Proton Beam Therapy and Novel Radiotherapeutic Approaches to the Treatment of Prostate Cancer

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Introduction

Radiation treatment of malignancies with curative intent requires maximizing the chance of tumor eradication while minimizing the risk of normal tissue injury, the so-called collateral damage of radiotherapy. There has been a gradual evolution in radiotherapy approaches over time in an effort to achieve this goal. Much of this evolution has centered on advances in the technological aspects of radiotherapy treatment planning and delivery. Appropriate delineation of clinical target volumes through improvements in imaging technology (CT, MRI, PET) is one example. Another example is in the development of three-dimensional conformal radiotherapy planning and the introduction of intensity-modulated radiotherapy (IMRT), discussed in the previous chapter.

The overwhelming majority of radiation treatments are delivered with high-energy photons (x-rays) or electrons. The interactions of photons with and their transfer of energy to tissue are in general well understood and can be modeled with treatment planning systems, allowing for creation of a specific radiation treatment plan for a given patient. Various techniques to overcome the dosimetric restrictions of x-ray therapy have been implemented over time. There is also considerable interest in using proton beams in radiotherapy treatments. This chapter describes the rationale for this interest, controversies associated with proton radiotherapy, and results in its use for the treatment of prostate cancer. Results with high-dose hypofractionated therapy delivered with stereotactic body radiation therapy will also be discussed.

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Proton Therapy

Physical and Biological Characteristics of Proton Radiotherapy

There is a critical difference in energy deposition (via ionizations or excitations) by protons versus photons in their interactions with tissues [1]. Protons gradually decelerate in tissue with a sharp rise in linear energy transfer (LET) at the end of their path; this has been termed the Bragg peak. Importantly, there is no further energy transfer/dose beyond the peak (i.e., no "exit dose"). This is in stark contrast to photon dosimetry, wherein dose is delivered beyond the target tissue. The physicist Robert Wilson realized in the mid-1940s that the Bragg peak phenomenon could be exploited in the treatment of tumors and that protons may offer a significant advantage over photons since there is less integral energy transferred to nontarget critical tissues [1]. As a result, the ratio of tumor control probability/normal tissue complication probability should be maximized.

Accelerating protons to the high energies required for treating deep-seated tumors requires the use of particle accelerators such as cyclotrons and synchrotrons. Much of the high cost associated with proton therapy treatment facilities is associated with use and maintenance of these accelerators. Much as with x-ray therapy, proton therapy can be delivered through isocentric gantries, allowing for use of multiple, nonaxial beam arrangements.

Most proton treatments are currently delivered using passive scattering systems, wherein proton energy and range compensators define the distal edge of the proton beam's penetration. Since the Bragg peak is so narrow, multiple Bragg peaks are "summed" together by beams of differing energies to create a "spread-out Bragg peak." There is also significant interest in pursuing spot scanning technology, in

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which individual "spots" of protons of varying energies are deposited within a tumor [2]. Spot scanning improves on the conformality of treatment plans relative to that achieved with passive scattering proton plans. Spot scanning should also reduce the amount of neutron contamination seen with passive scattering treatments [3].

Generally speaking, high-energy protons have a biological effectiveness similar to that of x-rays, although there is an increase in density of energy deposition toward the Bragg peak, with a concomitant increase in biological effect. Many, but not all, particle therapy centers employ a biological effectiveness correction of 1.1. That is, the physical dose delivered with protons is reduced by a factor of 1.1 relative to what would be delivered with photons to achieve the same biological effect [4]. The effective dose delivered with protons is given units of GyE (Gray equivalents).

Proton Therapy: Treatment Planning Process

Proton treatments for prostate cancer are commonly delivered with opposed lateral beams, with one or two fields treated for each treatment session. With these arrangements, beams pass through but do not complete their range in the bladder and anterior rectal wall. A rectal balloon is often employed to mitigate intrafractional motion of the prostate and to distend the posterior rectum away from the lateral beam edge. Rectal balloons are not specific to proton therapy and can also be used for photon-based treatments [5]. The balloons are well tolerated by patients in general [6]. Harvard investigators have also reported on use of a single beam directed through the perineum [7]. Beam energies required for treatment are dependent on patient-specific anatomy and beam path length. Uncertainties in proton range must be determined during the treatment planning process and incorporated into additional margin around the distal edge of the clinical target volume [8].

Preclinical Comparisons of Proton and Photon Therapy

Numerous groups have compared proton and photon treatment plans in order to evaluate potential dosimetric superiority of one modality versus the other [9–11]. In general, proton therapy with opposed lateral beams reduces doses to the rectum and bladder in the low-dose range, whereas in the high-dose range, intensity-modulated photon treatment plans can reduce dose to these structures compared to proton plans. Dose to the posterior rectal wall is quite low since the posterior wall is blocked in proton treatment plans. This may contribute to the low overall late rectal toxicity rates (discussed further below) (Fig. 64.1). In one study, IMRT was better able to spare the radiation dose to the femoral heads, a function of the multiple modulated beams used with IMRT as opposed to the two-beam opposed lateral configuration with most prostate proton treatments [10].

Integral energy transferred to the body is reduced with proton plans relative to photon treatments. Other modeling studies have shown that protons may be associated with a reduced risk of developing a secondary, radiation-induced malignancy in comparison with photons as a result of this reduced energy deposition [12].

The Role of Proton Radiotherapy in Modern Radiation Oncology

The appropriate role of proton therapy in modern radiation oncology is controversial, particularly in the treatment of prostate cancer. The high costs associated with currently available treatment facilities and reimbursement for a course of treatment are a major factor in the controversy, with resulting debates over the cost-effectiveness of this treatment especially in the era of optimized 3D conformal and intensity-modulated x-ray therapy as well as the various brachytherapy methods [13–16]. These latter treatments allow for high-dose irradiation of the prostate with relatively low rates of acute and chronic GU and rectal toxicity. There have been arguments for and against the need for comparison randomized trials of proton and x-ray therapy made in the literature. It is important to note that similar clinical studies (of particle therapy versus "conventional" treatment) have indeed been conducted in the past [17]. As cost for facilities and treatments is reduced over time, and as intensity modulation methods are applied to proton therapy, cost-effectiveness debates will have to be readdressed [18].

Proton Radiotherapy for Prostate Cancer: Clinical Results

Institutional Experiences

Loma Linda University Medical Center (LLUMC) has extensive clinical experience employing proton therapy in prostate cancer management. In 2004, Slater et al. reported their experience with 1,255 patients with localized prostate cancer treated from 1991 to 1997 with protons or mixed proton/photon plans, without preceding surgery or androgen deprivation [19]. The radiation dose was 75 CGE in the patients treated with protons and photons and 74 CGE in the proton-alone patients. Lateral beams were used for the proton treatments. A rectal balloon was used for treatments. Median follow-up was 62 months. Estimated 5-year biochemical disease-free survival for all patients was 75 %. Initial PSA, PSA nadir, and Gleason score were all independently associated with

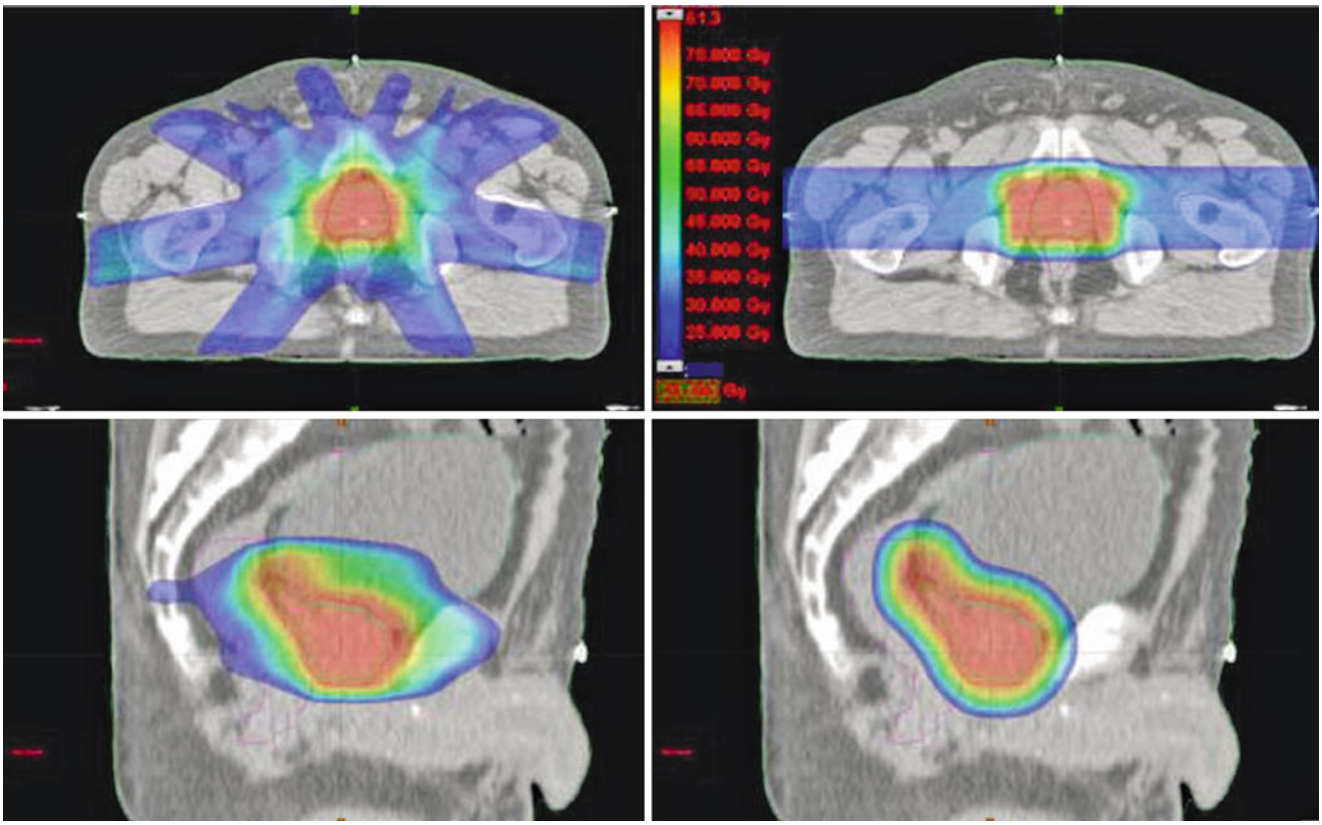

Fig. 64.1 Comparison of IMRT (*top* panel, *left side*, and *bottom left* panel) versus proton (*top* panel, *right side*, and *bottom right* panel) treatment plans for a patient with prostate cancer. Multiple modulated photon beams are used in the IMRT plan as opposed to two (opposed lateral) beams for the proton plan. Colors correspond to different radiation doses as shown in the top panel (Reproduced, with permission, from Zhang et al. [11])

biochemical disease-free survival. Acute grade 3 or higher gastrointestinal (GI) toxicity was seen in <1 % of patients, and the estimated 5-year freedom from grade 3 or higher late toxicity was 99 %. Freedom from grade 3 or higher late genitourinary toxicity was similarly excellent at 99 %.

Investigators from the Hyogo Ion Beam Medical Center in Japan reported on acute toxicity data for 287 patients with localized prostate cancer treated with proton radiation therapy (dose: 74 CGE) [20]. About 70 % of patients received neoadjuvant androgen deprivation therapy. No patients developed grade 2 (NCI-CTC version 2.0) or higher acute GI toxicity. Thirty-nine percent and 1 % of patients developed acute grade 2 and 3 GU toxicity, respectively. Most patients responded to use of alpha-1 blocking agents to aid with urination difficulties. Bladder dosimetry was not related to acute GU toxicity in any clear manner. The authors emphasized the sparing of the posterior rectal wall made possible by the opposed lateral beam arrangement and the possible implications for preventing rectal toxicity.

Clinical Trials

Investigators at Harvard began clinical studies with proton treatment for prostate cancer in the 1970s. Following early-phase clinical trials, a phase III study was conducted in which patients with locally advanced prostate cancer (T3–4, with or without involved pelvic lymph nodes) were treated with 50.4 Gy with photon therapy followed by a boost with 16.8 Gy with photons versus 25.2 GyE with protons (the latter delivered through a perineal-directed field) [21, 22]. A later report showed that the actual delivered dose for the patients in the proton-boost arm was 27 GyE for a total dose of 77.4 Gy. Although there were no differences in overall or disease-specific survival, likely a reflection of the locally advanced disease state, local control in the subset of patients with poor differentiation was higher in the high-dose arm. Grade 1–2 rectal bleeding was seen at a higher frequency in the high-dose arm. It is unknown if the rectal toxicity rates would have been even higher if the high-dose boost had been delivered with photons.

Gardner and colleagues reported on toxicity rates in long-term surviving patients treated on this protocol and on a preceding phase II study [22]. Thirty-nine patients were interviewed. Median follow-up was 13.1 years. Using the RTOG/EORTC Common Toxicity Criteria version 2.0, 15-year actuarial grade 2 or higher GI toxicity was 13 %, and grade 2 or higher hematuria was 47 %.

Table 64.1 Late toxicity outcomes following prostate irradiation from selected phase III and institutional series

Study (reference)	Dose (fractional dose)	Grade 2 GI (%)	Grade 3 GI (%)	Grade 2 GU (%)	Grade 3 GU (%)
Photon studies					
Peeters et al.[a] [26]	68 Gy (2 Gy)	27	4	41	12
Randomized phase III trial	78 Gy (2 Gy)	32	5	39	13
Kuban et al.[b] [27]	70 Gy (2 Gy)	13	1	8	5
M.D. Anderson Cancer Center					
Randomized phase III trial	78 Gy (2 Gy)	26	7	13	4
Dearnaley et al.[c] [28]	64 Gy (2 Gy)	24	6	8	2
RT01					
Randomized phase III trial	74 Gy (2 Gy)	33	10	11	4
Alicikus et al.[d] [29]	81 Gy (1.8 Gy)	3	1	16	5
Memorial Sloan-Kettering Cancer Center institutional series					
Proton and photon-proton studies					
Zietman et al.[e] [23]	70.2 Gy (1.8 Gy)	8	1	18	8
PROG/ACR 95–09					
Randomized phase III trial	79.2 Gy (1.8 Gy)	17	1	20	1
Slater et al.[f] [19]	74–75 Gy (1.8–2 Gy)	1.2 % Grade 3+			
Loma Linda University Medical Center institutional series					

[a]Modified RTOG/EORTC toxicity scoring criteria. Actuarial results at 5 years
[b]Modified RTOG/LENT toxicity scoring criteria. Actuarial results at 10 years
[c]RTOG toxicity scoring criteria. Actuarial results at 5 years
[d]CTC v3.0 toxicity scoring criteria. Actuarial results at 10 years. Patients in this series were treated with intensity-modulated radiation therapy
[e]RTOG toxicity scoring criteria. Patients were treated with 50.4 Gy to the prostate with photons. The remainder of the treatment was delivered with protons to the prostate alone
[f]RTOG toxicity scoring criteria

LLUMC and Massachusetts General Hospital/Harvard investigators collaborated on the Proton Radiation Oncology Group/American College of Radiology (PROG/ACR) 95–09 protocol [23]. PROG/ACR 95–09 was not a direct test of the value of proton radiotherapy versus other types of prostate cancer treatments, but rather a randomized trial comparing two dose levels for patients with T1b–T2b prostate cancer, namely, 70.2 GyE versus 79.2 GyE (without androgen suppression). The trial is nonetheless important for the evaluation of proton therapy as it involved nearly 400 patients enrolled on a phase III, dual-institution study, and provides level I evidence regarding radiation dose selection in which a significant portion of the total dose was delivered with proton beams. All patients received 50.4 Gy with photon therapy to the prostate and seminal vesicles. Depending on the randomization arm, 19.8 or 28.8 GyE was delivered to the prostate alone with protons. At most recent report, median follow-up was 8.9 years. Patients in the high-dose group had a lower rate of biochemical failure (Phoenix criteria) at 10 years – 17.4 % versus 32.0 % in the low-dose arm. The difference in freedom from biochemical failure was especially pronounced in the subset of low-risk patients. Need for subsequent androgen deprivation therapy was lower in the high-dose arm, as well. There was no difference in overall survival between the two groups. Late grade 3 (RTOG criteria) or higher GU rates were 2 % for both dose arms; 1 % of patients in the high-dose arm had late grade 3 or higher GI toxicity.

ACR 03–12 is a phase II study evaluating efficacy and tolerability of high-dose radiation (82 Gy at 2 Gy per fraction) delivered with protons alone. Initial toxicity rates were recently published [24]. High-grade acute toxicity was uncommon, but investigators found an actuarial risk of grade 3+ late gastrointestinal/genitourinary toxicity rate of 6.08 %. There was no clear correlation between rectal wall radiation dose and rectal bleeding. Tumor control rates are awaited following further follow-up.

Mendenhall et al. at the University of Florida Proton Therapy Institute recently reported preliminary toxicity results from three institutional protocols treating low-, intermediate-, and high-risk prostate cancer patients [25]. Four of 211 patients experienced grade 3 GU toxicity, and 10 % of patients developed grade 2+ GI toxicity by 2 years following treatment.

Table 64.1 summarizes data regarding treatment-related toxicity from various phase III and institutional series [19, 23, 26–29]. Recognizing that differing toxicity criteria makes comparisons difficult, it is apparent that photon and proton treatments are both associated with relatively low rates of high-grade (grade 3+) gastrointestinal and genitourinary toxicity.

Other Particles

Other particles such as neutrons, negative pi-mesons (pions), and carbon ions have also been studied as therapies for treating prostate cancer [30–32]. Neutrons are densely ionizing particles that tend to have a significantly higher biological effectiveness than photons, although this is not necessarily tumor specific and the actual therapeutic ratio does not appear significantly different than that achieved with photons. There may be an advantage to using neutrons for bulky and hypoxic tumors. Carbon ions share physical properties with protons (specifically, the Bragg peak) and also display some of the biological characteristics of neutrons. This combination is intriguing, and carbon ion facilities are conducting clinical studies evaluating the merits of carbon ion therapy for prostate and other cancers.

Stereotactic Radiation Therapy

Stereotactic radiation is the highly precise irradiation of a target, with rapid radiation dose falloff at the periphery of the target, therefore minimizing radiation dose to nearby organs [33–36]. Although some treatments are indeed delivered with help of a defined stereotactic coordinate system, the term "stereotactic body radiation therapy" has become an umbrella term used to describe high-precision, high-dose radiotherapy typically made possible by image guidance. The precision results from target definition (usually involving CT scan fused with MRI during the treatment planning process), patient immobilization, and sophisticated image guidance (usually with CT or x-ray images) to localize the radiation target [37]. In contrast with conventionally fractionated radiation therapy and its protracted treatment course of several weeks, stereotactic radiation is typically delivered in one to five treatments (a high dose given per treatment). Both x-rays and particle irradiation can be employed in stereotactic hypofractionated treatment courses, although published studies to date have used x-rays.

Stereotactic Radiation Technology

The target volume for radiation treatment includes the anatomical area of the cancer (e.g., prostate), which is expanded by a "margin" to account for imprecision of prostate location from 1 day to next (interfraction movement) and movement of the prostate during radiation treatment (intrafraction movement). In one study of 329 patients and 1,870 CT scans performed immediately prior to a daily radiation treatment, the prostate was found to vary in position by up to 2.5 cm left/right, 2.3 cm anterior/posteriorly, and 1.5 cm superiorly/inferiorly – although most were of much smaller magnitude [38]. Many centers in the United States now perform image-guided radiation treatment, using CT scans, fiducial markers (imaged with kilovoltage on-board imaging), or ultrasound to ascertain the location of the prostate prior to radiation treatment, therefore substantially reducing treatment setup error [39]. A potentially more difficult issue is the movement of the prostate during treatment, while the patient is on the treatment table and radiation is being delivered. This movement can be as much as 1 cm or greater and is unpredictable from patient to patient and from day to day [40, 41]. As mentioned above, use of prostate balloons can mitigate this motion. The need to radiate a larger area than the actual cancer to compensate for interfraction and intrafraction movement of the prostate means that parts of the nearby organs may also receive large doses of radiation treatment. For prostate cancer, these organs are the bladder and rectum, and radiation to these structures likely explains the long-term morbidity seen in some patients.

Similar to conventional radiation therapy, stereotactic radiation targets the entire prostate to a high dose of radiation. However, stereotactic radiation, with its ability to account for prostate interfraction and intrafraction movement, allows for reduction of the margin around the target, therefore reducing the amount of bladder and rectum irradiated [42]. Radiation planning studies comparing intensity-modulated radiation therapy (IMRT) to stereotactic radiation using the Cyberknife system showed that the latter can deliver a higher dose within the prostate, while reducing dose to the bladder and rectum [35, 42]. Therefore, stereotactic radiation holds promise for potentially increasing the effectiveness of treatment while reducing treatment-related toxicity.

Most of the currently published clinical data on stereotactic radiation for prostate cancer involve radiation delivery using the Cyberknife system. Cyberknife® (Accuray, Inc., Sunnyvale, CA) is a dedicated stereotactic radiation machine where a linear accelerator is mounted on a computer-controlled, six-joint, robotic arm [34, 43, 44]. The autonomous robotic arm allows delivery of radiation from coplanar and non-coplanar angles. The treatment table is also computer-controlled and has six degrees of freedom to allow for patient positioning adjustments. Prior to treatment, three to five fiducial markers (usually made of gold, 3–6 mm in length) need to be placed in the prostate via transrectal ultrasound by the urologist or radiation oncologist. Using a pair of diagnostic quality digital X-ray imaging devices, the Cyberknife system monitors the position of these fiducial markers (and thus the radiation target); the fiducial marker positions as detected on the x-rays are automatically interpreted by the system leading to adjustments to radiation delivery in real time [33, 42.]

Stereotactic radiation to the prostate can also be delivered using gantry-based (standard) linear accelerators (Linac-based

stereotactic radiation) with sophisticated image-guidance technology. Examples of such devices include the Novalis (BrainLab, Inc., Germany, Sweden), Trilogy (Varian, Inc., Palo Alto, CA), and Axesse (Elekta, Inc., Norcross, GA) treatment units [33, 34, 36]. The TomoTherapy Hi-Art System (TomoTherapy, Madison, WI), which uses a ring-shaped gantry delivering helical radiation therapy and on-board image guidance with megavoltage CT, can also be used.

Ideally, stereotactic radiation therapy, which uses a small margin around the prostate, needs to account for the intrafraction motion of the prostate [45, 46]. When a delivery system is used that cannot assess and/or track the prostate location in real-time during treatment, considerations for using immobilization devices such as the rectal balloon may be worthwhile.

Biologic Rationale for Hypofractionation

In conventional prostate cancer radiation therapy, 1.8–2 Gy of radiation is delivered each day for a total treatment duration of 8–9 weeks. Hypofractionation is the delivery of higher doses of radiation in each treatment, reducing the number of overall treatments and thus the overall treatment time course. Radiation treatment, and decisions about dosing and fractionation, takes advantage of the differential sensitivities of the tumor versus adjacent organs to radiation in order to maximize the therapeutic ratio (i.e., maximize tumor kill while minimizing toxicity) [36]. For most tumors, low dose of radiation per treatment accomplishes this. However, multiple studies and radiobiologic calculations have suggested that prostate cancer may be different [47–49]. Compared to the adjacent organs (such as bladder and rectum), prostate cancer may be more sensitive to high doses of radiation per treatment. In radiobiology, the sensitivity of tissue (or tumor) to radiation dose fractionation is expressed as the α/β ratio. While most cancers are thought to have an α/β ratio of approximately 10 Gy, and therefore standard fractionation is used, the α/β ratio for prostate cancer may be as low as 1.5 Gy [36]. Since this value is less than the typical α/β value of 2–3 assigned to normal tissues, these data suggest that, for prostate cancer, hypofractionation may be a strategy to maximize the therapeutic ratio.

Extreme hypofractionation is the delivery of very large doses of radiation each day. An older British study treated 209 patients from 1962 to 1984 with nonmetastatic prostate cancer to 36 Gy in six treatments (6 Gy/fraction) [50]. This was done prior to the era of 3D radiation planning, intensity-modulated radiation therapy, or stereotactic radiation. With 22 years of follow-up, long-term disease control and morbidity outcomes were similar to historical controls from the same era – confirming its safety and potential effectiveness.

More recently, using high-dose rate brachytherapy (HDR), similarly high doses of radiation could be delivered to the prostate. Long-term disease control outcomes using HDR demonstrate the clinical efficacy of extremely hypofractionated radiation dosing schedules for the treatment of prostate cancer. Martinez et al. reported the results from 248 patients treated with HDR at William Beaumont Hospital (38 Gy in four treatments) and California Endocurietherapy Center (42 Gy in six treatments) for low- and intermediate-risk prostate cancer [51]. With a median follow-up of over 4 years, the 5-year biochemical control rate was 88–91 % and similar to a comparison cohort of patients treated with low-dose-rate brachytherapy at William Beaumont Hospital. Similar results were observed by Yoshioka et al., in a series of 112 patients with localized prostate cancer treated with HDR brachytherapy to a total dose of 54 Gy in nine treatments within 5 days [52]. At a median follow-up of 5.4 years, the local control rate was 97 %. Five-year biochemical failure-free survival for patients with low-, intermediate-, and high-risk disease were 85, 93, and 79 %, respectively.

While HDR is a treatment modality that can deliver high doses of radiation very accurately to the prostate, it is an invasive procedure with associated risks of infection, bleeding, and anesthesia. It requires hospital admission with narcotic pain medication to help patients manage the pain from indwelling catheters. With development of stereotactic radiation technology, this could potentially be a noninvasive method of delivering the same dosing regimen as HDR [53]. To deliver high doses of radiation externally requires a system with high precision of dose delivery, which is capable of adjusting for interfraction and intrafraction target motion. The stereotactic radiation systems described above have these capabilities. The technologic advances in radiation therapy – and development of these systems – have now made extremely hypofractionated radiation treatment for prostate cancer clinically feasible.

Stereotactic Radiation as Monotherapy for Low- and Intermediate-Risk Prostate Cancer

Stereotactic radiation for low- and intermediate-risk prostate cancer has been a subject of intense study recently, with ongoing prospective trials accruing and multiple publications of institutional experiences. (Tables 64.2 and 64.3)

Boike et al. conducted a phase I dose escalation study of patients with low- to intermediate-risk prostate cancer [54]. Cohorts of 15 patients were successively treated to doses of 45, 47.5, and 50 Gy in five treatments, using LINAC-based stereotactic radiation with rectal balloon to minimize prostate motion. Median follow-up was 30 months. Biochemical control was achieved by 100 % of patients.

Table 64.2 Published studies on stereotactic radiation therapy for prostate cancer and disease control outcomes

First author	Study design	Stereotactic system	*N*	Risk group	Dose fractionation	Median follow-up (year)	Disease control measure	Death from prostate cancer
Prospective trial								
Boike [54]	Phase I	LINAC	45	Low and intermediate	45 Gy–50 Gy/5 fx	2.5	Biochemical control 100 %	X
Tang [66]	Phase I/II	LINAC	30	Low	35 Gy/5 fx	1	X	X
King [56]	Phase II	Cyberknife	41	Low and intermediate	36.25 Gy/5 fx	2.75	Biochemical control 100 %	–
Madsen [55]	Phase I/II	LINAC[a]	40	Low	33.5 Gy/5 fx	3.4	4-year FFBF 90 %	–
Prospective or retrospective series								
Freeman [59]	Combined analysis (Florida retrospective and Stanford prospective)	Cyberknife	41	Low	36.25 Gy/5 fx (Stanford), 35 Gy/5 fx (Florida)	5	bPFS 93 %	–
Friedland [58]	Single-institution	Cyberknife	112	Low, intermediate, and high	35 Gy/5 fx	2	Biochemical control 97 %	0
Katz [60]	Single-institution	Cyberknife	50	Low (69 %), intermediate (27 %), and high (4 %)	35 Gy/5 fx	2.5	Biochemical control 100 %	0
			254		36.25 Gy/5 fx	1.4	Biochemical control 98 %	X
Townsend [65]	Single-institution	Cyberknife	37	–	35 Gy or 37.5 Gy in 5 fx	1	–	X
Bolzicco [57]	Single-institution	Cyberknife	45	Low (49 %), intermediate (51 %)	35 Gy/5 fx	1.7	Biochemical control 100 %	0
Jabbari [46]	Single-institution	Cyberknife	20	Low or intermediate	38 Gy/4 fx	1.5	Biochemical control 100 %	0

X follow-up too short for meaningful results, *LINAC* linear accelerator, *Fx* fraction, *FFBF* freedom from biochemical failure, *bPFS* biochemical progression free survival
[a]Patients treated in flex-prone position

Table 64.3 Acute and late GI and GU toxicity from stereotactic radiation therapy for prostate cancer

	Acute (%)				Late (%)			
First author	Grade 2 GI	Grade 3 GI	Grade 2 GU	Grade 3 GU	Grade 2 GI	Grade 3 GI	Grade 2 GU	Grade 3 GU
Prospective								
Boike	2.5[a]	0[a]	18[a]	2[a]	–	–	–	–
Tang [66]	7	0	13	0	[b]	[b]	[b]	[b]
King [56]	–	–	–	–	15	0	24	5
Madsen [55]	13	0	21	2	8	0	20	0
Retrospective								
Freeman [59]	–	–	–	–	2.5	0	7	2.5
Friedland [58]	–	–	–	–	–	–	–	–
Katz [60] (35 Gy)	4	0	4	0	0	0	2	0
(36.25 Gy)	4	0	5	0	3	0	6	1
Townsend [65]	0	0	2	3	–	–	–	–
Bolzicco [57]	24	0	11	0	2	0	0	2
Jabbari [46]	17	0	39	0	3	0	8	5

GI gastrointestinal, *GU* genitourinary

[a]Worst toxicity was reported and did not distinguish between acute and late

[b]The percentage of patients with grade 2 or grade 3 GU and GI symptoms at 3 and 6 months were no higher than baseline

Madsen et al. published results of 40 patients with low-risk prostate cancer from the phase I/II trial of Stereotactic Hypofractionated Accurate Radiotherapy of the Prostate (SHARP) [55]. Patients were treated in the flex-prone position from 2000 to 2004 and received 33.5 Gy in five treatments. After a median follow-up of 41 months, three biochemical failures were seen. The 48-month actuarial freedom from biochemical relapse rate was 90 %.

A Stanford phase II trial treated patients with low- and intermediate-risk prostate cancer after 2003 [56]. Patients received 36.25 Gy in five treatments. In an interim report of 41 patients with median follow-up of 33 months, no patient experienced biochemical failure. The median PSA nadir was 0.32 ng/mL (range 0.03–2.65). Multiple other studies have confirmed that patients treated with stereotactic radiation therapy achieve a similarly low PSA nadir [55, 57, 58]. In a follow-up report pooling Stanford patients with long follow-up with patients from Naples, Florida (who received 35 Gy in five treatments), 5-year biochemical progression-free survival rate for patients with low-risk disease was 92.7 % [59].

Large retrospective series have confirmed the results from these trials. In a study of 304 patients treated at Winthrop University Hospital from 2006 to 2008, two dosing schedules were used. The first 50 patients received a total of 35 Gy (in five treatments), while the subsequent 254 patients received 36.25 Gy. Four patients experienced biochemical failure (two with low-risk and two high-risk disease) [60]. Friedland, reporting the full experience of patients treated in Naples, Florida, analyzed results from 112 patients with median follow-up of 24 months [58]. Three experienced biochemical failure.

Rates of acute and late gastrointestinal and genitourinary toxicity are similar to those reported for external beam radiation (photon) or proton radiation (Table 64.1). Acute grade 2 gastrointestinal (GI) toxicity has been reported at 0–24 % in different series, and grade 2 genitourinary (GU) toxicity at 2–39 % (Table 64.3). Late grade 2 GI toxicity ranged from 0 to 15 %, and GU toxicity 0–24 %. Grade 3 GI and GU toxicity is rare. It is important to note that these results are from early clinical experiences using stereotactic radiation for prostate cancer. With increased experience using this technology, toxicity rates will likely be lower.

Several studies examined patient-reported quality of life. In the SHARP study, median American Urological Association (also called the International Prostate Symptom Score) score measuring urinary symptoms increased at 1 month following treatment but returned to baseline values by subsequent follow-up time points [55]. Similarly, in the Stanford trial, the AUA score worsened by 3 months but improved to be better than baseline at 1- and 2-year time points [56]. This initial increase in urinary symptoms with subsequent recovery to baseline has also been reported by two large series and appears to be a consistent finding [58, 60]. The Stanford trial reported that patient-reported rectal symptoms, measured by the Expanded Prostate Cancer Index Composite (EPIC), showed increased rectal symptom at 3 months, and about 50 % of patients continued to report "very small/small problem" at 1 and 2 years. In contrast, Katz et al., using the same instrument, reported that bowel symptoms returned to baseline after an initial worsening [60]. Using a rectal assessment score, Friedland et al. reported resolution of symptoms by 4 months [58].

Patient reported sexual function has also been examined. Using the Sexual Health Inventory for Men (SHIM), Friedland reported decreased scores during treatment but return to baseline within 1 month [58]. Of patients who

Table 64.4 Published dose-fraction schedules for stereotactic radiation therapy in prostate cancer

Total dose (Gy)	Number of fractions	Dose per fraction (Gy)	Biologically equivalent dose (Gy) (when given in 2 Gy/fraction)[a]
33.5	5	6.7	78
35	5	7	85
36.25	5	7.25	91
37.5	5	7.5	96
38	4	9.5	119

[a]Assuming α/β ratio of 1.5 for prostate cancer

reported erectile function sufficient for sexual intercourse at baseline, 82 % retained this ability at 1 year and 81 % at 2 years. Similar rates were reported in the Katz series (87 % patients maintained potency at median follow-up of 18 months) [60] and by the SHARP trial (77 % maintained potency at median follow-up of 30 months) [55]. Using the EPIC instrument, Wiegner reported sexual function results in 32 patients from the Stanford trial with at least 12 month follow-up [61]. This study demonstrated a gradual decline in the sexual domain summary score up to 48 months of follow-up. Age was found to be an important factor in patient's ability to maintain sexual function after treatment. For patients younger than 70 years, 60 % maintained satisfactory erectile function; in contrast, only 12 % of patients ≥70 years did ($p = 0.008$). No significant association was found between radiation dose to the penile bulb and sexual function.

As described above, there are currently multiple dose fractionation schedules for stereotactic radiation being used for prostate cancer treatment (Table 64.4). The biologically equivalent dose of these extremely hypofractionated treatment regimens, when compared to conventionally fractionated radiation given at 2 Gy per day, all represent dose-escalated radiation therapy. Some of the regimens may represent delivery of doses much higher than currently possible with conventional (nonstereotactic) radiation technology. The available literature shows that these schedules have promising results in disease control and toxicity, but the comparative effectiveness of the different schedules will require further study. In addition, some of the treatment regimens use "heterogeneous" dose planning, intentionally planning radiation treatment to mimic the doses given by HDR brachytherapy, with doses inside parts of the prostate (such as the peripheral zone) significantly higher (up to 40 %) than the dose to the periphery of the prostate [34, 46, 53]. The rationale for this type of planning and delivery is to deliver even higher radiation doses to within the prostate. Other institutions plan stereotactic radiation using "homogeneous" dosing, in order to deliver a relatively even dose to all parts of the prostate [34, 56, 58]. Both types of planning are currently being investigated in multicenter phase II trials. Whether heterogeneous or homogeneous dosing results in differential disease control and/or toxicity rates awaits further study as well.

Stereotactic Radiation as a Boost for Intermediate- and High-Risk Prostate Cancer

For patients with intermediate- or high-risk prostate cancer, where the risk of extra-prostatic disease extension is higher, conventionally fractionated radiation therapy could be used to treat a larger area around the prostate and seminal vesicles, and stereotactic radiation used for additional high dose given to the prostate ("boost" radiation dose). Several retrospective series have been published, describing the tumor control efficacy and toxicity of this combination treatment regimen.

The largest published series included 73 intermediate- and high-risk patients treated at Winthrop University Hospital (Mineola, NY) with external beam radiation to 45 Gy (1.8 Gy per fraction) plus stereotactic radiation boost ranging from 18 Gy (in three fractions) to 21 Gy (in three fractions) [62]. Thirty-six patients (49 %) received androgen deprivation therapy also for a median duration of 4.8 months. With a median follow-up of 33 months, the 3-year actuarial biochemical control rates for intermediate-risk patients was 89.5, and 77.7 % for high-risk patients. Overall, 6.8 % of patients experienced acute grade 2 urinary toxicity, and 6.7 % grade 2 rectal toxicity; there was no acute grade 3 toxicity. Late grade 2 urinary and rectal toxicity rates were 4.1 and 8.2 %, respectively; one patient (1.4 %) experienced late grade 3 urinary toxicity.

In another series, 50 patients with mainly intermediate- and high-risk disease were treated with 64 Gy of conventionally fractionated radiation, followed by stereotactic radiation boost of 10–16 Gy in two fractions [63]. Thirty-three patients also received androgen deprivation therapy. Five-year biochemical disease-free survival was 98 %. The 5-year rates of grade ≥2 GI and GU toxicity-free survival were 72 and 82 %, respectively.

Results from additional smaller series of patients have shown results consistent with the above [46, 64, 65].

Take Home Messages

Reduced overall irradiation to nontarget normal tissues remains the primary appeal of proton therapy. To date, a direct comparison of proton- and photon-based treatments for prostate cancer has not been performed. Although the rates of acute and late toxicity associated with proton therapy are encouragingly low (along with disease-control rates appropriate for the doses delivered), nonrandomized inter-study comparisons with published photon series present challenges. Moreover, long-term data regarding hip fracture incidence and erectile function following proton irradiation are not yet available. In the face of highly conformal external beam photon therapy and brachytherapy, the debate about cost-effectiveness of protons as a radiotherapy option for

prostate cancer will continue. Optimization of proton therapy for prostate and other tumors remains an active area of investigation that may provide new fuel for this debate.

Stereotactic radiation for prostate cancer holds promise to be a radiation treatment modality that increases efficacy (by delivering a high dose of radiation each day) and decreases long-term toxicity (by taking advantage of the radiobiologic differences between prostate cancer and adjacent organs and by the precise radiation delivery using stereotactic technology) compared to standard fractionation radiation therapy. Early results appear consistent with these hypotheses, and data from prospective trials continue to mature. Stereotactic radiation therapy represents a dramatic shift in the way radiation treatment is delivered for prostate cancer, and shortens treatment time from 8–9 to 1 week. With longer follow-up, if stereotactic radiation therapy is shown to be similar or better than other treatment modalities in terms of disease control efficacy and long-term toxicity, then the noninvasive nature and short treatment duration of this treatment may make it an attractive option [36].

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