Intensity-Modulated Proton Beam Therapy of Prostate Cancer-History, Results, and Future Directions

Carl J. Rossi Jr.

Abstract

Proton beam radiation therapy is a form of external—beam radiation treatment which takes advantage of the superior physical properties of positively charged subatomic particles (i.e., low entrance dose and lack of exit dose) to deliver highly conformal radiation therapy with a lower integral dose (dose to normal tissue) than can be achieved with photon-based treatments. Proton beam radiation therapy first became available on an extremely limited basis in the late 1950s, and was initially used to treat prostate cancer in the late 1970s. More recently, intensity—modulated proton therapy (IMPT), in which all beam shaping and modulation is performed electromagnetically, has become available at a number of proton centers. This improvement in proton beam treatment delivery significantly expands the utility of proton therapy by allowing for treatment of complex target volumes such as the whole pelvis and by permitting the creation of highly individualized nonuniform dose distributions, including the use of simultaneous integrated boosting. This chapter will review the history of proton beam therapy of prostate cancer, beginning with the initial patient treatments at the Harvard Cyclotron Laboratory and continuing up to the present day, with particular emphasis being placed upon emerging trends in proton beam treatment technology and their potential impact on the future of proton beam therapy in prostate cancer.

Keywords

Protons · Prostate cancer · Intensity-modulated proton therapy

C.J. Rossi Jr. (✉)
Scripps Proton Therapy Center, 9730 Summers Ridge Road,
San Diego, CA 92121, USA
e-mail: Rossi.carl@scrippshealth.org

J.Y.C. Wong et al. (eds.), *Advances in Radiation Oncology*,
Cancer Treatment and Research 172, DOI 10.1007/978-3-319-53235-6_5

1 Introduction

Prostate cancer presents a major oncological dilemma for the developed world. In the United States there will be an estimated 226,000 new cases diagnosed in 2015, with approximately 27,000 deaths from this disease (Society 2015). Prostate cancer is the second leading cause of cancer deaths among American men and accounts for approximately 10% of all cancer related deaths in men. A similar incidence and death rate is seen in Western Europe, with the lowest reported incidence being in Eastern/Southern Asia. Over the past twenty-five years the discovery and use of Prostate Specific Antigen (PSA) as a screening tool has led to both an increase in the number of cases being diagnosed and a decrease in the proportion of men being diagnosed with advanced disease. This trend towards diagnosis with organ-confined disease has prompted the development and refinement of treatment methods directed at the prostate in the entirely reasonable hope of providing long-term disease free survival and cure.

From the radiotherapy standpoint virtually all technical advances in prostate cancer treatment have been implemented to reduce normal tissue toxicity by limiting the volume of adjacent bladder and especially rectum that receive moderate to high doses of radiation. A direct consequence of this improvement in dose conformality has been dose escalation, a successful treatment strategy whose favorable impact on biochemical freedom from relapse which has been tested and confirmed in one proton beam-based prospective randomized trial, and in numerous prospective non-randomized series.

The unique physical properties inherent in proton beams makes them particularly attractive to the radiation oncologist, for they permit a reduction in "integral dose" (defined as the total radiation dose given to the patient) over and above anything which can be achieved with any photon-based external beam treatment systems (Suit et al. 1977, 2003; Suit 2002).

However, proton beam therapy of prostate cancer is not without its detractors. Critics often correctly point out that a multitude of effective treatment methods exist for prostate cancer and that modern X-ray therapy employing intensity-modulated techniques (IMRT) and image-guided treatment delivery (IGRT) yield similar outcomes at less monetary cost to society, while still others question the wisdom of aggressively treating prostate cancer at all (Zietman 2007, 2008, 2016; Trofimov et al. 2007). This chapter will discuss the technical aspects of proton therapy, review the published experience to date with passive—scattered proton therapy, and discuss the impact of the ongoing clinical implementation of intensity—modulated proton therapy in the treatment of prostate cancer.

2 Technical Aspects of Proton Therapy

Protons are subatomic particles which are found within the atomic nucleus, indeed, they are the most abundant subatomic particle in the Universe. The clinical appeal of protons lies in their physical properties-in contrast to X-rays, which are massless

and changeless and are therefore only sparsely attenuated by passing through relatively low-density material such as the human body, protons are characterized by an energy deposition pattern in which the majority of their ionizing effect is found at the very distal end of the particle's path. Beyond that point, the particle comes to rest and no further ionizing radiation is deposited. As a result, an unmodulated proton beam will have an extremely low "entrance dose", a high dose spike at some energy and tissue density dependent depth, and no dose beyond that point. This is a description of the classic "Bragg Peak", discovered by physicist William Bragg in 1903, and the clinical utility of a particle with these properties is readily apparent. Indeed, the first published proposal to employ protons in radiation oncology appeared in Wilson's 1946 paper (Wilson 1946) with preliminary clinical efforts beginning in the late 1950s at the Harvard Cyclotron Laboratory, the Lawrence Berkeley Laboratory, and the Svedberg Laboratory in Sweden (Miller 1995; Olsen et al. 2007; Bonnett 1993).

The heart of all proton beam therapy centers is a particle accelerator, currently either a synchrotron or cyclotron, which is capable of accelerating protons to energies of 225–250 meV (=velocities of ~100,000 miles/second), producing a maximal range in human tissue of ~36 cm. After being extracted from the accelerator the protons are transported to the treatment room in a "beam line", a metal tube inside of which a high vacuum (akin to interplanetary space) is maintained. The beam line is surrounded by various focusing magnets which prevent the proton stream from striking the walls of the tube, while other "switching" magnets shunt the proton stream into whichever treatment room they are needed. Treatment rooms either utilize "fixed" beams, in which the treatment nozzle is fixed in position and all patient movement is by means of a robotic couch, or isocentric gantries in which the nozzle can rotate completely around the patient.

While a monoenergetic, unmodulated proton beam may be ideal for treating an extremely small tumor (such as a uveal melanoma) since the vast majority of clinical situations require radiation delivery to large, irregularly shaped targets, it is necessary to modulate the proton beam so that, the target volume can be irradiated in a homogeneous (or, as we shall see, a non-homogeneous) manner. This can be accomplished by one of two methods commonly referred to as passive-scatter proton therapy (PSPT) or intensity-modulated proton therapy (IMPT).

PSPT was the first method employed in clinical proton therapy, and it remains in widespread use to this day (Lomax 2009; Schippers and Lomax 2011). In fact, the majority of patients treated in the history of proton therapy have been irradiated with PSPT. As is illustrated below, this technique begins by taking a small (3–5 mm) proton beam and propagating this beam through a variety of physical devices whose ultimate purpose is to spread out the monoenergetic Bragg Peak so that, in effect, a uniform dose "plateau" is created which encompasses the desired target volume. Many of these devices such as the aperture and tissue compensator are patient—specific and beam—specific; for example, if a patient is to be treated with two fields there are two separate, unique sets of apertures and boluses required, each of which must be uniquely identified so as to assure that the proper aperture/bolus pair is being used in each beam.

One inevitable consequence of such a beam shaping is that while the radiation dose within the target is generally extremely uniform, it is not possible to significantly vary the radiation dose within that target if such is (as is often the case) clinically desirable. Another consequence is that the entrance and dose, or dose proximal to the target, is somewhat increased and in general is approximately 50–70% of the dose through the plateau. Of course, since there is no contribution to the entrance dose from any contralateral beam this still results in dose distributions which deliver a lower integral dose then is the case with intensity modulated X-ray therapy but, as we shall see, there exist more advanced proton therapy techniques which substantially decrease this proximal dose. A typical passive scatter treatment nozzle with associated hardware is illustrated in Fig. 1.

In contrast, intensity—modulated proton therapy obviates the need for physical beam—shaping devices. In IMPT a small (3–5 mm) beam of protons is electromagnetically scanned over the target volume, with dose being deposited in effect "layer by layer", with the typical layer thickness being on the order of 1 mm. Bragg Peak placement is achieved by dynamically varying the energy of the proton beam (Lomax 1999). Thus, treatment delivery is analogous to the operation of a 3-Dimensional printer that creates a complex, solid object by precisely depositing varying thicknesses of material. With IMPT, treatment dose can be optimized to the target itself and what is more, the delivery of differential radiation doses within the target becomes both feasible and easily achievable. In addition, since the beam manipulation is performed electromagnetically and not by patient-specific physical devices, IMPT plans can be rapidly altered (often within 24 h) to reflect changes in

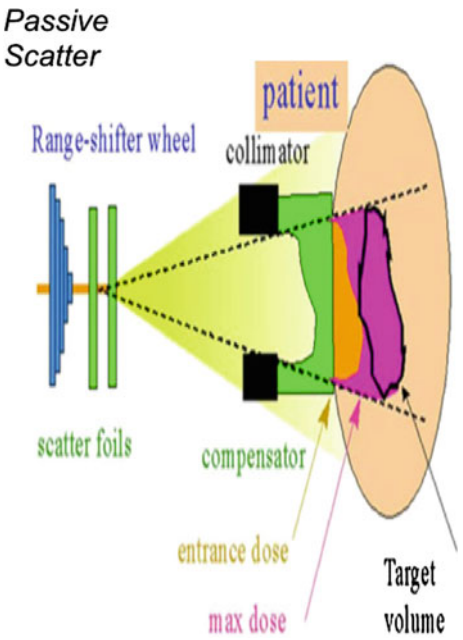

Fig. 1 A typical passive scatter treatment nozzle with associated hardware

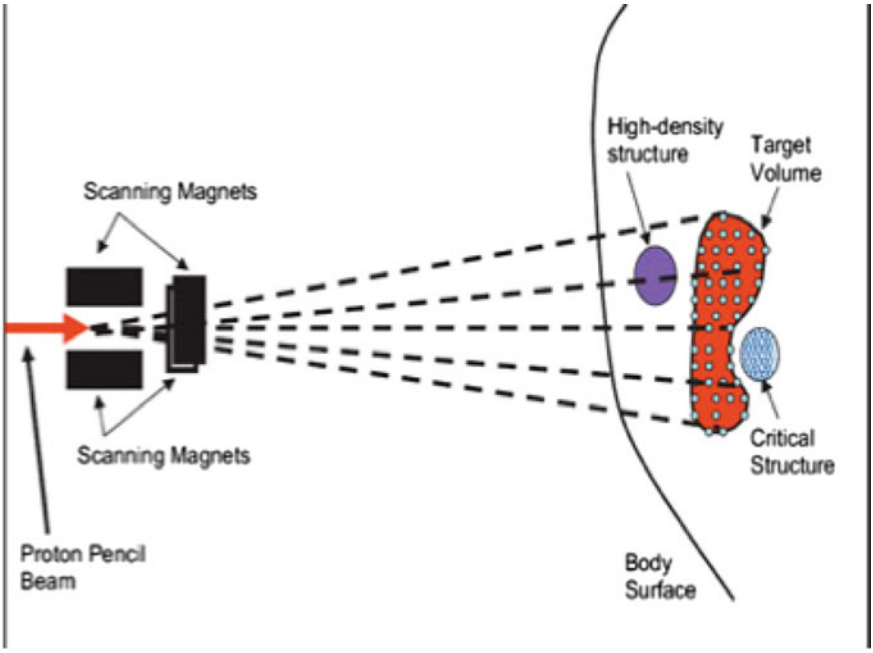

Fig. 2 A diagram of a typical IMPT treatment nozzle

patient anatomy and tumor configuration. The first IMPT treatment systems were developed in the early 2000s (Lomax et al. 2004), and this proton treatment method became available in the United States in 2008. Rapid advances in this technology have led to the construction of "IMPT-only" treatment facilities and indeed the vast majority of recently commissioned proton centers, and those under construction, are designed to employ this technology as their sole means of proton beam treatment delivery. A diagram of a typical IMPT treatment nozzle is shown in Fig. 2.

3 Treatment Planning

Whether employing PSPT or IMPT, all proton beam therapy planning, like modern X-ray therapy planning, is based upon creating a three-dimensional reconstruction of the target and adjacent normal tissues. In general, the patient positioning and immobilization techniques which are utilized in X-ray therapy are equally applicable to proton beam treatment. Similarly, the concepts of gross tumor volume (GTV) and clinical target volume (CTV) are also identical to those used in IMRT, however, the unique physical characteristics of a proton beam result in a modification of the X-ray therapy planning target volume (PTV) into either a beam—specific PTV (in the case of PSPT), or a "Scanning Target Volume" in IMPT

(Lomax et al. 2004). One of the primary differences between proton therapy and X-ray therapy dosimetry lies in the uncertainty as to exactly where a proton of any given energy will come to a stop. This "range uncertainty" is partly due to the need to convert tissue densities obtained from CT (which are quantified as Hounsfield Units) to proton stopping power; this process typically adds a range uncertainty of up to 3% to the precise location at which any given proton will come to rest (Lomax 2009). Since the protons range is also significantly affected by tissue density, it is a common planning practice to avoid to the greatest extent possible beam arrangements which traverse anatomic structures (such as small or large intestine) which vary widely in density and in anatomic location. This partly explains the reason that the vast majority of prostate cancer patients treated with protons have their treatment delivered through a left and right lateral field as this field arrangement minimizes density uncertainties within the beam path.

Another dosimetric issue which is unique to proton and other heavy charged particle beam treatment is the need to account for the Relative Biologic Effectiveness (RBE) of the proton so as to proscribe a radiation dose whose biologic equivalent is accurately linked to known doses and risks of normal tissue injury established by X-ray therapy. In general, a relative biologic effectiveness (RBE) of 1.1 is assumed for protons as compared to megavoltage X-rays and although this approximation is undoubtedly an oversimplification it has clinically proven to be an accurate value for predicting both disease response and the risk of normal tissue injury.

The clinical implementation of IMPT has, in a fashion analogous to what was seen with the implementation of IMRT, resulted in the introduction of additional complexity into the treatment planning process. For one thing, the ability to deliver differential radiation doses within any given target volume means that (again, in a fashion identical to IMRT) in effect a proton "fluence map" is created. Not only does this result in quality assurance needs which are identical to those utilized in IMRT, combining this fluence map with the confounding factors of proton range uncertainty as well as patient positional uncertainty has led to the introduction of a property known as "robustness" in IMPT planning (Lomax 1999, 2008; Lomax et al. 2004). Robustness is in effect a probability analysis which graphically displays (typically by means of dose—volume histograms) the likely range of dose distributions for any given beam arrangement and the probability that any one given treatment plan will accurately and reproducibly irradiate the target structure while simultaneously minimizing radiation dose to normal tissues. Robustness is influenced by a number of factors including the degree of patient immobilization, the depth of the target, the density of the tissues proximal to the target, and whether or not the patient is being treated with a single—field optimization (in which all proton beams "see" the entirety of the target) or a multi-field optimization (in which any one given beam may only "see" a portion of the target, with the summation of all beams resulting in the desired radiation dose to the target). Because of its favorable anatomic location IMPT prostate plans tend to be very robust although they are still sensitive to factors such as patient rotation (which may alter the density of bone between the skin surface and the prostate) and the presence of distensible organs such as the bladder or rectum within the beam path.

4 Early Proton Beam Treatment Results

The ability to use proton beam therapy to treat deep organs was and remains greatly dependent on the concurrent development of cross-sectional imaging technology (CT, MRI) and modern computers, hence it is not surprising that proton beam therapy of prostate cancer did not commence until the late 1970s. Beginning in 1977, Shipley and associates at the Massachusetts General Hospital (MGH) initiated a Phase I trial in which proton beam radiotherapy was used to deliver a boost dose to patients with locally advanced disease who were also receiving photon radiotherapy. At that time, this boost dose was felt to be over and above what could be safely given with existing 2-Dimensional photon technology. Seventeen patients with stage T2–T4 disease received a perineally-directed proton beam boost of 2000–2600 rads (given at a rate of 180–200 rads per day) which was proceeded by treatment of the prostate and pelvis to a dose of 5040 rads with 10 MV photons delivered as a four-field box. A perineal approach was mandated because this was the only anatomical pathway that allowed the 160 meV proton beam generated by the Harvard Cyclotron to reliably encompass the entire prostate gland. Acutely, the treatment was well tolerated and after a follow up period ranging from 12 to 27 months no severe late rectal reactions were noted (Shipley et al. 1979).

These favorable toxicity results led directly to the initiation of a prospective randomized trial designed to test the benefits of proton beam dose escalation in patients with locally advanced disease. Patients with stage T3–T4 tumors were chosen as it was felt that this group stood to benefit the most from dose escalation. All patients received 50.4 Gy to the prostate and pelvis with megavoltage photons. They were then randomized to receive either an additional 16.8 Gy of photons (for a total prostate dose of 67.2 Gy) or 25.2 GyE of protons for a total prostate dose of 75.6 Gy. Adjuvant hormonal therapy was not permitted. The limited availability of the Harvard Cyclotron significantly impacted patient accrual; nonetheless, two hundred and two patients were eventually enrolled, with one hundred and three being treated in the high dose proton boost arm and ninety-nine in the standard dose arm.

With a median follow up of 61 months there were no differences seen in overall survival, disease-specific survival, total relapse-free survival, or local control between the arms. Patients with high-grade tumors who were treated on the high dose arm did experience a trend improvement in local control at five and eight years (92 and 77% vs. 80 and 60%, $p = 0.89$). Patients whose digital rectal exams normalized following treatment and who underwent subsequent prostate biopsy revealed a lower positive biopsy rate in the high dose arm (28 vs. 45%) and, perhaps most surprisingly, the local control rates for patients with Gleason grade 4–5 tumors (57 patients total) were significantly better at five and eight years in the high dose patients (94 and 84% vs. 68 and 19%, $p = 0.0014$). High dose treatment was associated with an increase in late grade 1–2 rectal bleeding (32 vs. 12%, $p = 0.02$) (Shipley et al. 1995).

Some critics have repeatedly and in my opinion incorrectly cited these results as evidence that proton-beam dose escalation is of doubtful utility. It should be noted that the patients treated in this trial were at a high risk of not only local failure but also of distant failure and therefore one should not be surprised that overall survival was unaffected. In addition, patients with these adverse characteristics would not, if undergoing treatment today, receive radiotherapy as monotherapy and instead would be treated with a multi-modality approach. I believe that the two most important points learned from this study are (1) high dose radiotherapy did decrease local failure, and this decrease was most profound in those patients with the most aggressive tumors and (2) Dose-escalation by means of a perineal proton beam (an approach which has virtually universally been abandoned today as higher energy machines become available) could be performed safely with acceptable toxicity.

The improvement in local control seen with dose escalation prompted a very logical question: If patients with earlier stage disease who are less likely to have already experienced metastatic failure are treated with dose escalation will we see a positive effect on survival? This intriguing hypothesis has been tested in a prospective randomized multi-institution trial and its conclusions will be covered presently.

The completion in 1990 of the world's first hospital-based proton treatment center at Loma Linda University Medical Center (LLUMC) marked the beginning of a transition in proton beam therapy from the research laboratory setting to that of clinical radiation oncology (Slater et al. 1988, 1992). Beginning in late 1991 prostate patients at LLUMC was treated on a clinical trial that set out to confirm the efficacy and toxicity data generated at MGH. Between December 1991 and December 1995 643 patients were treated to total prostate radiation doses of 74–75 GyE. Patients who were deemed to be at a low risk for occult nodal metastasis were treated with lateral proton beams alone while those who were felt to benefit from elective nodal radiation received 45 Gy to the pelvis with 18–23 MV photons delivered via a multi-field 3-D conformal technique. Patient characteristics are shown in Table 1 (Slater et al. 1998).

Table 1 LLUMC Patient Characteristics

		# Patients
Stage	1A/1B	28
	1C	91
	2A	157
	2B	173
	2C	157
	3	37
Gleason	2–5	232
	6–7	324
	8–10	54
Initial PSA	≤ 4.0	53
	4.1–10.0	280
	10.0–20.0	175
	> 20.0	85

With a median follow up of 43 months, the overall biochemical disease-free survival (bNED) rate was 79% as per the original American Society for Therapeutic Radiology and Oncology (ASTRO) definition of three successively rising PSA values above a nadir equating to biochemical failure. The risk of biochemical failure was strongly dependent on the pre-treatment PSA with five-year bNED survival rates varying from 53% in patients with pre-treatment PSA's of 20–50 to 100% with PSA's of <4.1 (Fig. 3). bNED survival was also significantly influenced by post-treatment PSA nadir (Fig. 4). A multi-variant analysis of failure predictors

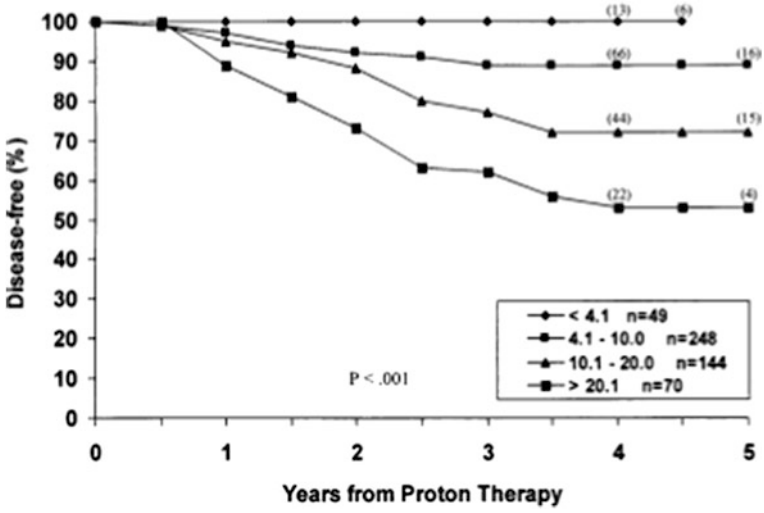

Fig. 3 bNED survival in relation to pre-treatment PSA

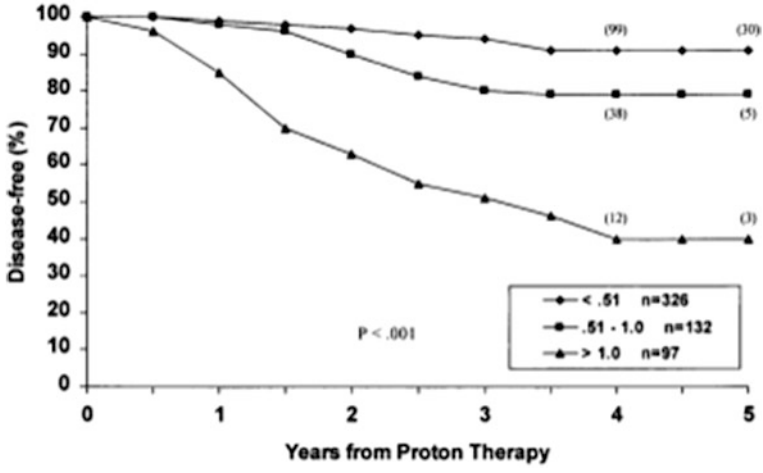

Fig. 4 bNED survival in relation to post-treatment PSA nadir

Table 2 Predictors of local/distant failure, initial LLUMC experience

		Local failure (%) 5 year	*p*	Distant metastasis (%) 5 year	*p*
Initial PSA	≤ 4.0	0		0	
	4.1–10.0	3	0.06	4	< 0.001
	10.0–20.0	4		12	
	> 20.0	16		17	
Gleason	2–5	2		6	
	6–7	6	0.01	6	0.11
	8–10	19		24	
T stage	1A/1B	4		0	
	1C	0		0	
	2A	2	0.009	5	< 0.001
	2B	5		7	
	2C	11		15	
	3	20		27	

demonstrated that initial stage, PSA, and Gleason Score were all strong predictors of biochemical failure at five years (Table 2). Similar to what was reported in the MGH trial, treatment was by and large well tolerated. Acute toxicity was minimal and all patients completed the prescribed course of radiotherapy. Proctitis remained the most common late toxicity with Grade 2 toxicity occurring in 21% of patients at three years; for the majority of patients this represented a single episode of rectal bleeding. No ≥ Grade 3 GI toxicity was seen. Grade 2 GU toxicity (primarily gross hematuria) was seen in 5.4% of patients at three years, with two patients developing Grade 3 bladder toxicity. Interestingly, no significant difference in late toxicity was seen between those patients treated with protons alone and those receiving pelvic X-ray therapy. The excellent biochemical control rates and acceptable toxicity seen in this trial confirmed the earlier MGH data and led to the implementation of a prospective randomized dose escalation study in organ confined prostate cancer.

A further update of the initial LLUMC experience was published in 2004. This study encompassed 1255 patients with stage T1–T3 disease who were treated with proton beam radiotherapy alone (i.e., no prior or concurrent hormonal therapy) to a dose of 74–75 GyE. As was seen in the earlier trial initial PSA, Gleason Grade, and PSA nadir were all strong predictors of bNED survival (Fig. 5a–c). Treatment continued to be well tolerated with rates of RTOG Grade ≥ 3 GI/GU late morbidity of <1% (Slater et al. 2004).

5 PROG 95-09 Trial

Beginning in 1996, LLUMC and MGH embarked on the Proton Radiation Oncology Group/American College of Radiology (PROG/ACR) 95-09 trial, a prospective, randomized dose-escalation study for patients with organ-confined

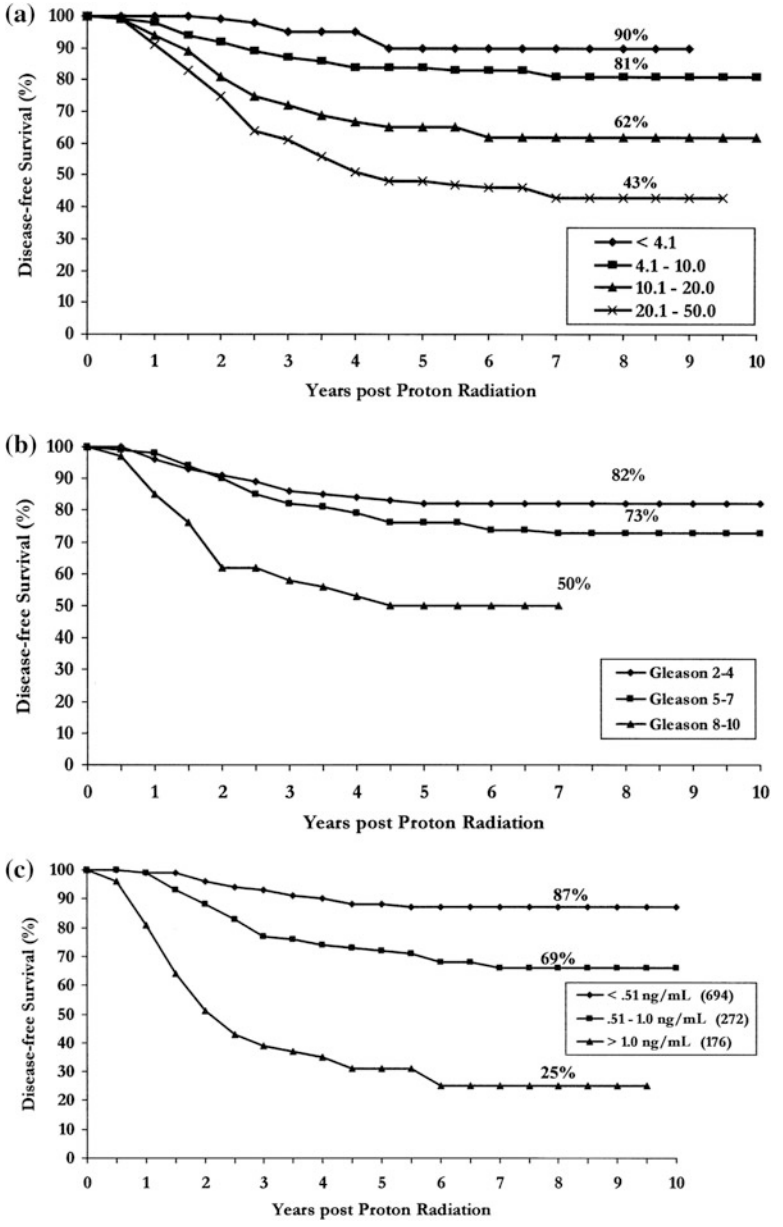

Fig. 5 Effect of pre-treatment PSA on bNED survival (a) Gleason score on bNED survival (b) PSA nadir on bNED survival (c)

prostate cancer. This study was designed to test the hypothesis that dose escalation from 70.2 to 79.2 GyE would result in a statistically significant decrease in local failure, biochemical failure, and overall survival. Eligibility criteria included stage T1b–T2b disease (as per the 1992 American Joint Committee on Cancer staging system), a PSA of ≤ 15 ng/ml, and no evidence of metastatic disease on imaging studies (bone scan, abdominal-pelvic CT scan). Gleason score was not an exclusion criterion, and no prior or concurrent androgen-depravation therapy was permitted. Pre-treatment patient characteristics are shown in Table 3.

Patients were randomly assigned to receive a total prostate dose of 70.2 or 79.2 GyE. Radiotherapy was administered sequentially in two phases. In Phase I, conformal proton beams were used to treat the prostate alone. Depending on randomization either 19.8 or 28.8 GyE in 11 or 16 fractions was delivered. The clinical target volume (CTV) was the prostate with a 5 mm margin. Beam arrangement was facility dependent with patients at LLUMC being treated with lateral proton beams of 225–250 meV energy, while at MGH a perineal 160 meV proton beam was employed. Before each proton beam treatment, a water balloon was inserted into the rectum and inflated with 100 ml of saline; this served the dual purpose of distending the rectum lumen to decrease the volume of rectum receiving any radiation and minimizing prostate motion.

In the second phase of treatment all patients received 50.4 Gy of photons given in 1.8 Gy fractions. The CTV was the prostate and seminal vesicles. No effort was made to include the pelvic lymphatics. Three-dimensional planning was used on all patients and photon energies of 10–23 MV were employed. The use of photons for this portion of the treatment was solely to allow both institutions to participate in this trial, for at the time the trial commenced MGH patients were still restricted to treatment at the Harvard Cyclotron Laboratory and the limited throughput of that facility meant that the most efficient use of protons was as a boost and not as monotherapy. The randomization schema is shown in Fig. 6. A total of 393 patients were randomized between January 1996 and December 1999.

The results of the trial were initially published in Zietman et al. (2005), with an update in Zietman et al. (2010). At a median follow-up of 8.9 years there is a persistent and statistically significant increase in biochemical freedom from relapse amongst patients randomized to the high dose arm (Fig. 7a, b). This difference was seen when using both the original ASTRO and the more recent Phoenix definition (in which biochemical failure = a PSA elevation of >2 ng/ml above a nadir). Subgroup analysis showed a particularly strong benefit in 10 year bNED survival amongst the "low risk" patients (defined as PSA < 10 ng/ml, and Gleason score < 7 and stage < t2b), with 92.2% of high dose patients being disease free versus 78.8% for standard dose ($p = 0.0001$). A strong trend towards unproved bNED similar was also seen in the intermediate risk patients but this has not reached statistical significance (Fig. 8). In addition, patients in the standard dose arm are twice as likely to have been started on androgen depravation therapy as high dose patients (22 vs. 11, $p = 0.47$) with such treatment usually being initiated due to a rising PSA. To date, there is no statistically significant difference in overall survival between the arms.

Table 3 Pre-treatment patient characteristics PROG 95-09 trial

	Assigned Dose			
	70.2 GyE (n = 196)		79.2 GyE (n = 195)	
Characteristic	No.	%	No.	%
Age, years				
45-59	43	22	34	17
60-69	92	47	106	54
70-79	61	31	55	28
≥ 80	1	0.5	0	
Median	67		66	
Range	45-91		47-78	
Race				
White	175	89	178	91
Hispanic	4	2	7	3
Black	12	6	5	3
Other	5	3	5	3
PSA, ng/mL				
< 5	54	28	47	24
5 to < 10	114	58	119	61
10-15	28	14	29	15
Median	6.3		6.2	
Range	1.24-14.68		0.67-14.30	
Karnofsky performance status				
80	8	4	9	5
90	52	27	47	24
100	136	69	139	71
Combined Gleason				
2-6	148	75	147	75
7	29	15	30	15
8-10	18	9	15	8
Unknown	1	1	3	2
T stage				
T1b	1	1	0	
T1c	120	61	120	61
T2a	43	22	50	26
T2b	32	16	25	13
N stage				
N0	0		2	1
NX	196	100	193	99
Risk groups*				
Low	111	57	116	59
Intermediate	75	38	69	35
High	10	5	7	4
Not classified	0		3	2

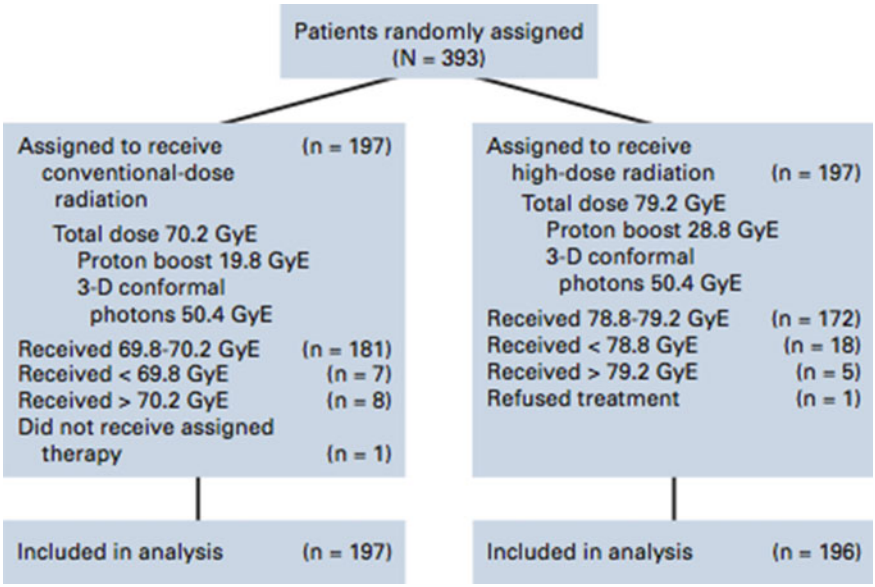

Fig. 6 PROG 95-09 randomization schemata

As was seen in the previously reported proton trials treatment was well tolerated. Only 2% of patients in both arms have experienced late GU toxicities of Grade ≥ 3 and 1% have experienced late GI toxicity of Grade ≥ 3. Interestingly, as opposed to what has been reported in some photon-based randomized dose escalation trials high dose radiotherapy delivered via a conformal proton beam boost did not result in an increase in late Grade ≥ 3 GI morbidity amongst the high dose patients (Table 4). This encouraging finding has been confirmed in a patient-reported sensitive quality of life instrument which did not report any greater morbidity than the physician-reported scores, and which revealed equal and high satisfaction with quality of life between both arms (Talcott et al. 2010).

Thus, the PROG/ACR 9509 trial provides "Level One" evidence verifying the importance of radiation dose-escalation in organ confined prostate cancer and while this study was not designed to directly compare the efficacy of conformal proton beam radiotherapy against other conformal techniques or modalities it does demonstrate that conformal proton beam radiotherapy is an effective treatment for this disease, with minimal risk of severe treatment-induced toxicity (Goitein and Cox 2008; Goitein 2010).

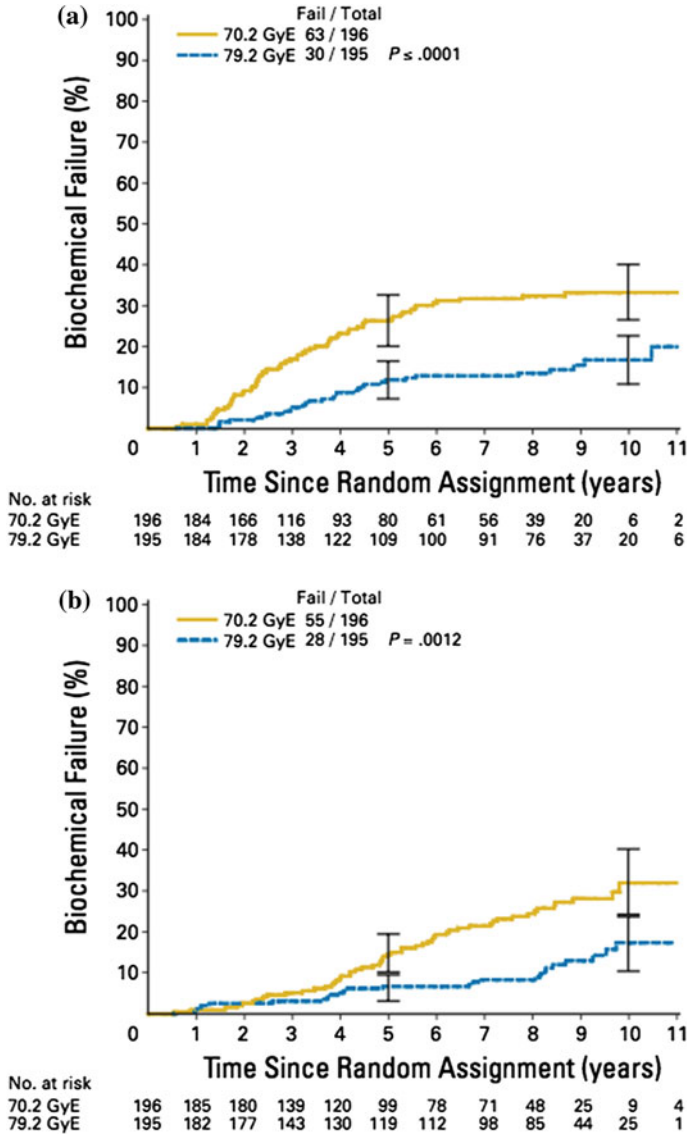

Fig. 7 bNED survival per ASTRO consensus (a) and Phoenix definition (b)

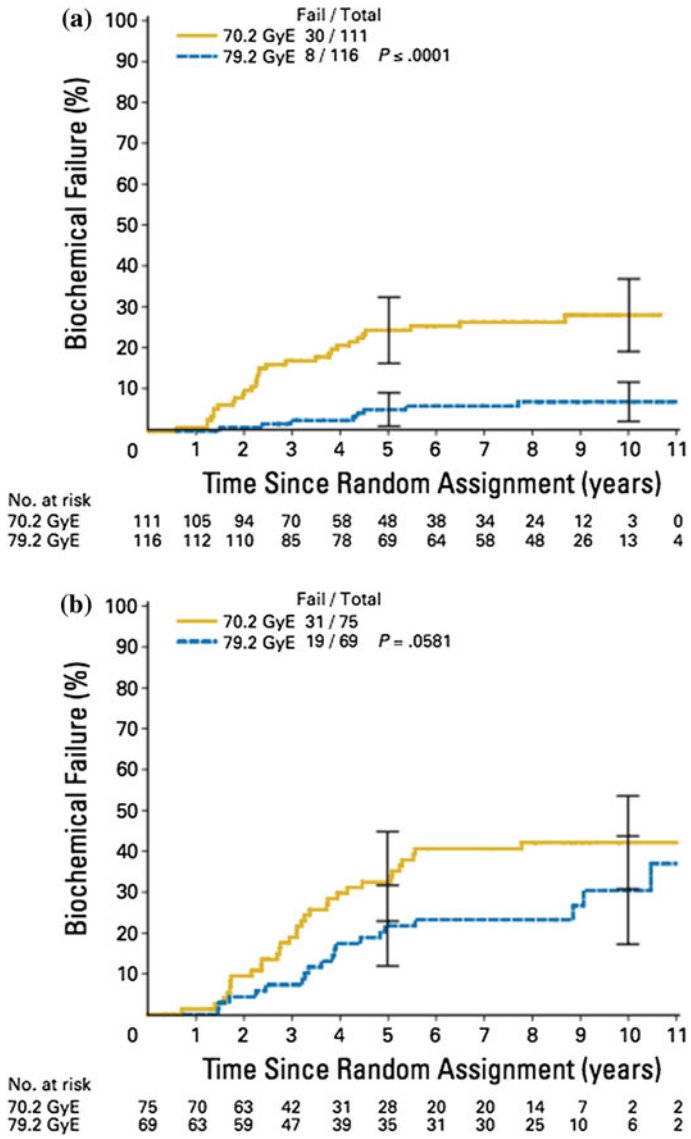

Fig. 8 bNED survival by low (a) and intermediate risk (b) group

6 University of Florida Experience

The University of Florida Proton Therapy Institute commenced prostate cancer treatment in the summer of 2006. From 2006 thru 2010 patients were treated on one of several prospective trials, all of which delivered 78–82 Gy (RBE) in 2 Gy

Table 4 Sequel of treatment PROG 95-09 trial

	Grade 2 (%)	Grade 3 (%)
GI	21	0
GU	5.4	0.3
Total	26	0.3

fractions. After excluding patients who also received concurrent chemotherapy, received IMRT for elective pelvic node radiation, GI/GU follow up data were unavailable, and patients with less than 2-year biochemical follow-up for reasons other than death 1214 patients remained eligible for analysis. Virtually all patients were treated with either lateral or posterior-oblique fields, IMRT treatment of pelvic nodes was performed in those with >15% risk of node involvement per nomogram, and androgen-depravation therapy was administered to 18% of the patients.

With a median follow up of 5.5 years, freedom biochemical failure was 99% in the low-risk patients, 94% in the intermediate risk patients, and 74% in the high-risk patients. Statistically significant predictors of biochemical included Gleason Score (4–7 vs. 8 vs. 9–10; $p = 0.02$), PSA (0 < 10 vs. 10–20 vs. >20; $p = 0.02$), perineural invasion (yes vs. no; $P = 0.01$), and percentage of positive zones on biopsy (<50% vs. $\geq 50\%$; $P = 0.02$).

Grade 3+ Acute/late GU toxicity was seen in 5.4% of patients (70/1289), with 58/70 being late events, 9 being acute events, and 3 patients who experienced both acute and late events. One patient experienced a Grade 4 toxicity, while no Grade 5 events have occurred. The primary reason for Grade 3 toxicity in both the acute and late patients was obstruction. Late Grade 3 GU toxicity was associated with use of androgen suppressive therapy ($P = 0.0243$), prescription anticoagulants ($P = 0.0316$), prostate volume < 40 cc vs. 40–60 cc vs. >60 cc ($P < 0.0001$), pretreatment alpha-blocker use ($P < 0.0001$), diabetes ($P = 0.0210$), pretreatment TURP ($P < 0.0001$), any pretreatment urologic symptom management ($P < 0.0001$) and numerous bladder and bladder wall dose-volume histogram parameters. The five-year actuarial incidence of late Grade 3 GI toxicity was 0.6%. The authors reported that both the rates of biochemical freedom from relapse and GU/GI toxicity compare favorably with large published IMRT series. The authors also note that while the incidence of bladder and rectal toxicity are similar to what is reported with IMRT, the primary benefit of proton beam therapy over IMRT is not in reducing the volume of bladder, rectum, or penile bulb receiving a high dose but in the volume of these structures receiving moderate doses (30–60 Gy), and this dose reduction may be expected to result in less erectile dysfunction, diarrhea, and bowel urgency as opposed to less rectal bleeding, urethritis, or urethral stricture (Mendenhall et al. 2012, 2014; Bryant et al. 2016).

7 Intensity-Modulated Proton Therapy

The recent development and deployment of Intensity-Modulated Proton Therapy (IMPT) now permits proton beam threat to be given in a fashion similar to IMRT, while using a beam that carries with it all of the physical advantages of protons over X-rays.

IMPT is being rapidly integrated into clinical proton beam therapy. It first became available in the United States in 2008 when the University of Texas MD Anderson Proton Treatment Center deployed this capability in one treatment room and it is now found in a number of existing centers, as well as being installed from inception at most new facilities being constructed worldwide. The Scripps Proton Therapy Center became the first "IMPT only" center in the United States when it opened in 2014.

To date, there exists only one published comparison of quality of life (QOL)/toxicity in men treated with proton beam therapy for localized prostate cancer between those who were treated with passively scattered proton therapy and intensity modulated proton therapy. Pugh and colleagues at M.D. Anderson performed a comparison between 226 men treated with PSPT and 65 men treated with IMPT. Quality-of-life was assessed by the expanded prostate cancer Index composite questionnaire (EPIC) which was administered at baseline and every 3–6 months after proton beam therapy. Clinically meaningful differences in quality of life were defined as $\geq 0.5 \times$ baseline standard deviation. In addition, the cumulative incidence of modified RTOG grade ≥ 2 GI or GU toxicity and the need for argon plasma coagulation (APC) were determined by the Kaplan–Meier method. Both groups of patients were treated with opposed right and left lateral beams with both fields being treated daily, and all patients received a total dose of 76 Gray (RBE) delivered in 38 fractions. The authors noted that both PSPT and IMPT conferred low rates of grade ≥ 2 GI and GU toxicity with preservation of meaningful sexual and urinary QOL at 24 months. A "modest yet clinically meaningful decrement in bowel QOL" was seen throughout the follow-up period, but there were no differences seen in toxicity or QOL between the two different delivery techniques. The authors did note that many of the patients treated with IMPT were some of the first patients treated with this technique both at their institution and within North America and hence postulated that the possible existence of a "learning curve effect" could have skewed the results somewhat (Pugh et al. 2013).

8 IMPT-Examples

The following treatment plans serve well to illustrate the flexibility and capability of IMPT in various clinical situations:

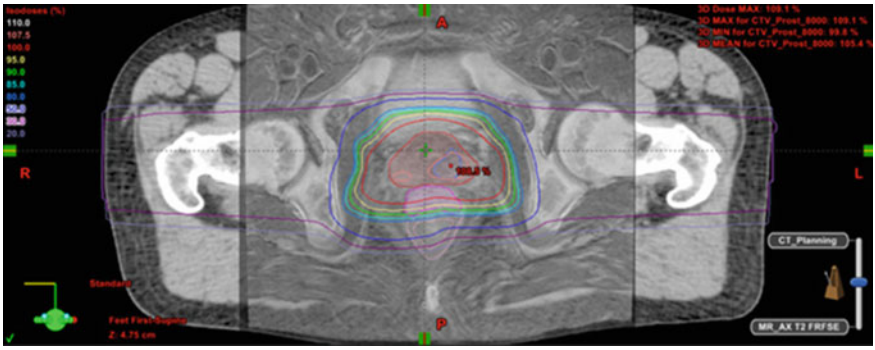

Fig. 9 The isodose image illustrates coverage of the prostate gland with simultaneousdose-escalation of the MRI-defined DIL

1. Conventional fractionation with simultaneous integrated boost (SIB) of a dominant intra-prostatic lesion (DIL). This 53-year-old gentleman had organ confined, intermediate risk prostate cancer. His IMPT planning included a thin-slice CT of the pelvis and multi-parametric MRI, both of which were performed with him in his treatment position. A SpaceOAR rectal spacer was also placed prior to imaging. The isodose image illustrates coverage of the prostate gland with simultaneous dose-escalation of the MRI-defined DIL (Fig. 9).

   Dose-volume histograms (DVH) for this patient are shown below. In this case, the patient underwent adaptive pelvic CT and MRI scans weekly during treatment to monitor the stability of his rectal spacer. The resulting composite DVH nicely illustrates both the high dose conformity achievable with IMPT and the low dose to the anterior rectal wall (pink contour) courtesy of the spacer (Fig. 10a).

   In order to monitor the status of his rectal spacer this patient underwent weekly adaptive pelvic CT and MRI scans. The dose-volume histogram demonstrates the reproducibility of his treatment plan while also illustrating the utility of the rectal spacer in reducing radiation dose to the anterior rectal wall (pink isodose lines) (Fig. 10b).
2. High-risk prostate cancer with treatment of the whole pelvis, plus prostate gland including SIB of DIL (Fig. 11).
3. Modestly Hypofractionated IMPT including SIB directed at DIL (Fig. 12).

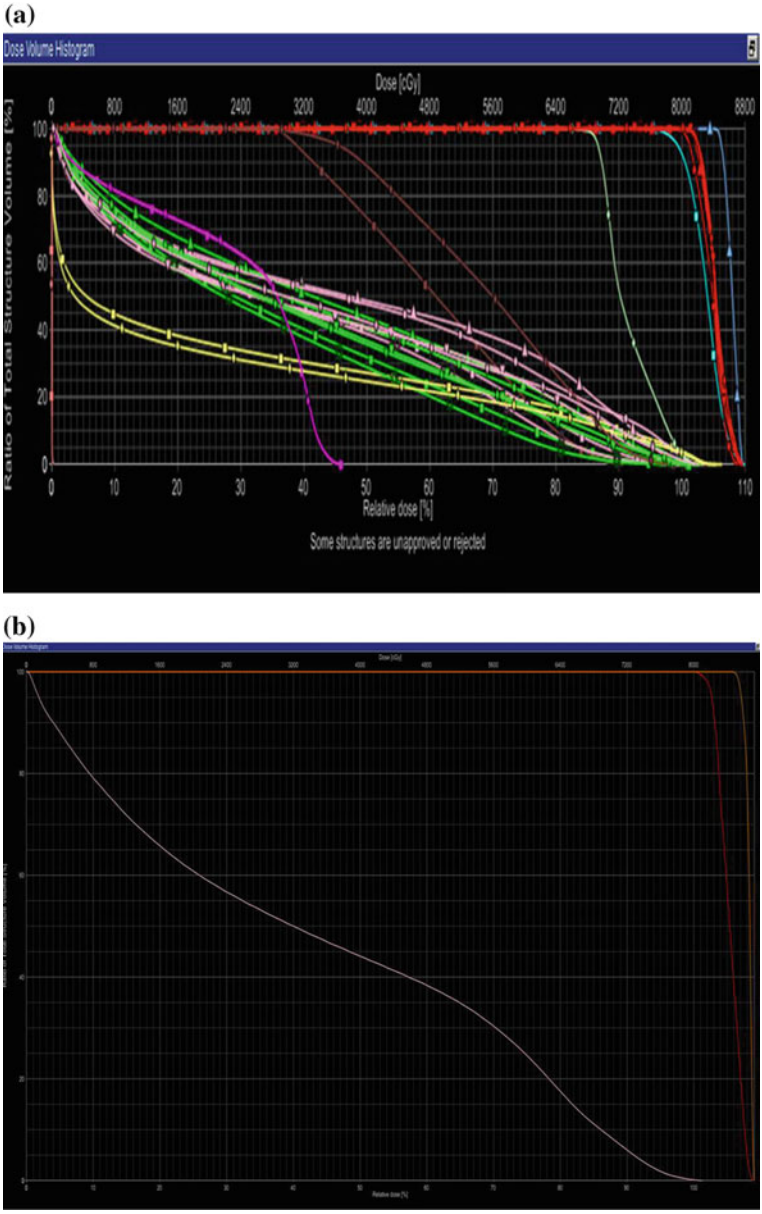

Fig. 10 **a** Composite DVH for patient with SpaceOAR Rectal Spacer. Prostate is in Red, DIL is Blue, Anterior Rectal Wall Pink, Whole Rectum Green, Bladder yellow. **b** Magnified View of static DVH, DIL in Orange, Prostate in Red, Anterior Rectal Wall Pink

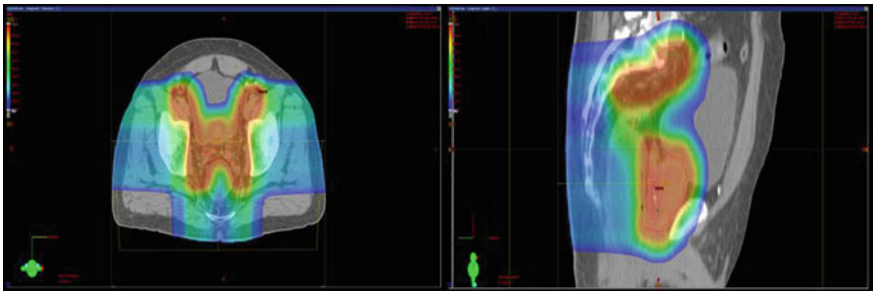

Fig. 11 High-risk prostate cancer with treatment of the whole pelvis, plus prostate gland includingSIB of DIL

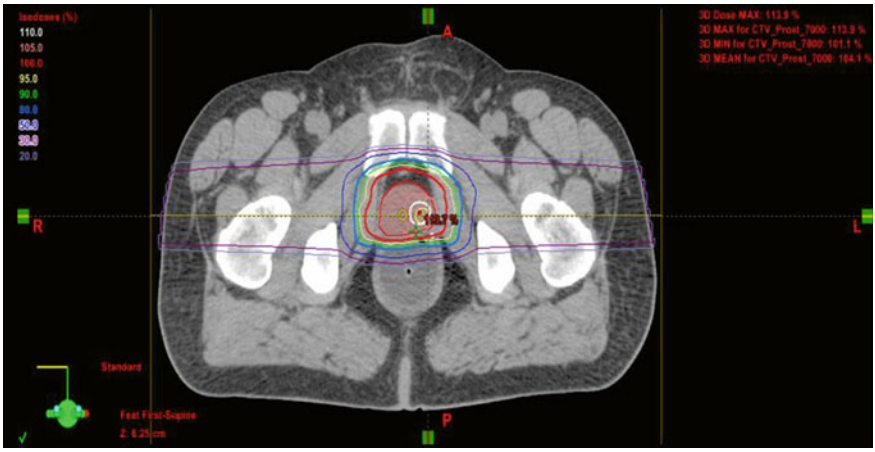

Fig. 12 Modestly hypofractionated IMPT including SIB directed at DIL

9 Conclusion

The implementation of IMPT has brought about a substantial leap in clinical capabilities including the ability to efficiently treat large, complex shapes while simultaneously producing both uniform and non-uniform dose distributions. In prostate cancer treatment these improved capabilities are at last bringing to proton therapy the same clinical utility which has existed with IMRT for the past decade and carries with it the promise of further improving the clinical utility of this treatment modality. Although to date the limited data on direct comparisons between IMPT and PSPT has shown little if any difference in efficacy or morbidity it is reasonable to anticipate that as the availability of IMPT becomes more widespread the further reduction in normal tissue doses associated with this modality will begin to manifest themselves as clinically meaningful differences in toxicity as compare to PSPT and IMRT-based treatment systems.

References

Bonnett DE (1993) Current developments in proton therapy: a review. Phys Med Biol 38 (10):1371–1392

Bryant C et al (2016) Five-year biochemical results, toxicity, and patient-reported quality of life after delivery of dose-escalated image guided proton therapy for prostate cancer. Int J Radiat Oncol Biol Phys 95(1):422–434

Goitein M (2010) Trials and tribulations in charged particle radiotherapy. Radiother Oncol 95 (1):23–31

Goitein M, Cox JD (2008) Should randomized clinical trials be required for proton radiotherapy? J Clin Oncol 26(2):175–176

Lomax A (1999) Intensity modulation methods for proton radiotherapy. Phys Med Biol 44 (1):185–205

Lomax AJ (2008) Intensity modulated proton therapy and its sensitivity to treatment uncertainties 2: the potential effects of inter-fraction and inter-field motions. Phys Med Biol 53(4):1043–1056

Lomax AJ (2009) Charged particle therapy: the physics of interaction. Cancer J 15(4):285–291

Lomax AJ et al (2004a) The clinical potential of intensity modulated proton therapy. Z Med Phys 14(3):147–152

Lomax AJ et al (2004b) Treatment planning and verification of proton therapy using spot scanning: initial experiences. Med Phys 31(11):3150–3157

Mendenhall NP et al (2012) Early outcomes from three prospective trials of image-guided proton therapy for prostate cancer. Int J Radiat Oncol Biol Phys 82(1):213–221

Mendenhall NP et al (2014) Five-year outcomes from 3 prospective trials of image-guided proton therapy for prostate cancer. Int J Radiat Oncol Biol Phys 88(3):596–602

Miller DW (1995) A review of proton beam radiation therapy. Med Phys 22(11 Pt 2):1943–1954

Olsen DR et al (2007) Proton therapy—a systematic review of clinical effectiveness. Radiother Oncol 83(2):123–132

Pugh TJ et al (2013) Quality of life and toxicity from passively scattered and spot-scanning proton beam therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 87(5):946–953

Schippers JM, Lomax AJ (2011) Emerging technologies in proton therapy. Acta Oncol 50(6):838–850

Shipley WU et al (1979) Proton radiation as boost therapy for localized prostatic carcinoma. JAMA 241(18):1912–1915

Shipley WU et al (1995) Advanced prostate cancer: the results of a randomized comparative trial of high dose irradiation boosting with conformal protons compared with conventional dose irradiation using photons alone. Int J Radiat Oncol Biol Phys 32(1):3–12

Slater JM, Miller DW, Archambeau JO (1988) Development of a hospital-based proton beam treatment center. Int J Radiat Oncol Biol Phys 14(4):761–775

Slater JM et al (1992) The proton treatment center at Loma Linda University Medical Center: rationale for and description of its development. Int J Radiat Oncol Biol Phys 22(2):383–389

Slater JD et al (1998) Conformal proton therapy for prostate carcinoma. Int J Radiat Oncol Biol Phys 42(2):299–304

Slater JD et al (2004) Proton therapy for prostate cancer: the initial Loma Linda University experience. Int J Radiat Oncol Biol Phys 59(2):348–352

Society AC (2015) Cancer facts and figures 2015

Suit H (2002) The Gray Lecture 2001: coming technical advances in radiation oncology. Int J Radiat Oncol Biol Phys 53(4):798–809

Suit HD et al (1977) Clinical experience and expectation with protons and heavy ions. Int J Radiat Oncol Biol Phys 3:115–125

Suit H et al (2003) Proton beams to replace photon beams in radical dose treatments. Acta Oncol 42(8):800–808

Talcott JA et al (2010) Patient-reported long-term outcomes after conventional and high-dose combined proton and photon radiation for early prostate cancer. JAMA 303(11):1046–1053

Trofimov A et al (2007) Radiotherapy treatment of early-stage prostate cancer with IMRT and protons: a treatment planning comparison. Int J Radiat Oncol Biol Phys 69(2):444–453

Wilson RR (1946) Radiological use of fast protons. Radiology 47(5):487–491

Zietman AL (2007) The Titanic and the Iceberg: prostate proton therapy and health care economics. J Clin Oncol 25(24):3565–3566

Zietman A (2008) Active surveillance: a safe, low-cost prognostic test for prostate cancer. BJU Int 101(9):1059–1060

Zietman AL (2016) Making radiation therapy for prostate cancer more economical and more convenient. J Clin Oncol 34(20):2323–2324

Zietman AL et al (2005) Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. JAMA 294(10):1233–1239

Zietman AL et al (2010) Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. J Clin Oncol 28(7):1106–1111