proton therapy (DS/US). These sites are referred to as standard indications for proton therapy and were generally accepted as the cases that would benefit most from protons. The improved clinical outcomes for most of these sites have been demonstrated through several clinical studies at legacy proton therapy centers such as LBL and Massachusetts General Hospital (MGH) [23]. On the right side of the dashed line, we list the cancers that are now treated on a daily basis employing PBS. These cases represent the vast majority of sites that are treated with external beam radiation therapy. Based on our clinical experience at the Provision Health Care where we treat patients with both IMRT and PBS, it is estimated that more than 80% of all external beam cases will have a better treatment plan (dosimetric advantage) with PBS than with the most advanced x-ray therapy techniques. The critical point is an improved treatment plan, not necessarily improved clinical outcomes since clinical outcomes depend on many other parameters. However as the history of the technology evolution revealed, it is expected that this will also translate to improved clinical outcomes or an increased therapeutic ratio. In the following sections, we will review how PBS has impacted breast, lung and thoracic, high-risk prostate, and head and neck treatments.

Breast treatments: The breast is a superficial treatment site, with the clinical target volume extending nearly to the skin. However, it is still desirable to achieve some degree of skin sparing. Photon therapy treats with inherent skin sparing due to dose build up. For 3D proton delivery methods, skin sparing is impossible due to the fact that the breast can vary greatly in thickness. With US and DS methods, the beam modulation was fixed by the largest thickness of the target in the beam direction. For the thinner areas of the breast, the beam modulation required by the thick portion would pull the high dose back to the surface of the skin, with no opportunity for skin sparing. With PBS techniques, the whole breast can be treated while keeping the skin surface to approximately 90% of the prescribed dose. The high entrance dose to the skin, when protons are delivered by US and DS techniques, has restricted the use of protons in treating the whole breast. Experience with this technology is reported in breast patients treated post-mastectomy using conventional fractionation [26,27].

Clinical evidence now supports the safety and effectiveness of hypo-fractionated x-ray whole breast radiotherapy in patients with breast cancer [28]. Advantages for hypo-fractionation include patient convenience and decreased patient and healthcare system costs. The Provision Center for Proton Therapy (PCPT) in Knoxville, TN is now using this whole-breast proton treatment technique in patients receiving hypo-fractionated whole breast radiotherapy after partial mastectomy (The so-called Canadian fractionation schema). The prescribed dose is 42.72 Gy_{RBE} in 16 fractions to the whole breast. Typically, a tumor bed boost of 10.00 Gy_{RBE} in 4 fractions follows. Skin sparing is measured as the dose to the proximal 5 mm of the breast. The ultimate goal is to keep the skin dose as close as possible to 90% of the prescription while still covering the CTV, situated just 5 mm beneath the skin surface, with a minimum of 90% of the prescribed dose. Per RTOG, the coverage goal is at least 95% of the target receiving 95% of the prescription dose. Our ongoing experience has shown that patients tolerate treatment well and are able to complete the treatment course without interruption and with minimal side effects, e.g. radio dermatitis. The bigger advantage of PBS for breast cancer treatments is perhaps in cases when the lymph nodes (axillary, internal mammary and supraclavicular nodes) need to be treated [29]. Breast treatments typically utilize one en-face beam at a ±30 degree gantry angle with the patient immobilized in the supine position and the patient's chest angled up by 10 - 15 degrees using a breast

board. A second beam is often used if the nodes cannot be covered robustly with a single beam. A typical dose distribution for an intact breast case and the associated dose volume histograms (DVH) are shown in figure 7.

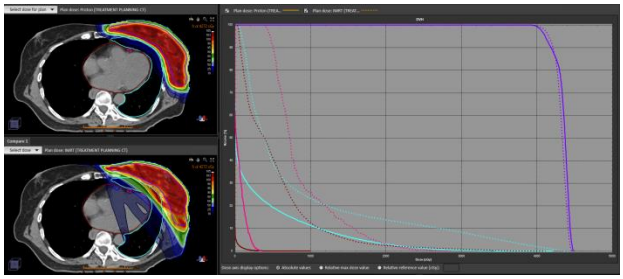

Figure 7. A typical dose distribution for an intact breast case. Top, left: Proton, single beam. Bottom, left: Photon, 7 beam. Right: Dose volume histogram (DVH) comparison, solid: proton, dashed: photon. Purple: Breast CTV, light blue: left lung, pink: LAD, red: heart.

Lung and Thoracic Treatments: The benefits of treating lung and other thoracic lesions with proton therapy are very well documented [30, 31]. These benefits are even greater for centrally located targets where the unwanted dose to the cardiac system can cause significant acute and long-term life threatening complications [32]. The safety aspects of treating moving thoracic lesions with PBS have been debated for some time. However, today it is generally accepted that the dose uncertainties from motion interplay effects between adjacent dose spots and dose layers are mitigated when more than 10 fractions are delivered to a moving target [33]. Modern day PBS beam delivery systems allow for layer repainting, which means the dose in a layer can be subdivided into several sub-layers and can be delivered sequentially before the system proceeds to deliver the next energy layer. Repainting layers between 5 and 25 times is common, which means that the equivalent number of fractions is the fraction count multiplied by the number of repaints. This means e.g. that a 10 fraction hypo-fractionated treatment delivered with 10 repaints will be equivalent to a 100 fraction treatment, from a target motion perspective. This is another huge advantage that PBS offers over IMRT, where this is simply not a practical solution.

Respiration gating for proton beam deliveries are easy, but to determine where the target is at any given moment is not so easy. The other problem with gating, specifically in a multi room proton therapy center, is that it increases the treatment time in a treatment room which adversely affects the throughput in other treatment rooms, since they are receiving the proton beam from the same accelerator. To avoid the need for gating, it is common practice to define an internal target volume (ITV) that covers the entire motion envelope of the gross tumor volume (GTV), and to treat the ITV plus a certain margin to the desired dose. Due to the reduced integral dose with PBS, the volume of lung that receives 20 Gy or less is often significantly less than even a gated photon beam delivery, despite the fact that the ITV is significantly larger than the GTV. The next generation proton therapy systems will allow for much faster inter-room beam switching and beam delivery times, which allow for a more time efficient implementation of respiration gated treatments.

High-Risk Prostate Treatments: High-risk prostate treatments regularly require that a significant portion of the pelvic nodes be treated, in addition to the prostate gland and seminal vesicles. This results in a very complex target shape with the small bowel, bladder, and rectum that must be spared. Comparisons between PBS, planned with robust optimization, and VMAT for the treatment of high-risk prostate cancer have been performed at PCPT to validate the use of PBS (MFO) for high-risk prostate treatments. This study confirmed that robustly planned PBS significantly reduced the dose to normal tissues in the pelvis while maintaining target coverage. Rectum and bladder dose reduction with PBS may improve the therapeutic response beyond the levels accomplished with VMAT [34].

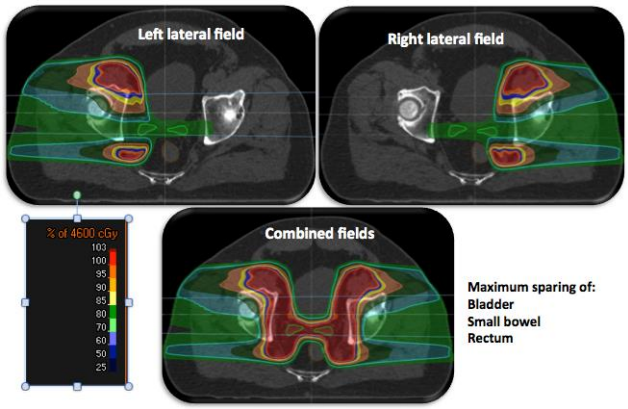

Figure 8. A typical high-risk prostate plan employing two lateral fields. Each lateral field treats the nodes on that respective side and the entire prostate gland. The sum of these two fields constitutes the complex dose map shown in the bottom panel. Red = 46 $Gy_{(RBE)}$, Light green = 36.8 $Gy_{(RBE)}$

Patients with high-risk prostate cancer are now treated on a routine basis at the PCPT facility, targeting the prostate gland, seminal vesicles, and pelvic nodes to a dose of 46 - 50 $Gy_{(RBE)}$, followed by a boost dose to the prostate gland for a cumulative dose of 78 $Gy_{(RBE)}$ using PBS. Most importantly, suspicious or positive nodes can be boosted to a higher dose simultaneously with the prostate boost to dose levels exceeding 60 – 66 Gy_{RBE}, depending on bowel proximity. This is illustrated in figure 8, which shows a treatment plan for a high-risk nodal prostate treatment.

The implementation of PBS also benefits low and intermediate risk prostate patients, but more so for cases where the prostate droops significantly over the rectum

and for patients with a hip replacement. In those cases, PBS allows for shaping the beam over the rectum, which was not possible with DS or US deliveries. The latest long-term outcome (median follow-up time of 5.5 years) data for prostate treatments published by the University of Florida revealed that the 5-year freedom from biochemical progression (FFBP) rates were 99%, 94%, and 74% in low-risk, intermediate-risk, and high-risk patients, respectively [35]. These treatments were performed with DS beam delivery techniques.

Augmenix INC. recently introduced SpaceOAR hydrogel that is inserted between the anterior rectal wall and the prostate, displacing the rectum away from the prostate [36]. The gel insertion typically creates a space, occupied by the gel, ranging between 10 and 15 mm. PBS, together with SpaceOAR, allowed for reducing the volume of rectum receiving 90% of the prostate dose to less than 1%, on average. At PCPT, we have been using SpaceOAR since April 2015 on the majority of prostate patients. This technique further reduced the already low grade 1 and grade 2 toxicities previously experienced by the patients treated without SpaceOAR gel, and has so far totally eliminated any grade 3 acute toxicities.

Head and Neck Treatments: Head and neck (H&N) cancers present one of the most complex shaped and challenging targets to the Radiation Oncologist. In most cases, the lymph nodes on at least one side of the neck, and often on both sides of the neck, need to be treated to doses higher than 60 Gy. Several dosimetric studies were conducted to evaluate the feasibility of using PBS for these cancers [37, 38, 39]. A general consensus is that in treating oropharyngel cancers, PBS reduces normal tissue exposure in particular the posterior pharynx and oral cavity without sacrificing target coverage. Treating patients for H&N cancers at many proton therapy institutions with PBS revealed that these dosimetric advantages appeared to translate into lower rates of acute treatment-related toxicity including mucositis, dysgeusia, and nausea, compared with IMRT [37, 38, 39]. Our own experience at PCPT, predominantly treating bilateral neck, is that the patients tolerate the H&N treatments generally well with acute toxicity not too dissimilar to IMRT but with more rapid and complete recovery of swallowing function, taste and saliva. Weight loss during treatment does occur and often requires adaptive plans, which are relatively easy with PBS.

VII. COST EFFECTIVE PROTON THERAPY FACILITIES

One of the main hurdles that proton therapy facilities had to overcome is cost. The cost of these facilities was often driven by the size of the equipment and the time it took to develop a facility. During recent years, several companies embarked on developing more compact systems that can be pre-assembled in a factory and installed on-site, requiring shorter installation times. Mevion, INC developed a compact single room system, where the accelerator is mounted on a rotating gantry. IBA, INC developed a dedicated single room system employing a limited angle gantry plus a dedicated cyclotron. Protom and Hitachi developed similar limited angle gantries, but they use synchrotrons to accelerate the protons. The legacy large systems that were initially developed by Varian, IBA, Sumitomo, and Mitsubishi are still commercially available and are typically purchased by the larger academic institutions. Although they are legacy by design, they are equipped with the latest technologies, e.g. CBCT and PBS.

The use of superconducting technologies entered the field of proton therapy in the early 2000's when the first superconducting isochronous cyclotron was built by ACCEL technologies (Acquired by Varian in 2005). Since then, several companies have started to develop superconducting synchrocyclotrons to reduce the size and cost of the accelerator. The most pertinent example is the MEVION synchrocyclotron, weighing less than 20 tons. Table 1 lists common commercial cyclotrons and synchrocyclotrons. The IBA C230 machine is a room temperature isochronous cyclotron and has been installed in the majority of the IBA facilities worldwide.

Table 1. Commercial cyclotrons for hadron therapy

	Mevion S250	IBA S2C2	Varian ProBeam	IBA C230
Type	SC Syn	SC Syn	SC Iso	NC Iso
Size (m)	1.8	2.5	3.1	4.3
Mass (tons)	20	<50	<90	250
Energy (MeV)	250	230	250	235
Peak B field	8.90	~6.56	<4	2.2
Power (kW)			≤115	320

SC: Superconducting, Syn: Synchrocyclotron, Iso: Isochronous

ProNova Solutions is the newest proton therapy system manufacturer and is developing a compact system employing superconducting magnets on a 360-degree rotating gantry that reduces the sizes of the gantry by almost a factor of three, compared to the legacy gantries. The ProNova system is based on beam line technologies developed at the Indiana University Cyclotron Facility [40]. This system employs separate energy modification systems for each room, making the treatment rooms independent from the main beam production system and allows for rapid (< 3 msec.) beam switching between treatment rooms.

The Provision Center for Proton Therapy (PCPT) is a state-of-the-art proton therapy facility equipped with the legacy IBA system comprising of three proton therapy rooms. PCPT also purchased the first ProNova SC360 system, which has been installed in the same building as

the IBA system. The SC360 system is going through final FDA testing and submission process, as of writing. PCPT is planning to start patient treatments using the SC360 system by the end of 2016, after the 510K clearance has been obtained from the FDA. A layout drawing of the PCPT building is shown in Figure 9. The difference in footprint between the legacy IBA system and the ProNova system is apparent in this figure.

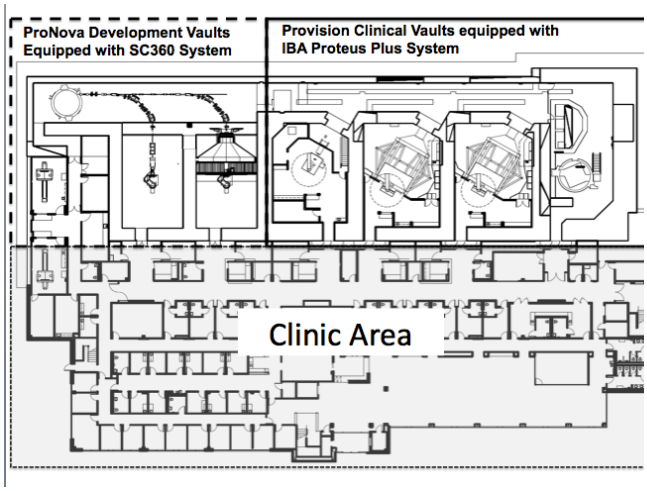

Figure 9. A layout of the first floor of the PCPT building, showing the IBA Proteus Plus system (Solid lines) and the ProNova SC360 system (Dashed line). The clinic area, containing the exam rooms and patient changing and waiting areas, are indicated with the gray shaded area.

VIII. The Future of Proton Therapy

The future of proton therapy is very promising. The immediate positive impact that PBS has had on the clinical landscape is beyond reproach. Although this was evident since the first patients were treated at the Paul Scherrer Institute (PSI) in 1996 [41], it became more evident when PBS became a clinical reality in many more treatment centers across the globe. The clinical teams at the University Medical Center in Groningen (UMCG) in the Netherlands, under the leadership of Dr. Hans Langendijk, realized the advantages that PBS can bring to their clinical program. They undertook an intensive investigation into the need for proton therapy at the UMCG, doing retrospective analyses of normal tissue complication probabilities that occurred in several cohorts of patients treated at the UMCG [42]. Figure 10 shows a bar graph (reproduced with permission from Dr. Langendijk) of the projected future utilization of a PBS based proton therapy system at UMCG, which is now under construction [42]. It is interesting to note that 75% of PBS utilization is for prevention of complications and secondary cancers. Only 20% of the cases they plan to treat will aim at improving local control, while only 5% will be for standard indications. The standard indications are more or less what proton therapy has been used for until the clinical realization of PBS. In other words, the standard indications in figure 10 represent the same indications listed on the left side of the dashed line in figure 6. This means that the potential clinical benefit of PBS is far beyond what was expected or predicted in the earlier days of proton therapy.

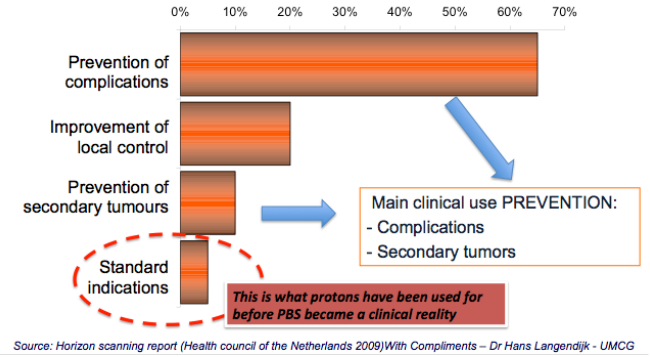

Figure 10. The projected clinical utilization of the UMCG proton therapy facility that is now under construction in Groningen, the Netherlands (Reproduced with permission from Dr. H Langendijk).

IX. Conclusions

Wilson first proposed the use of accelerated protons for radiation therapy purposes in 1946 [5] and the first patients were treated with protons in 1954 at the LBL [6]. After many years of dedicated work from many people in the field of particle radiation therapy, we finally reached a stage to declare that proton therapy is now ready for mass adoption in the clinical practice. This adoption is happening at a rapid pace. Arthur Schopenhauer (1788-1860) stated that all truth passes through three stages. First, it is ridiculed, second it is violently opposed and third it is accepted as being self-evident. It is our opinion that the clinical realization of PBS, together with many technological advances, made it possible for proton therapy to advance to the third stage of Schopenhauer's hierarchy. We will continue to see a near exponential growth in the number of proton therapy treatment vaults over the next decades. This growth in proton utilization will, in turn, allow for reducing the costs and construction times even further. The clinical realization of PBS allows for exploiting the full potential of accelerated proton beams in the pursuit of increasing the therapeutic ratio. It is the opinion of the authors that PBS will have an even more significant impact on cancer treatment outcomes than the introduction of IMRT had to-date. Bringing PBS to mass clinical adoption is a true testimony of the importance of the radiation therapy technology evolution that started with Roentgen's discovery of x-rays in 1896.

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