Stereotactic Radiosurgery for Prostate Cancer

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Preface

There has been a significantly increased interest in the use of stereotactic body radiosurgery (SBRT) for the treatment of prostate cancer. With the availability of carefully designed treatment plans, tight margins around the clinical target volume, image-guided therapy, and integrating MRI into treatment planning and target delineation, opportunities now exist to safely target high doses of irradiation condensed into a short treatment schedule. Single-institution experiences have been published, demonstrating excellent PSA relapse-free survival outcomes using SBRT for clinically localized prostate cancer. Currently, several randomized trials are ongoing comparing SBRT to either conventionally fractionated external beam radiotherapy or moderately hypofractionated regimens, and these experiences will certainly provide key information as to the role of SBRT in the management of various disease states of prostate cancer.

This book is unique in that it is dedicated exclusively to the role of SBRT in the management of prostate cancer and focuses on the selection criteria for SBRT, delineation of the prostate contour in the most optimal fashion, and safe treatment delivery using tight normal tissue dose-volume constraints—all to minimize long-term toxicity. There are important discussions related to treatment planning considerations as well as the management of organ motion and use of imaging to design optimal dose-volume histogram constraints for target and normal tissue to further reduce toxicity. Chapters are devoted to summarizing expected tumor control outcomes for low-, intermediate-, and high-risk disease and how these compare to established outcomes with conventionally fractionated treatment. Finally, there is discussion regarding what we know currently based on the published literature of expected acute and long-term toxicity and the quality of life impact SBRT has on the treated patient.

This area of radiation oncology is rapidly evolving and the insights here on SBRT will hopefully provide valuable information to the reader.

New York, USA — Michael J. Zelefsky

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1 Optimizing Selection of Patients for Prostate SBRT: Overview of Toxicity and Efficacy in Low, Intermediate, and High-Risk Prostate Cancer

Amar U. Kishan and Christopher R. King

1.1 Introduction

Radiotherapy (RT) has long been considered a standard treatment option for localized prostate cancer (PCa). Stereotactic body radiotherapy (SBRT)—a unique form of radiotherapy in which a small number ($\leq$5) of fractions, each of comparatively high dose, are delivered to the target volume using highly conformal techniques to minimize dose to adjacent organs-at-risk—is primed for use in PCa, given that classical radiobiology analyses have suggested that PCa appears to be particularly sensitive to large doses of radiation per fraction. The clinical evidence supporting SBRT in the treatment of low- and intermediate-risk PCa is predominantly derived from single-institution prospective studies, multi-institutional phase I/II trials, and pooled consortium data synthesizing many of these reports [1]. As a result of the promising biochemical recurrence-free survival (BCRFS) outcomes of these studies, the American Society for Therapeutic Radiology and Oncology (ASTRO) model policy update in 2013 recognized SBRT as an alternative to conventionally fractionated radiotherapy for PCa, noting "SBRT could be considered an appropriate alternative for select patients with low to intermediate risk disease" [2]. Since 2014, the National Comprehensive Cancer Network (NCCN) guidelines have included the following statement: "extremely hypofractionated image-guided IMRT/SBRT regimens (6.5 Gy per fraction or greater) are an emerging treatment modality with single institutional and pooled reports of similar efficacy and toxicity to conventionally fractionated regimens. They can be considered as a cautious alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise [for low- and intermediate-risk PCa]" [3].

In this introductory Chapter, we will focus on the optimal selection of patients for prostate SBRT based on NCCN risk grouping and anatomical characteristics and review the evidence for its safety and effectiveness.

1.2 Brief Overview of Risk Stratification and a Historical Perspective

Treatment decisions in the management of PCa are often driven by pre-intervention risk stratification schemes, such as the one presented in the NCCN guidelines for PCa [3]. The modern, five-tiered risk stratification scheme is adapted from a three-tiered scheme initially proposed in 1998 on the basis of 5-year BCRFS rates in a cohort of 1872 men treated between January 1989 and October 1997 with radical prostatectomy,

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Table 1.1 Prostate cancer risk stratification

Risk Group	Criteria
Very Low	T1c, GS $\leq$ 6, PSA $<$ 10 $<$3 cores + $\leq$ 50% cancer in any core PSA density $<$0.15 ng/mL/g
Low	T1-2a, GS $\leq$ 6, PSA $<$ 10
Intermediate	T2b-T2c, GS 7, PSA 10–20
High	T3a, GS 8–10, PSA $>$ 20
Very High	T3b–T4 Primary GP 5 $>$4 cores with GS 8–10

brachytherapy or external beam RT [4]. The current five-tiered scheme is presented in Table 1.1; an in-depth review of the evidence supporting this scheme is beyond the scope of the present Chapter. For a variety of practical considerations, the first two prospective investigations of SBRT for PCa in North America—out of Virginia Mason [5] and Stanford University [6]—enrolled patients with low-risk disease. As the results of these studies matured, the inclusion criteria for other prospective single-institution and multi-institutional trials broadened to include intermediate-risk disease. However, it is important to note that the clinical inception of prostate SBRT predates these risk-stratification schemes by several decades and has its roots in 1962. At that time, Lloyd-Davies et al. were inspired by the use of hypofractionation to facilitate the incorporation of hyperbaric oxygen treatments and began treating PCa with a regimen of 55 Gy in 12 fractions delivered over 28 days [7]. They subsequently adopted a regimen of 36 Gy in six fractions over 18 days [8]. Ultimately, they reported five- and 10-year overall survival rates of 54 and 18% among 232 patients, comparable to conventional RT outcomes at the time [9]. Despite the fact that ^{60}Co-based teletherapy was employed in 49% of cases, only two instances of rectal strictures were seen. Consistent with accrual in a pre-PSA screening era, 145 of these 232 patients (62.5%) had locally advanced disease, and 52 (22.4%) had poorly-differentiated lesions, and only 117 (50.4%) had well-differentiated lesions. It is therefore likely that many of these patients would have been classified as having high- or at least intermediate-risk PCa in modern times. Nonetheless, the favorable outcomes in this historical study, combined with emerging radiobiological data (reviewed in the next Chapter), were the impetus for investigating SBRT in a low-risk setting in the modern era.

1.3 Definitive Treatment for Low and Intermediate Risk Prostate Cancer: Review of the Clinical Evidence

Madsen et al. from Virginia Mason reported the first modern series of SBRT for PCa in 2007, utilizing a linear accelerator (LINAC) to deliver 33.5 Gy in five 6.7 Gy fractions to 40 patients with low-risk PCa (Table 1.2) [5]. The 4-year actuarial BCRFS was 90% and rates of acute Radiation Therapy Oncology Group (RTOG) grade 1-2 genitourinary (GU) and gastrointestinal (GI) toxicities were 48.5 and 39% respectively; one patient had acute grade 3 GU toxicity. Late grade 1-2 GU and GI toxicities were seen in 45 and 27% of patients, respectively, with no late grade 3 toxicity. Erectile dysfunction (ED) developed in 33% of patients with normal erectile function at baseline. King et al. from Stanford University subsequently reported the first SBRT series utilizing the CyberKnife system (Accuray, Sunnyvale, CA), treating 67 patients with low-risk PCa with 36.25 Gy in five 7.25 Gy fractions [6, 10]. The initial 21 patients received daily fractions, but due to observed GI toxicity, a q.o.d. fractionation scheme was subsequently tested. The 4-year BCRFS rate was 94%, late RTOG grade 2 GU and GI toxicities were seen in 5 and 2% of patients, respectively, and late RTOG grade 3 GU toxicities were seen in 3.5%. The incidence of ED increased from 38% at baseline to 71% at a median of nearly 3 years after treatment [11, 12].

There have since been multiple series reporting results for treating patients with SBRT. Short-term efficacy and toxicity results of single institution and small multi-institutional studies are presented in Table 1.2. Pooling across all studies, outcomes for a total of 2926 patients treated with SBRT have been reported. The longest-term published data have been reported by Katz et al. in a series of manuscripts. The

Table 1.2 Efficacy and toxicity results for SBRT monotherapy

References	# patients	Follow-up (years)	Regimen	Risk profile	BCRFS	Physician-reported toxicity
Single institution series or multi-institutional trials						
Virginia Mason [5]	40	3.4	33.5 (6.7 × 5)	Low: 100%	4-Year: 90%	RTOG Acute GU 1–2: 48.5% 3: 2.5% GI 1–2: 39% Late GU 1–2: 45% GI 1–2: 27%
Stanford [6, 10]	67	2.7	36.25 (7.25 × 5)	Low: 100%	3-year: 94%	RTOG Late GU 2: 5%; 3: 3.5% GI 2: 2%
Naples [52]	112	2	35–36 (7–7.2 × 5)	Not reported	Crude: 97.3%	AUA Score Increased from 8.9 to 12.8 acutely, then to baseline by 4 mos RAS Score Increased from 1.8 to 4.6 acutely, then to baseline by 4 mos
Flushing [13, 15, 16, 53, 54]	515	7	35–36.25 (7–7.25 × 5)	Low: 62.9% Int:29.7% High: 7.4%	8-year Low: 93.6% Int: 84.3% High: 65.0%:	RTOG[a] Acute GU 2: 4.4% GI 2:4.4% Late GU 2: 9.6% 3: 1.7% GI 2: 4%
San Bortolo [55, 56]	100	3	35 (7 × 5)	Low: 41% Int: 42% High: 17%	3-year: 94.4%	RTOG Acute GU 2: 12% GI 2: 18% Late GU 2: 3% 3: 1% GI 2: 1%
Erasmus [57, 58]	50	1.91	38 (9.5 × 4); did allow boost to 11 × 4 if visible lesion)	Low: 60% Int: 40%	2-year: 100%	RTOG Acute GU 2: 15% 3: 8% GI 2: 12% 3: 2% Late GU 2: 10% 3: 6% GI 2: 3%
UTSW Trial [20–23]	91	4.5	50 (10 × 5) in 67.7%	Low:36.3% Int: 63.7%	5-year: 98.6%	CTCAEv3.0 Acute GU 2: 22.0% GI 2:20.9% 3: 1.1% 4: 1.1% Late GU 2: 20.9% 3: 4.4% 4 1.1% GI 2: 13.2% 3: 4.4% 4: 2.2%

(continued)

Table 1.2 (continued)

References	# patients	Follow-up (years)	Regimen	Risk profile	BCRFS	Physician-reported toxicity
Korea Institute of Radiological and Medical Sciences [59]	44	3.3	32–36 (8–9 × 4)	Low: 11.4% Int: 22.7% High: 65.9%	Crude: Low: 100% Int: 100% High: 90.9%	CTCAE v 3.0 Acute GU 2: 13.6% GI 2: 9.1% Late GU 2: 6.8% GI 2: 11.4%
United States Multi-Center Trial [60]	45	3.7	35–36.25 (7–7.25 × 5)	Low: 100%	3-year: 97.7%	CTCAEv4.0 Acute GU 2: 19% GI 2: 7% Late GU 2: 17% 3: 2.2% GI 2: 7% 3: 4.4%
UCSF [61]	20	1.53	38 (9.5 × 4)	Low: 45% Int:45% High:10%	Crude: 100%	CTCAE v 3.0 Acute GU 2: 45% GI 2: 17%[b] Late GU 2: 8% 3: 5% GI 2: 3%
Georgetown [62, 63]	100	2.3	35–36.25 (7–7.25 × 5)	Low: 37% Int:55% High: 8%	2-year: Low: 100% Int: 100% High: 87.5%	CTCAEv3.0 Acute GU 2: 35% GI 2:5% Late GU 2: 17% 3: 1% GI 2: 1%
Sunnybrook [64]	84	4.58	35 (7 × 5)	Low: 100%	5-year: 98%	CTCAE v 3.0 Acute GU 2: 19% 3: 1% GI 2:10% Late GU 2: 5% GI 2: 7% 4: 1%
Humanitas [65, 66]	90	2.25	35 (7 × 5)	Low: 58.9% Int: 41.1%	Crude: Low: 100% Int: 95%	CTCAE v 4.0 Acute GU 2: 32.2% GI 2: 6.6% Late GU 2:2.2%
Twenty first century oncology [67]	102		40 (8 × 5)	Low: 100%		CTCAE v 3.0 Acute GU 3: 0.98%
Genesis Healthcare [68]	79	3.5	38 (9.5 × 4)	Low: 50.6% Int: 49.4%	5-year: Low: 100% Int: 92%	CTCAE v 3.0 Acute GU 2: 10% GI 2: 0% Late GU 2: 9% 3: 6% GI 2: 1%

(continued)

Table 1.2 (continued)

References	# patients	Follow-up (years)	Regimen	Risk profile	BCRFS	Physician-reported toxicity
Salamanca [69, 70]	45	1.15	27.4–28.25 (5.48–5.65 × 5)	Low: 28.9% Int: 37.8% High: 33.3%	Crude: 97.8%	CTCAE v 4.0 Acute GU 2: 22.72 GI 2: 20.45% Late GI 2: 5%
The Catholic University of Korea [31]	45	5.3	36 (7.2 × 5)	Low: 13.3% Int: 57.8% High: 28.9%	5-year: 89.7%	CTCAE v 4.0 Acute GU 2: 4.4% GI 2: 4.4% Late GU 2: 4.4% 3: 4.4% GI 2: 4.4%
Royal Marsden Hospital [71]	51	1.21	36.25 (7.25 × 5)	Low: 19.6% Int: 68.6% High: 11.8%	1-year: 100%	RTOG Acute GU 2:22% GI 2: 14%
Virginia Hospital Center [72]	102	4.3	35–40 (7–8 × 5)	Low: 36.3% Int: 54.9% High: 7.8%	Crude: 100%	RTOG Late GU 2:9.9% GI 2: 3%
Gyeongsang National University [73]	39	2.5	37.5 (7.5 × 5)	Low: 41% Int: 59%	3-year: 93.9%	CTCAE v 4.0 Acute GU 2: 25.6% GI 2: 30.8% Late GU 2:10.3% GI 2: 7.7% 3:5.2%
Taipei [74]	31	3	37.5 (7.5 × 5)	Int: 48.4% High: 51.6%	3-year Int: 100% High: 82%	CTCAE v 4.0 Acute GU 2: 22.6% GI 2: 3.2% Late GU 2:16.2%
Multi-center US [75]	66	3	37 (7.4 × 5)	Low: 49% Int: 51%	3-year Low: 100% Int: 100%	CTCAE v 4.0 Acute GU 2: 23% GI 2: 4% Late GU 2: 9% GI 2: 5%
Philadelphia [76]	150	3.8	35–37.5 (7–7.5 × 5)	Low: 44.7% Int: 34.0% High: 21.3%	Crude Low: 98.5% Int: 96.1% High: 87.5%	RTOG Acute GU 3 3.3% GI 3: 0.3%
Gilwice [77]	400	1.25	36.25 (7.25 × 5)	Low: 53% Int: 47%	1-year Low: 97.7% Int: 97.9%	RTOG Acute GU 3 0.5% GI 3: 0.3%

(continued)

Table 1.2 (continued)

References	# patients	Follow-up (years)	Regimen	Risk profile	BCRFS	Physician-reported toxicity
Olsztyn [78]	68	2	33.5 (6.7 × 5)	Low: 10% Int: 90%	2-year Low: 100% Int: 100%	RTOG Acute GU 2: 35.3% GU 3 1.5% GI 3: 10.3% Late GU 2: 11.8% GI 2: 4.4%
Kuopio [79]	240	1.9	35–36.25 (7–7.285)	Low: 22% Int: 27% High: 51%	2-year Low: 100%, Int: 96.6% High: 92.8%	CTCAE v 4.0 Acute GU 2: 1.4% GI 2: 0.4%
Duke [80]	60	2.3	37 (7.4 × 5)	Low: 33% Int: 67%		CTCAE v 4.0 Acute GU 2: 25% GI 2: 5% Late GU 2: 6.7% GI 2: 8.3%
Messina [81]	21	1.8	38 (9.5 × 4)	Low: 43% Int: 57%		CTCAE v 3.0 Acute GU 2: 0 GI 2: 4.8% Late GU 2: 4.8% GI 2: 4.8%
Cleveland Clinic [82]	24	2.1	36.25 with boost to 50 (7.25 × 5 with boost of 10 × 5)	Int: 46% High: 54%	2-year crude Int: 100% High: 84.6%	CTCAE v 3.0 Acute GU 2: 38% GI 2: 0% Late GU 2: 8% GI 2: 8%
Western Australia [83]	45	1.5	36.25 (7.25 × 5)	Low: 25% Int: 62% High: 13%		CTCAE v 3.0 Acute GU 2: 11.1% GI 2: 2.2%
Total	2926					
Pooled analyses						
Consortium [17, 84]	1100	3	36.25 (median)	Low: 58% Int:30% High:11%	5-year: Low: 95% Int:84% High:81%	Reported as EPIC QOL decline, see text
RSS Registry [85]	437	1.67	36.25 (most common)	Low: 43.2% Int:49.25 High:7.6%	Low: 99% Int:94.5% High:89.8%	CTCAE v 3.0 Acute GU 2: 4% GI 2: 1% Late GU 2: 8% GI 2: 2%

(continued)

Table 1.2 (continued)

References	# patients	Follow-up (years)	Regimen	Risk profile	BCRFS	Physician-reported toxicity
RPCR [18]	2000[a]	2	35–40 Gy in 4–5 fractions	Low: 41% Fav-Int:6% Unfav-Int: 25% High:11%	Low: 99% Fav-Int:97% Unfav-Int: 85% High:87%	CTCAE v 3.0 Late GI 3: 0.05%

[a]Toxicity data based off 6-year median followup, BCRFS based off 7 year median followup
[b]For GI, Jabbari et al. reported pooled toxicity including 18 additional patients treated with an SBRT boost

7-year BCRFS in a cohort of 477 men (67.9% with low- and 22.1% with intermediate-risk) PCa was 95.6 and 89.6% for low and intermediate-risk groups, respectively [13, 14]. Patients received either 35 Gy in five fractions or 36.25 Gy in five fractions, either daily or every other day. The investigators reported no acute RTOG grade 3–4 toxicity, with late grade 3 GU toxicity in 1.7% of patients. A recent update of this series reported similarly excellent 8-year BCRFS outcomes [15]. Katz subsequently reported the long-term outcomes of 239 men with low-risk PCa (median follow-up of 108 months), all of whom received 35–36.25 Gy in five fractions [16]. The 10-year BCRFS was 93%, with a 10% incidence of grade 2–3 GU toxicity and 4% incidence of grade 2 GI toxicity. EPIC QOL scores declined initially in the bowel and urinary domains, before returning to baseline. EPIC sexual QOL scores continued to decline by about 40%.

Several SBRT consortium and registries have published short-term results. In the most prominent such report, King et al. presented the outcomes for 1100 patients enrolled in eight separate prospective clinical trials (including many in Table 1.2) [17]. Fifty-eight percent of patients had low-risk disease, 30% had intermediate-risk disease, and 11% had high-risk disease. With a median follow-up of 36 months, the 5-year BCRFS was 95, 84, and 81% for low-, intermediate-, and high-risk patients (93% overall). Among the 193 patients with a minimum follow-up of 5 years, the 5-year BCRFS was 99 and 93% for those with low- and intermediate-risk PCa, respectively. Freeman et al. have reported short-term outcomes of 2000 men treated across 45 sites participating in the registry for prostate cancer radiosurgery, 86% of whom received SBRT monotherapy [18]. The 2-year BCRFS was 92%, no late grade 3 GU toxicity was seen, and only one patient (0.05%) developed late grade 3 GI toxicity. Erectile function was preserved in 80% of men less than 70 years old.

Recently, Kishan et al. reported the long-term outcomes of a large consortium of 1644 patients (54.3% with low-risk disease and 45.7% with intermediate-risk disease) with a median-follow-up of 7.2 years [19]. Of note, 297 patients (18.1%) had at least 9 years of follow-up. Fractionation schemes ranged from 33.50–40 Gy in 4–5 fractions. No patients died of PCa. By Kaplan–Meier analysis, 5- and 10-year BCRFS rates were 98 and 94% in the low-risk group and 96 and 90% in the intermediate-risk group. Five patients (0.3%) experienced grade 3 acute genitourinary (GU) toxicities, including urinary retention, hematuria, and frequency. 30 (2%) experienced grade 3 late GU toxicity, including urinary strictures, hematuria, and retention. One late grade 4 GU toxicity (hemorrhagic urethritis) and one late grade 4 gastrointestinal toxicity (fistula-in-ano) were seen.

There have been reports of high toxicity following SBRT, and these mandate critical review. Higher rates of serious toxicity were observed in the UTSW-led multi-institutional phase I/II of dose-escalated SBRT [20–23]. In the phase I portion, patients were sequentially enrolled into three dose echelons (45, 47.5, and 50 Gy in five fractions). Despite particular care to mitigate

toxicity—Fleet enema and rectal balloon placed for each treatment, 4 mg dexamethasome for each treatment, and alpha-adrenergic antagonist usage—one of 14 patients in the 50 Gy dose stratum developed late CTCAEv4.0 grade 4 GI toxicity (ulceration). This was thought to be related to immunosuppressant medication use and 50 Gy was used as the prescription dose for the phase II portion of the trial. However, four of 47 patients developed late grade 3 rectal toxicity in the phase II portion, with another experiencing late grade 4 toxicity (rectal pain requiring colostomy) and another developing acute grade 4 GI toxicity (bleeding Dieulafoy lesion). Three patients developed late grade 3 GU toxicities, and one developed late grade 4 GU toxicity (cystitis requiring ureteroileal diversion). Notably, the preliminary results of the Cleveland Clinic dose-escalation experience suggest that SBRT in 50 Gy in five fractions can be well tolerated with aggressive sparing of certain organs-at-risk, with the caveat that the median followup of the study was only 25 months [24]. The FASTR phase I/II study of SBRT for high-risk PCa (which utilized a dose/fractionation regimen of five once-weekly doses of 8 Gy and 5 Gy to the prostate/proximal SVs and pelvic lymph nodes, respectively) also demonstrated an unexpectedly high rate of GI and GU toxicity; as discussed in the subsequent section, these were likely attributable to technical issues with image-guidance and contouring [25, 26].

Yu et al. performed a retrospective analysis of the Chronic Conditions Warehouse, identifying 1355 patients treated with SBRT and 2670 patients treated with IMRT from 2008 to 2012 [27], while Halpern et al. performed an analysis of the SEER-linked Medicare database to compare toxicity endpoints between 237 men treated with SBRT and 10,715 treated with IMRT between 2004 and 2011 who had at least 1 year of followup detail [28]. Both investigators reported an increased risk of GU toxicity (but not GI toxicity) with SBRT. However, significant methodological issues confound the interpretation and relevance of these findings. Both investigators used billing codes including diagnoses, diagnostic procedures, and therapeutic procedures to populate toxicity outcomes. These likely resulted in an overestimation of toxicity, as underscored by the purported 2-year rate of "urinary incontinence" of 19.9% after IMRT in the Halpern et al. study, which is far higher than incontinence rates reported in any IMRT series. Additionally, the investigators could not distinguish between kinds or degrees of toxicity, and simply being referred for assessment—which may be more frequent for patients treated on prospective trials and/or with an emerging technology—was taken as a surrogate for toxicity [29].

Importantly, several ongoing phase III trials are comparing outcomes between SBRT and more prolonged treatment courses (Table 1.3). Preliminary data from the HYPO-RT-PC trial have been presented in abstract form [30]. Among a cohort of 866 patients with a median follow-up of 4.2 years, Widmark et al. reported no significant differences in the prevalence of physician-reported grade 2+ GU toxicity (5.4% with SBRT vs. 4.6% with conventional fractionation) and GI toxicity (2.2 vs. 3.7%) at the 2-year time point. Patient-reported data also revealed no significant differences in any questionnaire item. There did appear to be transiently worse GU function in the SBRT arm at 1 year, and a small decline in bowel scores at the end of radiotherapy with SBRT (which then normalized). Sexual function was similar after either treatment.

Overall, a synthesis of these data seems to suggest excellent efficacy in both low and intermediate risk PCa patient cohorts. While published long-term data (i.e., >5 year median follow-up) are only available from two centers [15, 31], multi-institutional long-term data have been presented in abstract form [19]. The favorable outcomes suggest a long-term efficacy not only in low-risk PCa, but also in intermediate-risk PCa. Patients and providers alike should not view having NCCN intermediate-risk disease as a disqualification criterion for being a candidate for SBRT.

Table 1.3 Active clinical protocols comparing SBRT with conventional fractionation

Trial identifier	Treatment	Primary outcome(s)
NCT01434290 RTOG 0938	6.25 Gy × 5 vs. 4.3 Gy × 12 Low-risk	1. Proportion of patients with ΔEPIC-bowel score >5 points 2. Proportion of patients with ΔEPIC-urinary score >2 points
NCT01584258 Royal Marsden Hospital/PACE	(a) Laparoscopic prostatectomy vs. 6.25 Gy × 5 (b) 6.25 Gy × 5 vs. 2 Gy × 39 Low- and intermediate-risk (excluding Gleason 4+3)	1. BCRFS at 5-years
ISRCTN45905321 Swedish/HYPO-RT-PC	6.1 Gy × 7 vs. 2 Gy × 39 Intermediate-risk	1. BCRFS at 5 years
NCT01794403 University of Miami/ HEAT	6.25 Gy × 5 vs. 2.7 Gy × 26 Low- and intermediate-risk	1. BCRFS at 2 years
NCT03367702 NRG GU-005	7.25 Gy × 5 vs. 2.5 Gy × 28 Low- and intermediate-risk	1. ΔEPIC-bowel and urinary irritation scores between arms 1. Disease-free survival at 2 years

1.4 Patient Selection

Despite its oncologic efficacy in low- and intermediate-risk disease, not all patients in these risk groups are ideal candidates for SBRT. While a thorough discussion of toxicity following SBRT will be provided in subsequent chapters, we will provide a brief discussion of patient selection factors here. Outcomes following prostate SBRT in patients with large prostate volumes (for example, ≥50 cc) have not been widely reported. It is known from published experiences in the brachytherapy literature that large prostate size is associated with both acute and late genitourinary toxicity in particular [32–34]. To our knowledge, only the Georgetown group has published on toxicity outcomes following SBRT in patients with prostate volumes ≥50 cc [35]. In a small series of 57 such patients (median size 62.9 cc), they reported a significant increase in median AUA score (by 6 points), as well as a 17 point decrement in EPIC bowel scores, at a 1-month time-point following SBRT. Two patients experienced grade 3 GU toxicity, and the 2-year actuarial incidence rates of GU and GI toxicity ≥ grade 2 were 49.1 and 1.8%, respectively. There has historically been concern about brachytherapy following transurethral resection of the prostate (TURP) procedures [36] though with optimal patient selection, that risk might be mitigated significantly [37]. Nonetheless, absent further data, significant caution should be advised when considering SBRT in patients with prior TURPs. To our knowledge, the only published data are from a series of 68 patients treated with high-risk or locally-advanced PCa with SBRT at Tata Memorial Centre [38]. Twelve patients (17%) had prior TURP, and these patients did not have significantly increased risk of higher acute or late GU toxicity. However, median follow-up was only 18 months, and thus far no other centers have published data following TURP. As such, patients with large prostates and prior TURP may not be ideal candidates for SBRT, pending further published reports documenting safety. Similarly, though not rigorously reported or quantified, patients who have significant baseline urinary symptoms may not be ideal candidates for SBRT.

1.5 SBRT for High-Risk Prostate Cancer: Preliminary Results

The vast majority of patients included in the SBRT studies outlined above had low- or intermediate-risk PCa. While the details of SBRT for high-risk PCa will be covered

elsewhere, a brief overview of considerations of SBRT for high-risk PCa are presented here. The series with the longest reported follow-up comes from Katz et al., who recently reported 6-year BCRFS rates of 69% among 52 patients with high-risk PCa who received SBRT alone [39], comparing favorably to published IMRT data [40]. Several other published SBRT reports have included patients with high-risk PCa (see Table 1.2). While the capability to deliver doses as high as 86.4 Gy via conventionally fractionated EBRT is rapidly evolving [41], the BED provided by an initial course of EBRT followed by a brachytherapy boost is much higher, translating into a BCRFS benefit [42, 43] and potentially a systemic control benefit [44]. Successful experiences with HDR brachytherapy boosts in particular [45–47] provided the impetus to explore SBRT as an alternative means of providing dose-escalation. A brief overview of outcomes from published SBRT boost series is provided in Table 1.4. Overall, the data provided in Tables 1.2 and 1.3 indicate that published outcomes data for patients treated with SBRT are limited in scope (319 patients across all studies treated with SBRT monotherapy, and another 275 treated with SBRT boost) and follow-up (ranging from 1 to 7 years). Therefore, SBRT for high-risk PCa should be reserved for clinical trials. Indeed, multiple such trials are open for accrual (Table 1.5).

An open question is whether it is safe to deliver SBRT in the context of elective nodal irradiation. The recently published FASTR trial examined SBRT delivered in five once-weekly fractions of 8 Gy and 5 Gy to the prostate/proximal and PLNs, respectively, in combination with 1 year of ADT for patients with high-risk PCa [25]. Interim analysis showed disappointing toxicity results. Three patients (20%) had late grade 3 GI toxicity (rectal bleeding), and one (6.7%) had grade 4 toxicity (an obstruction requiring partial colectomy in a patient with a history of prior rectal bleeding and rectal incontinence). Of the late GU toxicities, three patients (20%) had worsening grade $\geq$3 ED, and 1 (6.7%) had increased urinary incontinence. As a result of these toxicities, the investigators opted to close the FASTR protocol and initiate the FASTR 2 trial, in which the prostate alone receives 35 Gy in 5 fractions with 18 months of ADT.

However, technical issues related predominantly to image-guidance and contouring issues confound the extrapolation of these toxicity data to other protocols investigating SBRT for high-risk PCa [26]. An ongoing phase II clinical trial at University of California, Los Angeles employs the same prescription doses as FASTR (albeit in q.o.d., rather than once weekly, fractions), with 9 months of ADT. The protocol requires intraprostatic fiducial markers (to guide treatment of both the prostate and the nodes [48]), MRI to guide contouring (unless contraindicated or refused), strict rectal distension criteria, strict bladder filling protocols, intrafraction image guidance, noninclusion of the SVs in the planning target volume (PTV), and physician supervision for each fraction. Early toxicity results of the first 73 patients treated on this protocol have been presented in abstract form [49]. Forty-six patients (63%) received ADT and 23 (32%) received nodal RT. With a median follow-up of 13.8 months, no grade 3 or higher genitourinary (GU) or gastrointestinal (GI) toxicities were seen. For patients receiving nodal radiation, rates of acute grade 1 and 2 GU toxicities were 18.2 and 4.5%; for those not receiving nodal RT, they were 23.5 and 17.6%. Rates of acute grade 1 and 2 GI toxicities were 9.1 and 9.1% with and 11.8 and 3.9% without nodal RT. Late grade 1 and 2 GU toxicities rates with nodal RT were 27.3 and 4.5%; without nodal RT, the rates were 18.6 and 7.0%. Late grade 1 and 2 GI toxicity rates were 13.6 and 13.6% with nodal radiation and 11.6 and 4.7% without it. Mean changes in EPIC urinary and bowel domain scores at 4 months were +0.13 and −4.17 with nodal RT, and +0.79 and −2.97 without it. Mean changes in EPIC urinary and bowel domain scores at 12 months were −1.52 and −5.12 with nodal RT and −1.71 and −5.67 without it. Overall, the receipt of nodal RT had no significant association with either physician- or patient-reported toxicity profiles. Similarly, the receipt of ADT had no significant association with any toxicity parameter. Two patients (2.7%) experienced

Table 1.4 Efficacy and toxicity results for SBRT as a boost to EBRT

References	# patients	Follow-up (years)	Regimen	Risk profile	BCRFS	Physician-reported toxicity
Barcelona [86]	50		10–18 Gy (5–8 × 2) After 64–64.4 Gy	Low: 10% Int: 24% High: 66%	Pooled 5-year BCRFS of 98% across risk groups	RTOG Late GU 2: 12% GI 2: 20% GI 3: 10%
Flushing [39, 87]	45	5	18–21 Gy (6–7 × 3) After 45 Gy	High: 100%[a]	6-year: 69%	CTCAE v 4.0 Late GU 3: 2.3% GI 2: 13.3%
Georgetown [88, 89]	108	4.4	19.5 (6.5 × 3) Before 45–50.4 Gy	Low: 3.7% Int: 41.7% High: 54.6%	Low: 100% Int: 100% High: 89.8%	Used EPIC-26
UCSF [61, 90]	50	3.56	19–21 Gy (9.5–10.5 × 2) After 45 Gy	Int: 29% High: 71%	3-year: 95% 4-year: 90% 5-year: 90%	CTCAE v 4.0 Acute GU 2: 27% GI 2: 10% Late GU 2: 25% 3: 2%
Taiwan [91]	39	3.5	21 Gy (7 × 3) After 45 Gy	High: 100%	4-year: 91.9%	CTCAE v3.0 Acute GU 2: 27% GI 2: 12% Late GU 2: 4%
South Korea [92]	42	4.47	21 Gy (7 × 3) After 45 Gy	Int: 51.3% High: 48.7%	4-year: Int: 100% High: 71.4%	CTCAE v3.0 Acute GU 2: 23% GI 2: 21% Late GU 2: 10.3% GI 2: 12.8%
Total	334					Any Grade≥3[b] Acute GU: 0 GI: 0 Late GU: 1.15% GI: 0

[a]Some patients with unfavorable intermediate-risk disease were included
[b]Omitting the Georgetown series, which did not score physician-reported toxicity (for total at-risk population of 173

biochemical failure; in both cases, the PSA never decreased after SBRT. Preliminary results of a third trial, conducted at Tata Memorial Hospital and delivering 35 Gy in 5 fractions to the prostate and 25 Gy in 5 fractions to the lymph nodes were recently presented [50]. Data from 30 patients, 22 with high-risk disease, were available, and, at a median follow-up of 2.08 years, identified just 1 incidence each of late grade 2 GI and GU toxicity. The 2-year BCRFS was 96.7%.

Overall, these data suggest that the negative outcome in the FASTR trial may not be intrinsic

Table 1.5 Active clinical protocols for high-risk prostate cancer

Trial identifier	Treatment	Primary outcome(s)
NCT01839994 Maria Sklodowska-Curie Memorial Cancer Center[a]	76–78 Gy vs. 50 Gy + 10 Gy × 2 (HDR or SBRT) Minimum of 3 months ADT	1. BCRFS at 3 years
NCT01985828 Advocate Health Care[a]	45–50.4 via EBRT + 7 Gy × 3 Boost, with 6–36 months ADT	1. BCRFS at 5 years
NCT02296229 UCLA	8 Gy × 5 to prostate, ± 5 Gy × 5 to lymph nodes 9 months of ADT allowed	1. BCRFS at 3 and 5 years 2. GU and GI toxicity by CTCAE v4.03 at 4 months through 5 years
NCT01953055 Sunnybrook "SATURN"	8 Gy × 5 to prostate, 5 Gy × 5 to lymph nodes	1. GU and GI toxicity by CTCAE v4.03 at 3 months
NCT02229734 FASTR 2	7 Gy × 5 to prostate 18 months of ADT	1. GU and GI toxicity by CTC at 1 year followup
NCT01664130 Cleveland Clinic	7.25 × 5 with boost of 10 × 5 ADT allowed	1. GU and GI toxicity by CTCAE v4.03 at 1.5–12 months
NCT02853110 Utrecht "Hypo-FLAME"	7 Gy × 5 to whole prostate with 10 Gy × 5 boost to visible lesion	1. GU and GI toxicity by CTCAE v4.03 at 3 months

[a]Protocols also allow for enrollment of patients with lower-risk disease

to an attempt to simultaneously perform SBRT to the prostate and the nodes. In support of this hypothesis, a recent dosimetric analysis pooling data from the FASTR study and a similar trial, the SATURN study, identified rectal dosimetry as a significant predictor of rectal bleeding [51]. This toxicity was much rarer in the SATURN study, which included the seminal vesicles in the lymph node volume (while the FASTR trial included the proximal 1 cm of the seminal vesicles in the 40 Gy volume).

Overall, SBRT for high-risk PCa, with or without nodal radiotherapy, is a promising treatment option but should remain investigational as data from the aforementioned trials mature.

1.6 Conclusions

Technological advances and an appreciation for the unique radiobiology of PCa have in concert led to the successful adoption of SBRT as an effective and safe treatment option for patients with low- and intermediate clinically-localized PCa. The published results of multiple prospective studies and institutional experiences with follow-up in the range of 2–5 years have demonstrated BCRFS rates of 90–100% for low-risk PCa and 84–100% for intermediate-risk PCa, with average incidences of serious GI or GU toxicity (grade$\geq$3 via RTOG or CTCAE) from 0.17–0.28% and 0.61–1.61% for acute and late effects, respectively. Published long-term data (i.e., follow-up >5 years) are limited, but preliminary results of a large consortium study with a median follow-up crossing 7 years indicate a similar efficacy and safety profile at later timepoints for both low- and intermediate-risk patients. These data strongly suggest that SBRT is an effective option not only for low-risk disease, but for intermediate-risk disease as well. For high-risk PCa, ongoing prospective studies indicate promising results, but the data are not yet mature enough to recommend treatment outside the context of a clinical trial. Published data do suggest that unexpectedly high toxicity may be seen with SBRT, but are likely to be related to technical factors associated with delivery or extremes of dose. While the outcomes of randomized trials comparing conventionally-fractionated or moderately-hypofractionated radiotherapy with SBRT are eagerly awaited, SBRT has manifested itself as an excellent treatment option for low- or intermediate-risk PCa.

Conflict of Interest

No conflicts of interest to disclose.

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Treatment Planning Considerations for Prostate SBRT and MRI Based Planning

2

Neelam Tyagi and Margie Hunt

2.1 Introduction

Without question, external beam radiotherapy for prostate cancer is in a period of rapid change and evolution. The radiotherapy community is witnessing a paradigm shift from conventional fractionation schemes with doses as high as 80–86 Gy and durations up to 9 weeks to hypofractionated approaches incorporating moderate (~2.5–4 Gy/fraction) to extreme (~6.5–9 Gy/fraction) fractionation [1–11]. Such techniques are gaining acceptance as being comparable to conventional fractionation both in terms of tumor control and toxicity. Furthermore, multiple trials are underway to determine the feasibility and efficacy of boosting dominant intra-prostatic lesions (DIL) using simultaneous integrated boost (SIB) techniques [12–16]. From a clinical standpoint, hypofractionated radiotherapy methods are an outgrowth of both the favorable radiobiological characteristics of prostate cancer [17–20] and patient convenience. However, without doubt, technological advances including image guided radiotherapy (IGRT) [21, 22], volume modulated arc therapy (VMAT) [23–26], magnetic resonance imaging (MRI) for segmentation and planning [27–30], and anatomic modulators such as bio-absorbable injectable rectal spacers [31–34] are what has made prostate hypofractionated treatment possible.

Of particular importance is the role of MRI in the simulation and planning for prostate stereotactic body radiotherapy (SBRT). Although CT has been the mainstay of radiotherapy planning for nearly 40 years and will likely continue as such for the near future, the superiority of MRI's soft tissue contrast for target and normal tissue segmentation has been appreciated for some time. Multiple studies have demonstrated the value of MRI to visualize the prostate gland and dominant lesions for external beam radiotherapy planning [35–37]. Furthermore, many groups have shown that CT-based segmentations of the prostate are consistently larger (up to 30–40%) than those from MRI [38–40]. The smaller MR-based segmentations result from improved visualization of the prostatic apex and base as well as the tissue planes differentiating the prostate from surrounding soft tissues. Although a strong argument can therefore be made that incorporating MRI decreases over-segmentation of the prostate, a wider transition to combined CT-MRI methods has been hampered by concerns about segmentation errors introduced by mis-registration of the image sets and the changes to the shape and location of the soft tissues (e.g. bladder, rectum, seminal vesicles) inherent when acquiring multiple image sets. Furthermore, scanner-induced distortions of the MR

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images have led to concerns about the geometric fidelity of the images and its subsequent impact on target localization.

Fortunately, recent advances in MR scanner hardware and software are addressing most of these concerns. With modern scanners, geometric distortions are relatively small and can be sufficiently characterized so as to be manageable for many radiotherapy patients, including those undergoing prostate radiotherapy [41]. Even more significantly, recent improvements have led to the commercial availability of MR-based and MR-only simulation systems [41–44]. Similar to CT simulators, MR simulators include flat tabletops with indexing, external laser positioning systems (ELPS), MR-compatible immobilization and radiotherapy specific scanning protocols. Figure 2.1 shows an example MR simulator along with the radiotherapy-specific components.

Another crucial requirement for MR-only simulation and planning for prostate radiotherapy that has only recently become commercially available is the so-called "synthetic-CT" or "pseudo-CT". A synthetic CT image is one created directly from an underlying base MR image using some method of tissue segmentation or classification and subsequent assignment of a CT or Hounsfield number which describes, with sufficient accuracy, the x-ray attenuation properties of the tissue. Generation of synthetic CT images has been an area of active research for many years, however recent progress has been spurred by the development of combined positron emission tomography (PET)/MR scanners for which a synthetic CT must provide the attenuation correction information required for accurate PET assessment. Synthetic CT images are, of course, also essential for MR-only planning because they provide electron density information for accurate dose calculation. Synthetic CT generation approaches can be broadly categorized into those that assign bulk electron densities to structures either manually segmented or obtained from multiple MR sequences to classify tissue types [45, 46] and those that use a patient atlas of paired CT and MR images and deformable

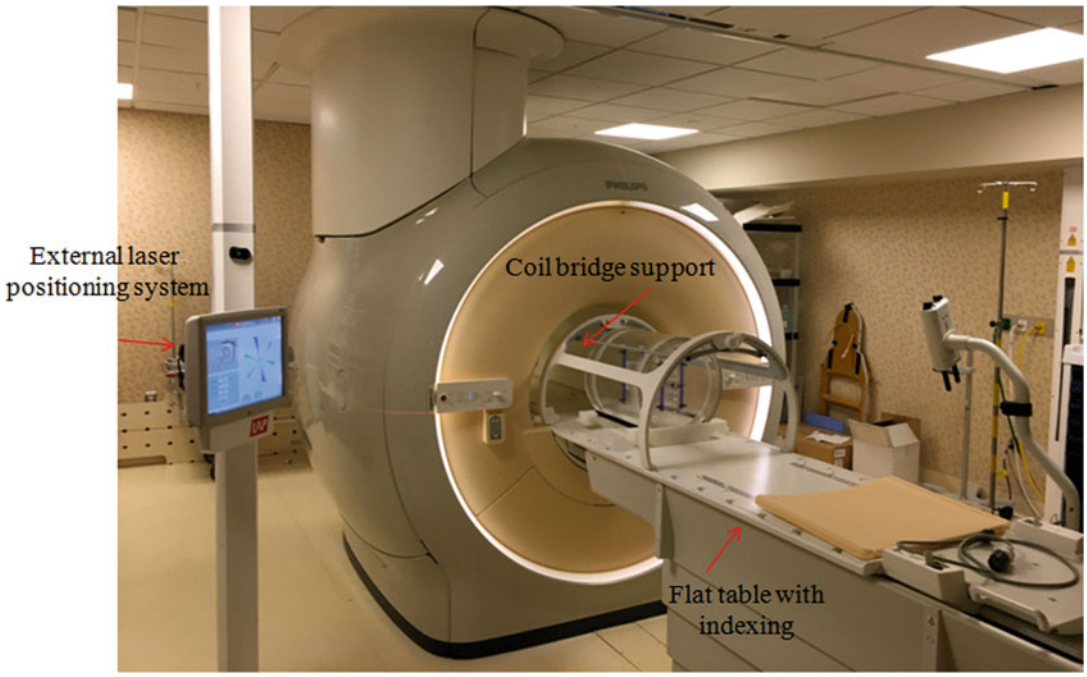


Fig. 2.1 MR simulator illustrating some of the radiotherapy-specific components such as external laser positioning system, flat table top with indexing and a coil bridge support

registration to assign CT numbers on a voxel-by-voxel basis to the MR image of a new patient [47, 48].

It is hopefully apparent that as a result of the advances described above, the radiotherapy community is now poised to transition to an era where MRI becomes the predominant imaging modality for segmentation and planning of prostate cancer. With this in mind, this chapter will focus on immobilization, simulation and planning for prostate SBRT, with an emphasis on MR-based techniques. Collectively with Chap. 5 (segmentation) and Chap. 4 (image-guided treatment delivery and motion management), the technical components of a SBRT prostate radiotherapy program are fully described. As with all radiotherapy, variations to the techniques described herein can be successfully applied and therefore, as appropriate, references to other methods are provided. The reader is also referred to the article by Clemente et al. [49] which provides a fairly comprehensive review of technical approaches for moderate and extreme hypofractionated prostate radiotherapy. When implementing SBRT for prostate cancer, it is important to remember that it is the cumulative effect of all aspects of the technical program that impacts the success of the clinical program. Therefore, the synergies and dependencies of different technical components (e.g. uncertainty in treatment delivery and margin definition) must be carefully considered and evaluated within the context of the entire program.

2.2 Simulation and Image Acquisition

Particularly with hypofractionated SBRT treatment paradigms, consistency and adherence to procedures for pre-simulation activities, immobilization, and the acquisition of images is crucial so that the conditions necessary for successful treatment can be created at the time of simulation and reproduced at each treatment to the greatest degree possible.

2.2.1 Pre-Simulation Considerations

The selection of a method to position and track prostate motion during treatment delivery is an important decision made prior to radiotherapy simulation since it may require the implantation of fiducials into the prostate gland. Implanted electromagnetic beacons [50–52] are incompatible with MR imaging for simulation and planning due to the creation of image artifacts and therefore, another method, such as implantation of gold seed fiducials, to aid image-based setup [53, 54] or track prostate motion during treatment [55] may be needed. In that case, preparation for SBRT radiotherapy may begin several weeks prior to simulation with the placement of three radio-opaque gold fiducial seeds (typically 3–5 mm in length and 0.9–1.2 mm in diameter) distributed evenly throughout the prostate (Fig. 2.2). Furthermore, the insertion of an anatomic modulator in the form of an injectable rectal hydrogel spacer [31, 32, 34, 56–58] should be considered to create distance between the anterior rectum and the prostate and reduce the rectal volume irradiated to the intermediate and high dose levels. Although additional outcome data are still needed, the use of a rectal spacer may significantly reduce the likelihood of high grade and acute rectal toxicity. A multi-institutional clinical trial [33] found that the injection of hydrogel into the prostate-rectal interface resulted in rectal dose reduction in more than 90% of patients. These results were observed even in the presence of significant variability in planning approaches and injection results across participating institutions. An analysis of the 12 month toxicity from this same trial [34] revealed a Grade 1 late GI toxicity rate of only 4.3%, no late Grade 2 or higher GI toxicity, and no evidence of ulceration, stricture or necrosis. The authors concluded that the use of the spacer was a safe and effective method for sparing the rectum from high radiation dose. Figure 2.2 demonstrates typical placement of a bio-absorbable gel to create a space of approximately 1 cm between the prostate and anterior

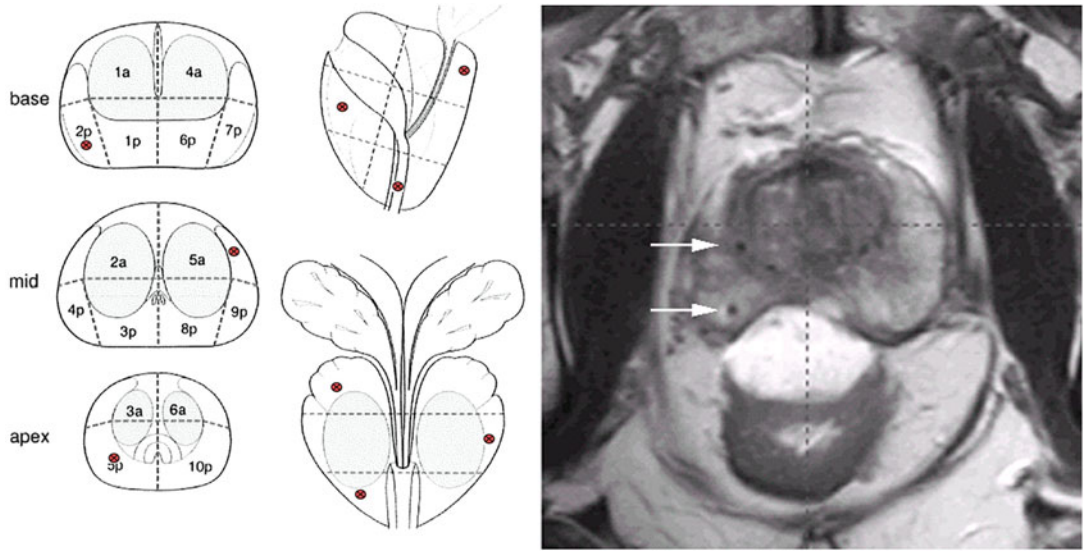


Fig. 2.2 (Left panel) Suggested placement of gold seed fiducials (red circles) within the prostate to ensure optimal visualization for pre- and intra-treatment image-guided radiotherapy. Courtesy of Tomer Charas, M.D. (Right panel) Representative T2-weighted MR image demonstrating both a bio-absorbable gel within the recto-prostatic interstitial space and gold seed fiducials (arrows)

rectal wall. When technically feasible, spacer placement can be offered to eligible patients at the same time as gold seed fiducial placement. The gel remains in the body for about 12 weeks which is sufficient time for SBRT simulation, planning and treatment, after which hydrolysis liquefies the implant, resulting in complete absorption.

Patient bowel and bladder preparation prior to simulation is an additional crucial first step in ensuring accurate planning and treatment delivery. At Memorial Sloan Kettering Cancer Center (MSKCC), the goal is reproducible filling at simulation and each treatment session with the rectum being as close to empty as possible and the bladder being tolerably full. The standard pre-simulation preparation includes a bowel preparation of Metamucil®[1] (1 Tbsp/8 oz) for 7 days prior to simulation, Fleet®[2] enema 3 h before simulation, and optional Gas-X®[3] (two tablets the night before and the morning of simulation). On the day of simulation, an initial evaluation of bowel evacuation is performed using a small number of CT or MR images. A rectal catheter is inserted to remove rectal gas if necessary. All SBRT patients are simulated and treated with a full bladder obtained by asking the patients to first void and then to drink one cup of water 45 min prior to their planned procedure. Patients continue with the Metamucil®, Fleet® enema and optional Gas-X®, as described above, daily throughout their course of SBRT.

2.2.2 Immobilization

Immobilization is another important step in the SBRT treatment planning process. With the advent of image-guided radiotherapy however, the focus of immobilization has been directed more toward daily setup reproducibility and management of motion during treatment than on rigid immobilization to ensure accurate set-up based on skin marks at the start of the treatment session. Historically, several immobilization approaches have been successfully used for prostate cancer including thermoplastic molds and foam or

[1] Procter & Gamble Company, Cincinnati, OH 45202.
[2] C.B. Fleet Company, Lynchburg, VA 24502.
[3] GlaxoSmithKline, Warren, NJ 07059.

vacuum bag body cradles [49]. These devices help to ensure reproducible initial positioning of the patient. Subsequently, daily image guidance (e.g. orthogonal kV radiographs and/or cone beam CT) must be used to ensure that the position of the prostate with respect to the isocenter is also accurate and within acceptable levels determined by the uncertainty of the image registration method [54, 59]. Without such a process, Algan et al. [60] demonstrated that the dosimetric impact could be underdosing of the prostate gland by 7% or more for conventional fractionation schemes and prostate margins of 5–7 mm (3–5 mm posteriorly).

At MSKCC, patients are simulated in a head first, supine position using a simple, flat custom-built board that can be indexed to the couch top and an anterior solid thermoplastic mold that extends from approximately mid-abdomen to mid-thigh (Fig. 2.3). The mold closely conforms to the contours of the inner leg and a knee cushion is standardly used to provide additional stability. Such an approach may potentially provide an improved rectum-prostate configuration [61].

2.2.3 Simulation Workflow 1: Primary CT Simulation with Secondary MR Imaging and Fusion

In this workflow, CT images are acquired from L1 to well below the ischial tuberosities and reconstructed at no more than a 2 mm slice thickness. Just prior to simulation, a Foley catheter is inserted to facilitate visualization and segmentation of the urethra. CT simulation is then followed by an MR session with the patient placed in his immobilization mold with an indexed flat tabletop, and initially positioned using ELPS. Anterior and posterior radiofrequency (RF) coils are both used for imaging. Particularly if the patient is immobilized with an open body mold, a coil bridge should be used so the patient's anatomy is not distorted by the anterior coil. Failure to do so has been associated with deformation of the anterior skin surface by up to 1.7 cm [62]. If, on the other hand, a sufficiently rigid immobilization mask is used (Fig. 2.3), the anterior coil can be placed directly on the immobilization mold itself with the added advantage of minimizing the distance between the coil and patient surface. If the MR scanner is equipped with a built-in posterior

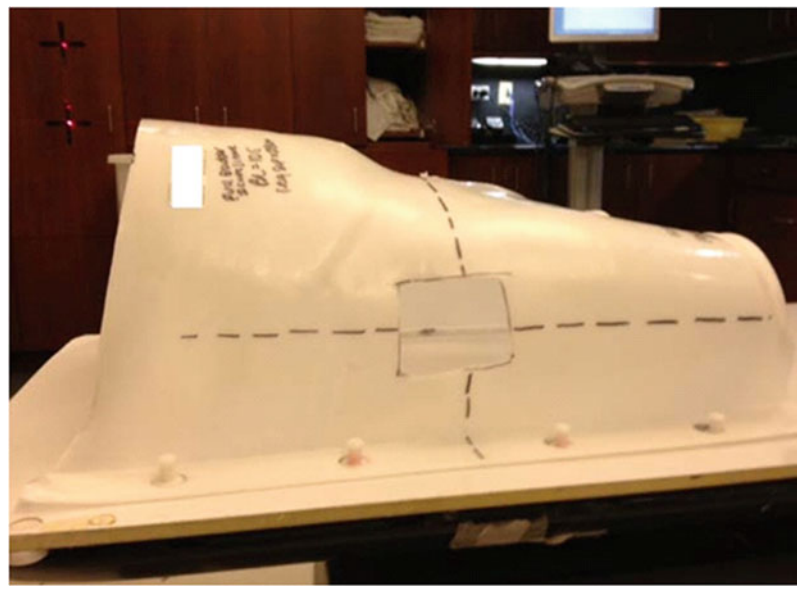


Fig. 2.3 Solid thermoplastic mold for SBRT prostate radiotherapy with cutouts for laser-based triangulation positioning

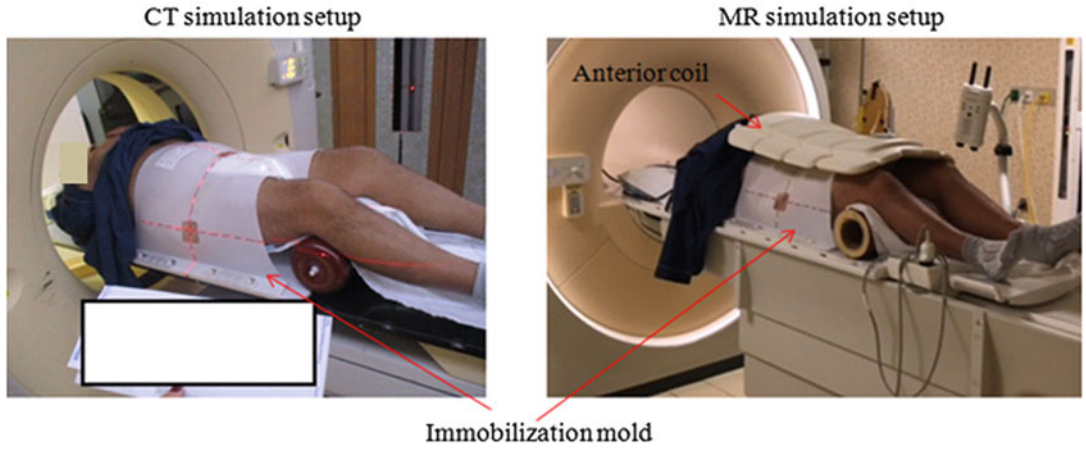


Fig. 2.4 Simulation setup in the CT and MR scanners for a multi-modality simulation workflow

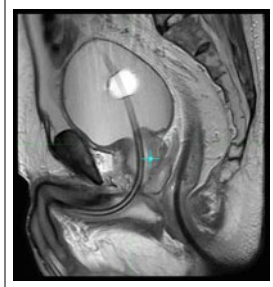
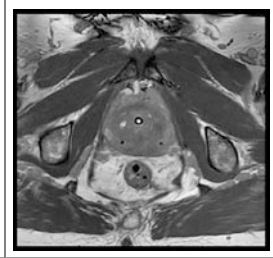
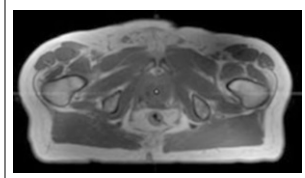
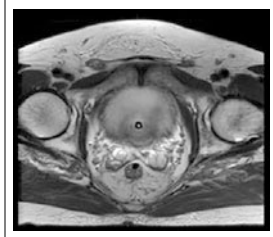
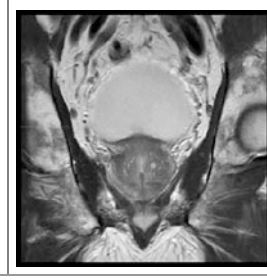
spine coil, care must also be taken to use a flat table top that minimizes the distance between the coil and patient. Some newer scanners provide an option for a flat table that does not add distance between the patient and coil. Such a table serves as a replacement for the standard curved diagnostic table and is preferred to a curved table with a flat table top add-on.

Patient positioning should be as close as possible for both the CT and MR imaging sessions. Registration inaccuracies of more than 2 mm have been reported when MR images acquired with the patient in the diagnostic position are used for planning [63] and such a workflow is not recommended for SBRT planning. For a combined CT and MR simulation workflow, registration uncertainty can be further minimized by keeping the time between the CT and MR sessions as short as possible, thereby maximizing consistency of the bladder and rectal contents. If the patient must void between sessions or is otherwise unable to complete both CT and MRI on the same day, an attempt must be made to ensure consistent rectal and bladder filling for both imaging procedures. To further reduce inaccuracies and improve the MR simulation, Foley catheter usage during CT and MRI should also be consistent and glucagon administration during the MRI can be considered to minimize peristalsis and the associated motion artifacts. Prior to placing the custom immobilization device on the patient during the MRI session, it is often helpful to first set the patient up using the ELPS to the reference marks from CT and then to assess patient straightening and bladder and rectal contents using a quick low resolution ($5 \times 5 \times 5$ mm^3) survey image set. Figure 2.4 demonstrates a typical patient setup on both the CT and MR simulators.

2.2.3.1 Contouring Considerations When Using MR as the Secondary Imaging Modality

Secondary MR images for contouring must be of high quality and therefore should be acquired with a field-of-view (FOV) just sufficient to encompass the prostate, seminal vesicles and nearby normal tissues such as the bladder, rectum and penile bulb. A small FOV axial T2w MRI and fiducial identification sequence should be sufficient for this purpose (see Table 2.1). Because the prostate is much smaller on MR compared to CT, CT-MR fusion in the region of the prostate can be quite challenging and the use of stable landmarks that can be observed on both image sets, such as the fiducials, can be particularly helpful for this task (Fig. 2.5 top panel). It should be kept in mind that the seminal vesicles move independently of the prostate and their location may differ on CT and MR depending on rectum and bladder filling

Table 2.1 MR simulation scanning guideline [64]

Sequences	Coverage	Scan parameters
Sagittal T2 2D TSE (For soft-tissue contouring)	Skin-to-skin (AP) L5 to anal canal (SI) Middle of femoral heads (RL)	
Goldseed Axial 3D BFFE (For fiducial identification)	Covering prostate and seminal vesicles	
MRCAT Source MR Axial 3D FFE mDIXON (For synthetic CT generation)	Skin-to-skin (AP) Skin-to-skin (RL) L4 below to proximal femur (SI)	
Axial T2 small FOV 2D TSE (For soft tissue contouring)	Outer body (AP) Femoral heads (RL) L5 to anal canal (entire rectum) (SI)	
Coronal T2 2D TSE (For soft tissue contouring)	Middle of femoral heads (RL) Entire prostate, bladder neck, rectum (SI) Entire prostate, bladder neck, rectum (AP)	

Abbreviations: *TSE* turbo spin echo, *BFFE* balanced fast field echo, *FFE* fast field echo)

[65, 66]. A larger CTV to PTV margin, especially for high risk patients, may therefore be needed around the seminal vesicles to encompass their position on both CT and MRI and ensure their inclusion within the high dose region. Questions often arise as to which structures should be segmented on MR when MR is used as the secondary imaging modality. Since, in such a workflow, CT is the primary imaging modality used for planning and image guided delivery, it is advisable to limit MR-based segmentation to the prostate and seminal vesicle target volumes and

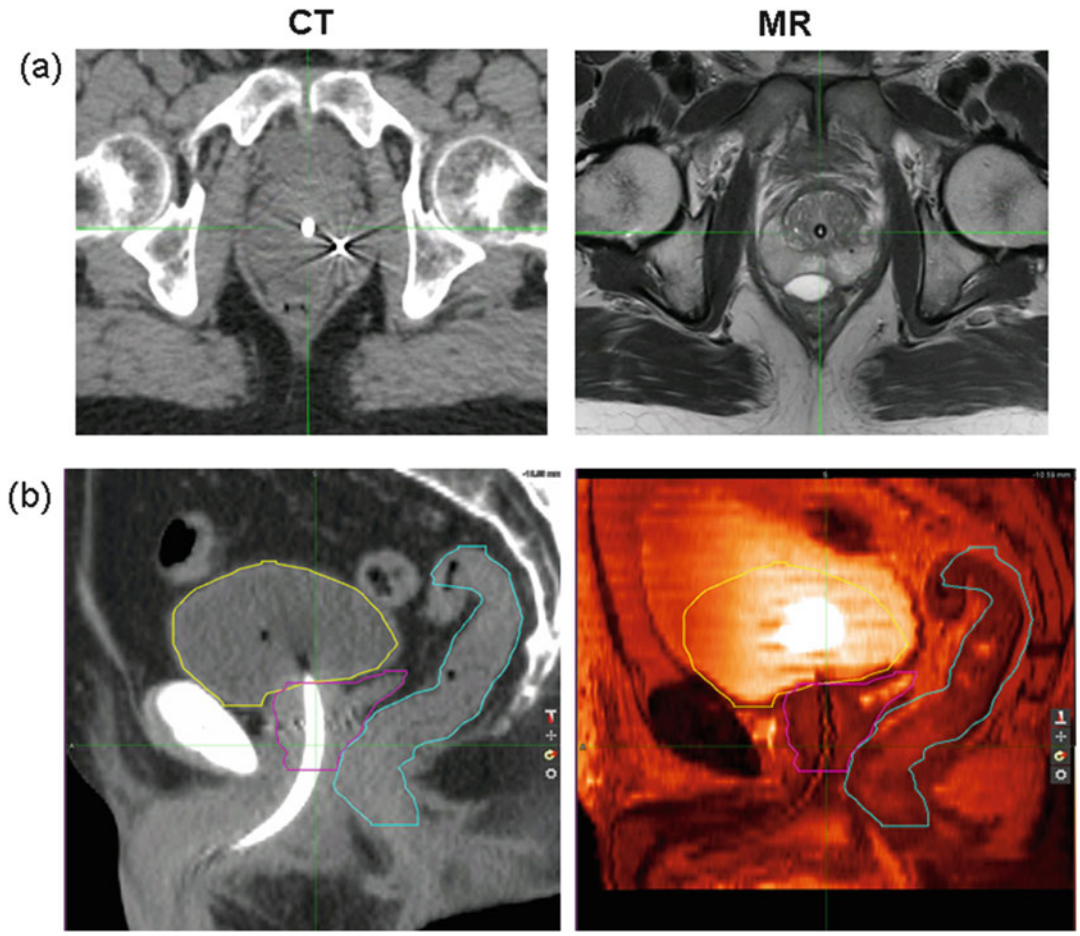


Fig. 2.5 (Top panel) Axial CT+MR fusion based on the implanted gold seed fiducials. Rectal spacer is clearly visible only on the MR. (Bottom panel) Sagittal CT+MR fusion for another patient illustrating contouring considerations when using MRI as the secondary imaging modality. Note the differences in the size and position of the tissues between the two studies

other secondary structures such as the rectal spacer, penile bulb and urethra (if a Foley catheter is not used) which are clearly visible only on MR. Normal tissues such as the bladder, rectum and bowel should be segmented on CT (Fig. 2.5 bottom panel).

2.2.4 Simulation Workflow 2: MR-Only Simulation

Because of changes in the anatomy (e.g. bladder and rectum filling) that can occur between the acquisition of two image sets and the ambiguity in contouring seminal vesicles, a workflow in which MRI is the primary and sole imaging modality is preferred over a combined CT and MRI workflow. In addition to minimizing segmentation errors introduced by mis-registration between the CT and MR, an MR-only workflow improves efficiency by reducing the number of imaging sessions, and reduces cost and inconvenience to the patient [43, 64, 67, 68]. However, additional considerations apply to an MR-only workflow including the need to (a) characterize the MR scanner for a larger FOV to ensure images of high geometric fidelity, (b) define a process for MR-only simulation and isocenter marking, (c) commission synthetic CT images generated from single or multiple MR image

sets for high geometric and dosimetric accuracy, (d) define MR acquisition and contouring guidelines and (e) commission a method to obtain 2-D digitally reconstructed radiographs (DRRs) and/or 3-D reference images from MR images with sufficient bone, soft tissue, and/or implanted fiducial visualization to guide image-based patient setup and treatment.

2.2.4.1 MR Scanner Characterization and Routine QA for MR-Only Simulation

MR scanner characterization and imaging protocol requirements for radiation therapy simulation are different and more stringent than those for a diagnostic scanner and therefore, a radiation oncology-specific quality assurance program is needed [44]. Radiation therapy requires images of high geometric fidelity with high spatial and contrast resolution to delineate disease extent and nearby organs at risk. The geometric fidelity of MRI is often questioned due to distortions arising from the scanner (system-specific distortions) or from the patient themselves (patient-specific distortions) [69–71]. Modern MR systems have been designed with tighter system level distortions, primarily those relating to B0 inhomogeneity and gradient nonlinearity due to improved magnet design as well as higher order corrections of gradient non-linearity and high order shimming. For radiation therapy planning, a QA procedure for geometric fidelity operating within a FOV of ±50 cm left-right, ±30 cm superior–inferior and ±35 cm anterior–posterior must be performed routinely to ensure that geometric distortion due to B0 inhomogeneity and gradient linearity do not exceed 2 mm. Patient-specific distortions of <1 mm have been reported for prostate patients and therefore, this is not a huge concern for MR-based planning [43].

MR simulators are also equipped with an external laser positioning system (ELPS) used to set up the patient to a specific location or to reference marks (skin tattoos) defined during CT simulation. The sagittal and coronal lasers help to evaluate and correct patient rotation. The ELPS are calibrated to send the patient directly to the scanner isocenter, similar to those on a CT simulator. A daily laser QA procedure should be performed to ensure the laser positions and the distance between the external laser position and the MR bore isocenter are within tolerance. The acceptance criteria should be <2 mm. A daily ELPS QA and biweekly geometric fidelity QA program is in place at our institution as part of our MR-only workflow.

2.2.4.2 MR-Only Simulation and Isocenter Marking

Although modern MR scanners can be equipped with an external laser positioning system, flat table top and coil bridge supports to perform MR simulation, there are additional requirements for MR-only simulation. These include a water bath in the vicinity of the MR scanner or the use of a slow dry mold for immobilization devices and an MR-compatible method for placing skin tattoos. It is important to note that allowing any immobilization mold to dry completely before imaging is necessary from an MRI safety perspective.

Unlike CT simulators, current MR simulation platforms do not provide virtual simulation capabilities for absolute isocenter marking. For MR-only simulation, a third party software such as MIM MAESTRO®,[4] or Eclipse™,[5] can be utilized if desired. At our institution, patients have their immobilization device constructed in the CT simulator which provides the additional benefit of allowing us to place initial tattoos at that time, thus providing a relative isocenter to serve as the reference for the MR simulation. A pair of orthogonal CT scout images is also acquired for use during a later QA step during which the locations of the three implanted fiducial markers on the MR images are verified against the CT scout. Three MR-compatible radio opaque Beekley™[6] markers (BBs) are placed on the initial reference tattoos in MR so that they are visible on the large FOV images. These markers are later used to create an isocenter at the triangulation point.

[4] MIM Software Inc. Cleveland, OH 44122.

[5] Varian Medical Systems, Palo Alto, CA 94304.

[6] Beekley Inc., Bristol, CT 06010.

2.2.4.3 Synthetic CT Generation

The lack of electron density information on the MR images is somewhat overcome by the use of synthetic CTs that are generated from these MR images. Various methods have been developed over the last few years to generate synthetic CTs from MR images for prostate radiotherapy. These methods can be broadly classified into:

(a) Bulk density assignment methods: These methods rely on manual contouring of structures. They provide reasonable accuracy but are not practical for routine use. Dose differences greater than 2.5% to the target have been reported with this method [67, 72, 73].
(b) Atlas-based methods: These methods rely on the generation of electron density maps from an atlas of co-registered CT and MR images. Large anatomical variation outside that captured in the atlas may compromise the accuracy of atlas based methods due to the limitations of deformable registration [47, 48].
(c) Classification-based methods: These methods rely on the use of a single or multiple MR sequences to classify the tissue types [43, 45, 46, 74, 75], with the inclusion of a bone atlas to further guide the classification [75, 76]. Such methods are practical for routine use and not limited by variation between patient anatomies. Both atlas-based and classification-based methods have reported a dosimetric accuracy of less than 1% when compared to CT based plans.

In addition to the synthetic CTs developed by different research groups, there are also two commercial options available for clinical use of synthetic CTs. One of them is a classification-based method called MRCAT[7] or MR for Calculating ATtenuation which is limited to a Philips MR scanner [77]. The other method (MRIplanner[8]) is scanner independent and currently only CE marked for clinical use in Europe [78]. Figure 2.6 shows an example case comparing synthetic CT, source MR and the original CT. Regardless of the synthetic CT method used, the synthetic CT images should be thoroughly commissioned for their geometric and dosimetric accuracy before using them clinically [43, 46, 78, 79]. Ideally, the synthetic CT generation method should be scanner and, if possible, sequence independent so that it could be widely adopted in the clinic. It goes without saying that the DICOM tags of the synthetic CTs must be configured and automatically set to indicate a "CT" imaging modality to allow for a streamlined export of the synthetic CT DICOM images to the treatment planning system (TPS) for dose calculation.

2.2.4.4 MR Acquisition and Contouring Guidelines

MR images with sufficient soft tissue contrast are needed for contouring both target and normal structures for MR-only workflow. Ideally, for efficient MR-only simulation, a single MR series could be used to generate the synthetic CTs while also providing sufficient soft tissue contrast to contour the target, normal structures and fiducials. This is currently not possible and most institutions rely on multiple MR series to achieve this. Table 2.1 shows the MR scanning guidelines at MSKCC for MR-only simulation of the prostate using a Philips 3T Ingenia[9] MR scanner. Images are acquired in the following order to minimize the possibility of motion between the adjacent sequences: T2w sagittal, Goldseed visualization, Synthetic CT, T2w axial, T2w coronal. It should be remembered that the ELPS must be turned off prior to scanning as it may otherwise introduce an image artifact [42]. While the MR images are being acquired, an initial image quality assessment is done by the MR technologists to ensure sufficient quality for contouring and gold seed fiducial visualization. The MR technologists are instructed to repeat any acquisition during which significant motion was observed.

[7] Philips Healthcare NA, Cleveland, OH.
[8] Spectronic Medical AB.
[9] Philips Healthcare NA, Cleveland, OH.

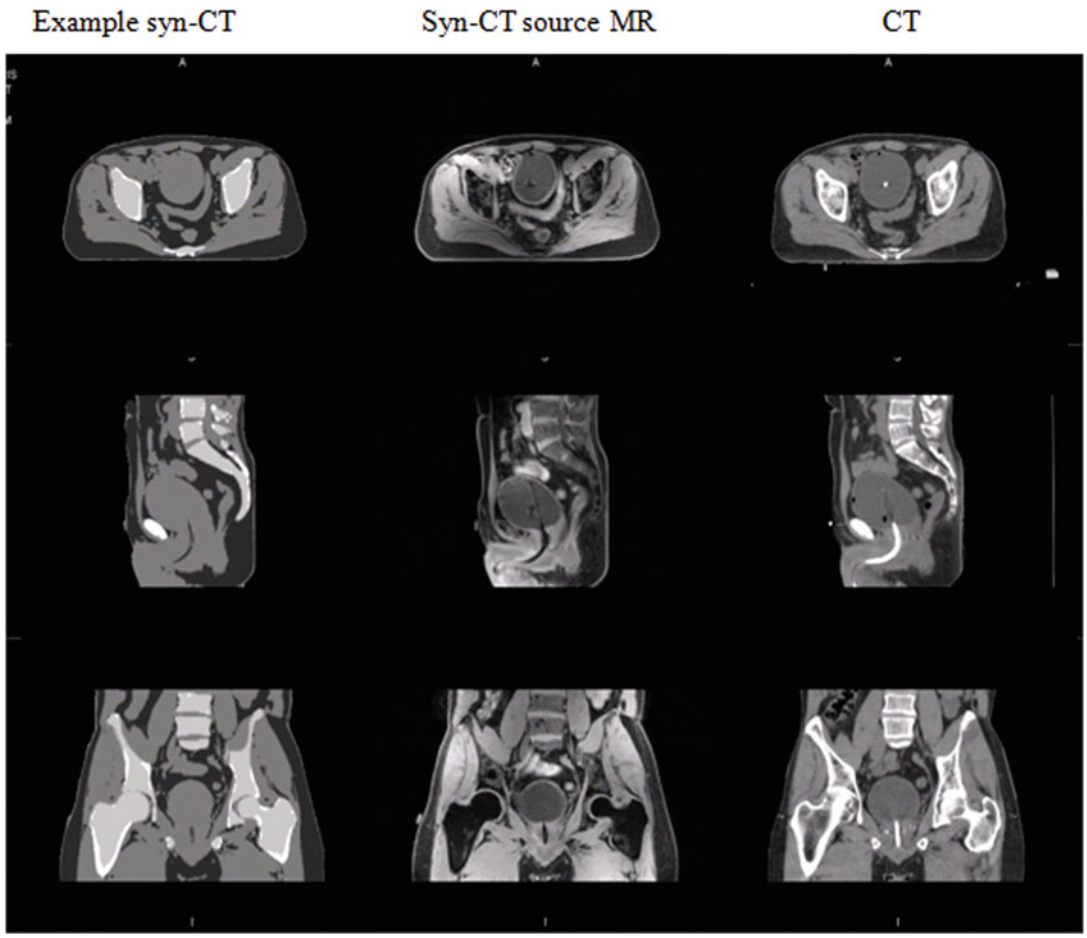


Fig. 2.6 Example of a synthetic CT, synthetic CT source MR and actual CT of a prostate patient

Motion-induced artifact is currently the biggest technical limitation of MR-only simulation. The development of motion-robust sequences may overcome this challenge in the near future.

Since there are multiple MR datasets for contouring, there is a strong need for an organized workflow to streamline inter-sequence registration and generate automatic image layouts for physicians. The total time for MR simulation is approximately 25 min, during which movement of the prostate and slight changes to bladder and rectal filling can occur. At MSKCC, we have developed a MIM-based contouring workflow that allows us to automatically break the DICOM frame of reference between the MR series and perform initial inter-sequence registration before contouring. Our MR-only workflows also provide a significant advantage for contouring both target and normal tissue structures from a single imaging modality through the creation of these multi-image page layouts as shown in Fig. 2.7. Physicians contour the CTV (prostate and seminal vesicles), bladder, bladder trigone, bowel, urethra, rectum, and rectal spacer on axial T2 MR images. Fiducials are identified on the Goldseed sequence and femurs on the synthetic CTs. The workflow ensures that all contours are automatically saved on the synthetic CT even though segmentation is done on the MR images exclusively.

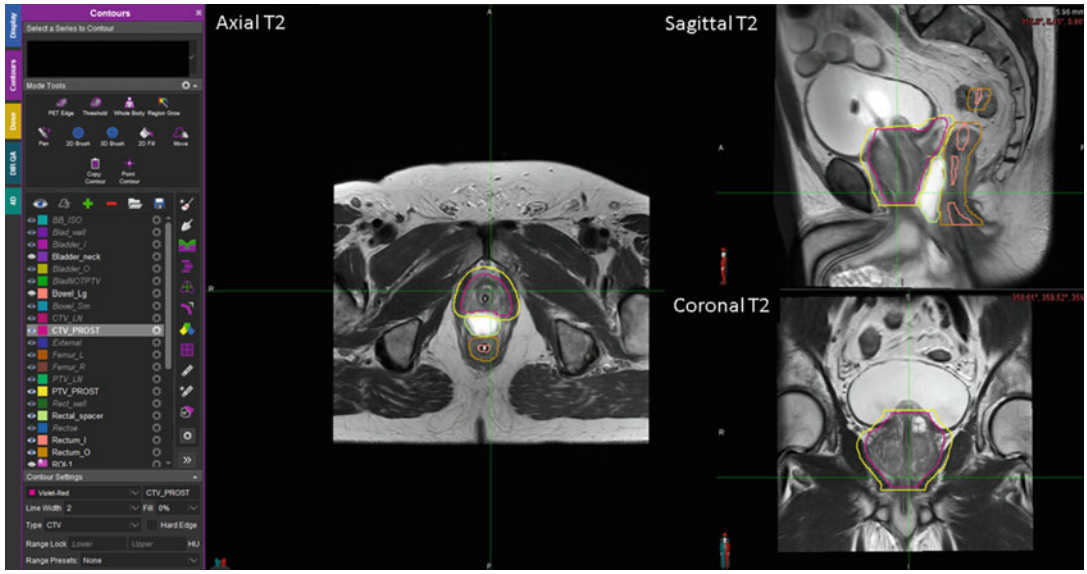


Fig. 2.7 Example physician contouring layout for the MR-only workflow. The layout displays native axial, sagittal and coronal MRI to facilitate contouring. The contours drawn on these MR images are automatically saved to the synthetic CT

2.2.4.5 Planar and Volumetric IGRT Using MR Only

In addition to the dosimetric accuracy, geometric accuracy of synthetic CTs for patient positioning is also very crucial. Planar and volumetric IGRT for prostate patients is performed using 2D DRRs and 3D CBCT. The reference bony DRRs generated from synthetic CTs must be verified with respect to CT based DRRs and commissioned for clinical use [43, 79]. Patient positioning is also often performed based on implanted gold fiducials. An ideal MR sequence should display sharp signal void in the implanted fiducials and show excellent contrast between fiducials and prostate to facilitate an accurate localization of fiducials. Phantom experiments must be performed to verify that the uncertainty in fiducial marker localization due to susceptibility does not exceed the fiducial location identified on the CT ground truth. Table 2.1 shows an example of a 3D balanced fast field echo sequence on a Philips scanner where T1/T2 dependence of the sequence, a sharp signal void and susceptibility of implanted fiducials yields a distinct contrast between the fiducials and nearby anatomy. Figure 2.8 shows an example of AP and lateral DRRs generated from a synthetic CT and compared with the on-treatment radiographs. The fiducials on the synthetic CT are represented as ROIs and not synthetically generated, although it is also possible to generate the synthetic fiducials on the synthetic CT if one desires. 3D CBCTs are also matched to the reference synthetic CTs based on fiducials. At our institution, the physicians also use the reference planning image to ensure reproducibility of the bladder and rectal filling on the pre-treatment CBCT. If the bladder and rectum contrast is not sufficient on synthetic CTs, physicians can also load the synthetic CT source MR on the on-board imaging console or the Varian ARIA™ offline review module.

2.3 General Planning Considerations for SBRT

With the advent of image guided radiotherapy (IGRT), volume modulated arc therapy (VMAT) and most recently, MR-guided or MR-based simulation, treatment planning for hypofractionated

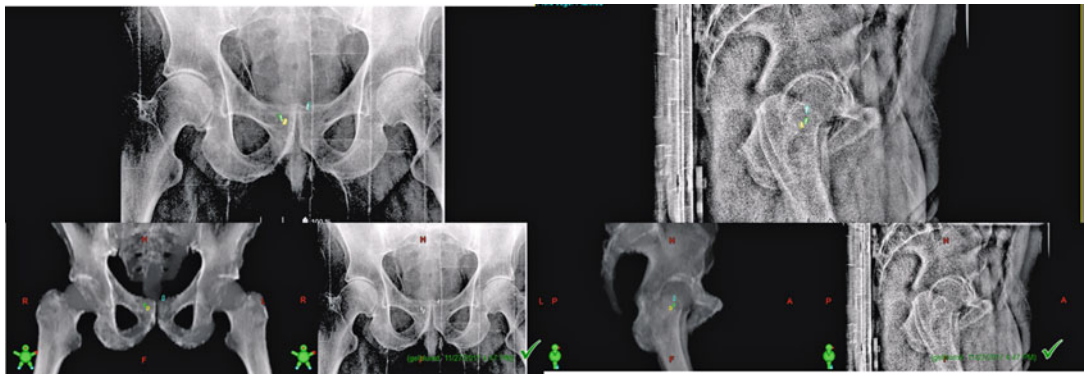


Fig. 2.8 Example AP and lateral DRRs generated from synthetic CT compared to on-treatment radiographs. The fiducials on the planning DRRs are displayed as ROIs

prostate cancer has evolved toward smaller treatment volumes and margins and tighter dose conformality; attributes that diverge significantly from historical approaches for conventionally fractionated treatment paradigms. This evolution has been facilitated by several technological advances:

1. The incorporation of MRI into the planning process resulting, on average, in a 30–40% decrease in prostate CTV volume.
2. A strong emphasis on patient bowel and bladder preparation applied consistently throughout the course of radiotherapy and the introduction of anatomic modulators (e.g. rectal spacer gels) to successfully implement smaller margins.
3. The widespread adoption of volume modulated arc therapy (VMAT) to increase dose conformality and reduce overall treatment delivery time by up to 50–60%, thereby facilitating margin reduction since shorter times result in less motion.
4. The routine use of daily pre-treatment image guidance using orthogonal radiographs, daily cone beam CT (CBCT) or both, to reduce margins.

Programmatic focus on all of these radiotherapy process aspects (patient preparation, imaging, simulation, planning and treatment delivery) has allowed us to decrease our CTV-to-PTV margins over time from circumferential 10 mm with 6 mm at the prostate-rectal interface prior to daily pre-treatment IGRT, to circumferential 6 mm with daily IGRT, and most recently to circumferential 5 mm with 3 mm at the prostate-rectal interface for SBRT patients receiving MR simulation, pre-treatment and intra-treatment motion monitoring. If the pelvis will be treated, a 5 mm or larger margin should be considered for the nodal CTVs in recognition of the fact that image-guided setup is focused on the prostate itself and that suboptimal dosimetric coverage of the nodal volumes is possible for patients with large differences in their bony and fiducial registrations and/or bladder filling observed at pre-treatment imaging [80].

For a combined CT and MR workflow, the final plan as well as the DRRs are generated based on the planning CT using the MR-based contours (Sect. 2.2.3.1). In case of an MR-only workflow, plans as well as DRRs are generated using the synthetic CT as the primary image set. An automated workflow ensures that all contours including the fiducial ROIs are automatically saved on the synthetic CT for planning (Sects. 2.2.4.4 and 2.2.4.5).

2.3.1 Volume Modulated Arc Therapy Planning for SBRT Prostate Radiotherapy

Volume modulated arc therapy (VMAT), whereby intensity modulated radiotherapy is delivered through a combination of dynamic

motion of the gantry and multileaf collimator and, often, simultaneous modulation of the dose rate has become a widely adopted planning and delivery method for prostate SBRT. Advantages include excellent dose conformality and reduced treatment delivery times which are important to reduce intra-treatment motion. Total in-room time and time from first beam on to last beam off with static field IMRT can exceed 15 and 10 min, respectively. With VMAT, these times can be reduced by approximately 40–50%. Several studies have compared dose distributions of static coplanar field intensity modulation (IMRT) and VMAT [24, 26, 81]. The study of 292 patients by Kopp et al. [81] is representative of the results in that it found that VMAT provided a higher level of conformality leading to decreases in high dose levels to the rectum and bladder. Bladder doses were lower at all volume levels evaluated while the volume of the rectum receiving intermediate doses was the same as IMRT but volumes receiving lower doses were higher. Doses to other evaluated normal tissues including the penile bulb and femoral heads were lower with VMAT, at least at selected volumes and/or dose levels.

VMAT dose distributions have also been compared to other methods used for prostate SBRT, most notably robotic radiosurgery (e.g. CyberKnife®[10]). In a study of eight patients comparing robotic radiosurgery, non-coplanar fixed field IMRT, and two commercially available VMAT methods, Seppala et al. [82], found higher target dose inhomogeneity and mean doses to the bladder and penile bulb with robotic radiotherapy but no significant difference in doses to the other normal tissues between any of the techniques. Dose conformality was best with one of the VMAT implementations and the VMAT techniques, in general, resulted in the lowest number of monitor units (MU). The conclusion of the study was that overall, the dosimetric differences between the techniques were small and therefore, accuracy and time required to deliver the treatment should be the dominant concerns when selecting a technique.

[10] Accuray, Sunnyvale, CA.

In the following sections, a brief overview of the VMAT planning process for prostate SBRT at MSKCC is provided.

2.3.1.1 Preparation for Planning and Generation of Optimization Structures

In addition to segmenting the target and organs-at-risk (OAR) (Sects. 2.2.3.1 and 2.2.4.4), optimization control structures such as rinds or shells can be created and used to control the dose distribution, particularly the dose fall-off beyond the target, during optimization. Optimization control structures created from logical combinations or expansions of other structures (e.g. PTV-rectum overlap, Urethra plus 2 mm) are also extremely helpful for controlling dose fall-off, hot or cold spots in specific parts of the plan. When using nested structures for optimization, as is common with control shells or targets with different dose levels for simultaneous integrated boost plans, results are often better if a small gap is left between adjacent structures. Other optimization control structures may be necessary for cases requiring pelvic nodal irradiation, a cone down or boost to a portion of the prostate CTV, or for cases where external beam radiotherapy is being delivered after a brachytherapy implant. Table 2.2 provides a few examples of optimization control structures which can be helpful for prostate SBRT planning scenarios.

2.3.1.2 SBRT VMAT Planning for Intact Prostate Patients

Typically, two full 360° arcs are used for prostate SBRT which are directed from the clockwise and counterclockwise directions and use collimator angles offset by approximately 90° to provide additional degrees of freedom during optimization and to minimize tongue and groove effects. In the presence of hip prostheses, skip arcs which prevent direct beam entry through the prosthetic device can be considered. However, in such a scenario, IMRT with seven to nine fixed fields may still be particularly useful due to the ability to more carefully control the beam directions and dose entering through the prosthetic devices. By using asymmetric jaws, isocenter placement in

Table 2.2 Examples of optimization control structures for SBRT radiotherapy of the intact prostate

Structure name	Structure definition	Structure purpose
PTV_Opt	Prostate PTV excluding OARs (PTV_Prostate *not* Rectum *not* Urethra *not* Bladder Trigone)	Control of PTV coverage
PTV_Bladder	Intersection of Prostate PTV and Bladder (PTV_Prostate *and* Bladder)	Control of PTV coverage and dose gradient between the PTV and bladder
Rind1	Axial expansion of PTV (PTV + 3 cm) *not* (PTV + 0.3 cm)	Control of dose falloff
Rind2	Axial expansion of Rind1 (RIND1 + 3 cm) *not* (RIND1 + 0.1 cm)	Control of dose falloff
Urethra_Ext	Axial and longitudinal expansion of Urethra (Urethra + 0.2 cm), Extend longitudinally beyond PTV by ~0.5 cm	Control of urethral dose

the center of the prostate works well for the vast majority of prostate SBRT cases, including those requiring nodal irradiation. Most commercial treatment planning systems allow for the creation of field definition templates which define basic field parameters including arc length, gantry start and stop angles, and collimator angles. Scripting may provide for more automation at this step in the planning process such that with little effort, the initial treatment fields can be prepared.

In virtually all treatment planning systems, VMAT optimization is initiated from a template of dose and volume objectives and priorities for the targets and normal tissues. Typically, maximum, minimum and dose volume objectives are used for the target and OARs (rectum, bladder, penile bulb, femoral heads) which are quite similar to but not necessarily identical to the clinical criteria that will be used to evaluate the quality of the plan. Optimization control structures including rinds, shells or Boolean structures are typically applied with relatively light priority. Analytical methods for controlling dose fall-off outside of the target such as the normal tissue objective (NTO) are also often very helpful during optimization [83].

Figures 2.9 and 2.10 illustrate typical VMAT dose distributions for prostate patients with and without rectal spacers receiving 40 Gy in five fractions. A comparison of the dose volume histograms (DVHs) is given in Fig. 2.11. For both patients, MRI was used to define the prostatic target yielding CTV volumes of 128 and 94 cc. Excellent, highly conformal coverage of the target and sparing of the rectum is possible in the presence of the rectal spacer which is clearly visible only on the MRI (Fig. 2.9). The loss of coverage at the prostate-bladder interface in this patient was a consequence of a dosimetric constraint placed on the dose to the bladder and bladder trigone. Coverage of the target is excellent as well for the patient without rectal spacer (Fig. 2.10) but at the cost of a higher dose to the rectum. Dose volume histograms of the PTV, rectum and bladder for both patients are compared in Fig. 2.11 demonstrating the advantage in rectal dose obtained with the spacer.

The current MSK criteria for evaluation of SBRT plans delivering 40 Gy in five fractions are provided in Table 2.3. For patients receiving slightly different fractionations, the absolute doses to the normal tissues are scaled up or down when clinically appropriate and physically possible. For example, for a fractionation of 37.5 Gy in five fractions, the PTV maximum dose and D95% criteria and the dose criteria for the rectum, bladder, skin, penile bulb and urethra are all proportionally lower than the 40 Gy criteria. However, the bowel doses are the same since at the time that we escalated the SBRT prescription from 37.5 to 40 Gy, clinical prudence dictated that the bowel criteria remain unchanged.

Similar criteria for evaluating plan quality have been developed by other institutions and cooperative groups. It should be remembered that dose volume metrics, structure segmentation and planning guidelines are interrelated and have often been developed from clinical practice over

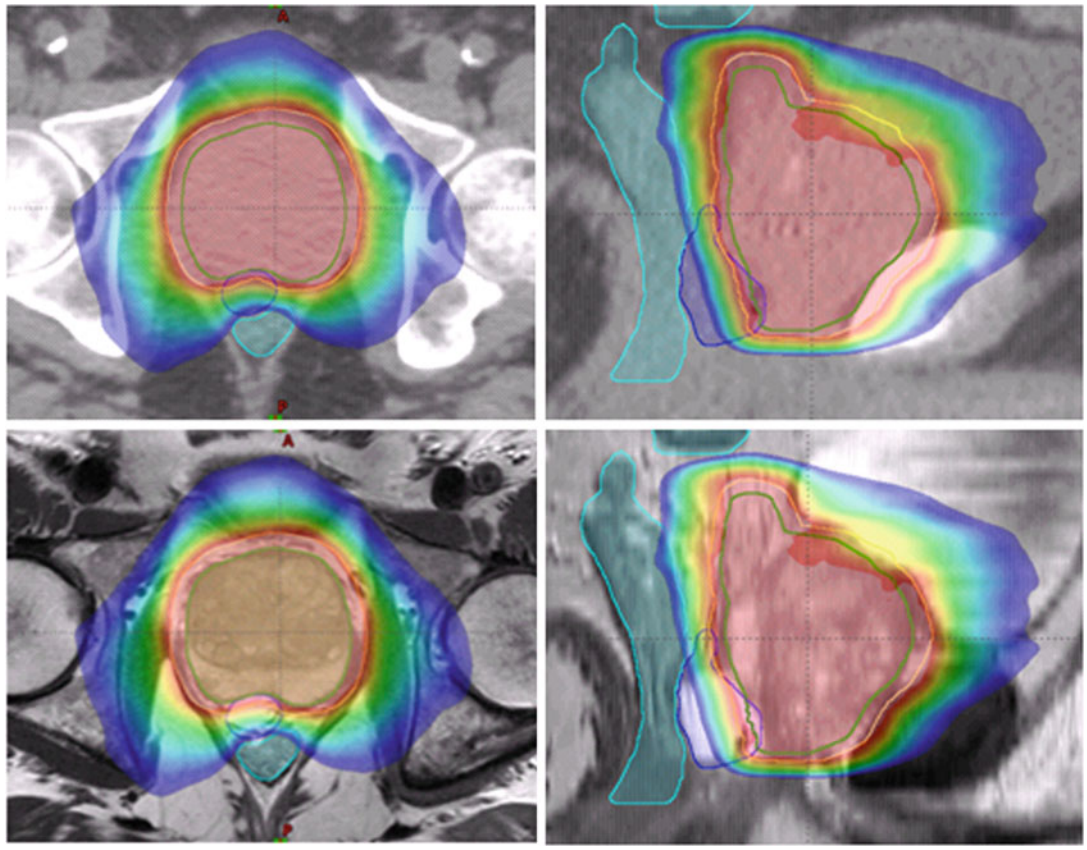


Fig. 2.9 Axial and sagittal VMAT dose distributions for a patient with a rectal spacer undergoing 40 Gy SBRT radiotherapy. The plan is shown on CT (top) and MR T2 (bottom) images. Structures indicated include the PTV (yellow), CTV (green), rectal spacer (purple) and rectum (cyan). The colorwash isodoses range from 20 Gy (blue) to 40 Gy (red)

many years. As a result, the adoption of specific dose volume metrics such as those listed in Table 2.3 should only be done in the context of developing a larger program that evaluates all aspects of the planning process.

SBRT is also being used, although not yet as widely, for other scenarios including in combination with LDR or HDR brachytherapy, when treating the pelvic lymph nodes, and for salvage treatment after prostatectomy or initial radiotherapy. Although the doses, plan evaluation metrics and criteria are quite different from the prostate-only approach described above, other aspects of the planning approach are very similar, particularly with regard to the segmentation of targets, normal tissues, beam arrangement and optimization structures.

2.4 Future Developments in Prostate SBRT Simulation and Planning

2.4.1 Segmentation and Focal Dose Escalation of the Dominant Intra-Prostatic Lesion (DIL)

There continues to be intense interest in identifying men who would benefit from segmental or focal therapies targeting dominant or index lesions within the prostate in an effort to avoid overtreatment and limit urinary and sexual function toxicity. It is clear that local failures after external beam radiotherapy tend to occur at the site of the original index lesion providing

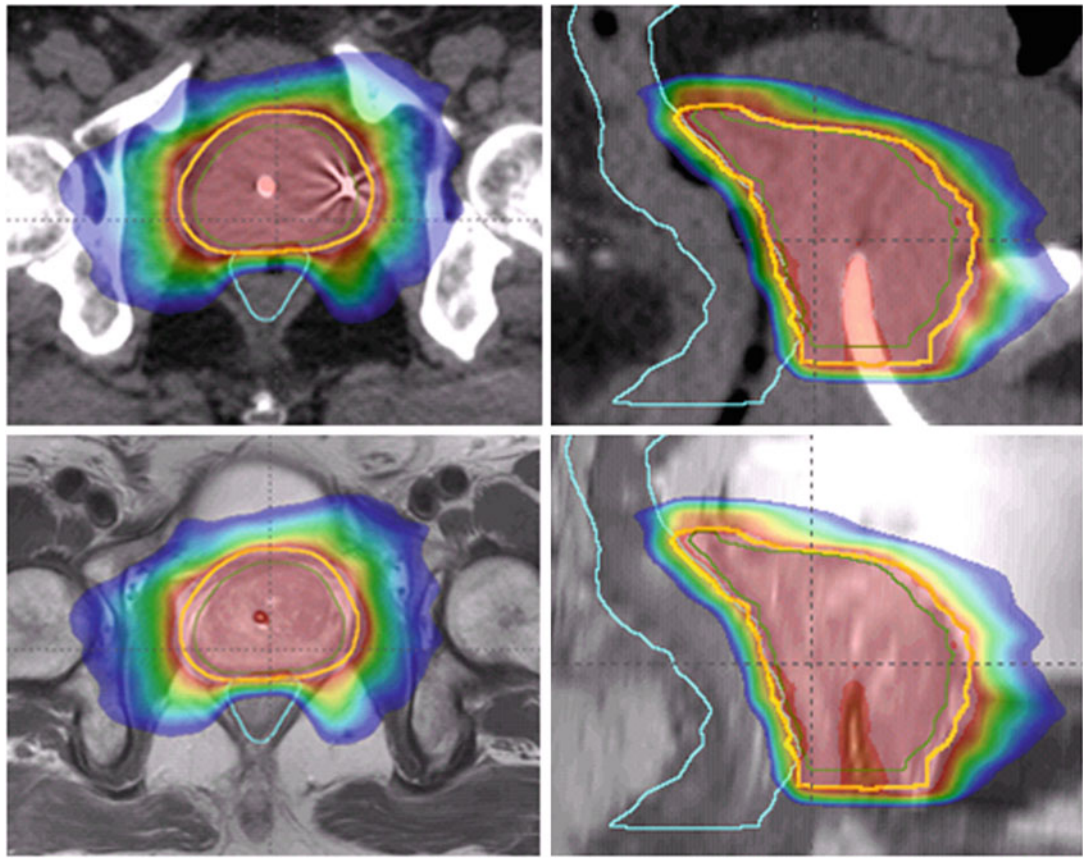


Fig. 2.10 Axial and sagittal VMAT dose distributions for a patient without a rectal spacer undergoing 40 Gy SBRT radiotherapy. The plan is shown on CT (top) and MR T2 (bottom) images. Structures indicated include the PTV (yellow), CTV (green), and rectum (cyan). The colorwash isodoses range from 20 Gy (blue) to 40 Gy (red)

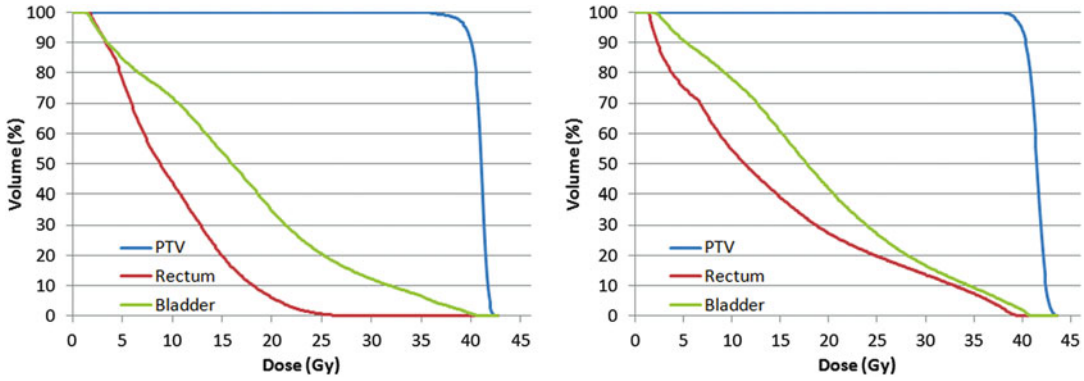


Fig. 2.11 Typical Dose Volume Histograms (DVHs) for the prostate planning target volume (PTV), rectum and bladder for patients with and without rectal spacers undergoing 40 Gy SBRT radiotherapy

Table 2.3 MSKCC plan evaluation criteria for SBRT extreme hypofractionation regimen of 40 Gy in five fractions

Structure	Metric	Criteria
PTV	Mean dose	101–103% (Acceptable range)
	Maximum dose	42.8 Gy (Acceptable) 44 Gy (Limit)
	$D_{95\%}$	40 Gy (Ideal) 36.25 Gy (Limit)
	Minimum dose	33.7 Gy–34.4 Gy
Rectum	Max dose	≤41.2 Gy
	$D_{1\ cc}$	≤38.5 Gy
	Mean dose	13 Gy (Ideal) 16.4 Gy (Limit)
	$V_{24\ Gy}$	≤25%
	$V_{30.15\ Gy}$	≤8 cc
	$V_{10\ Gy}$	≤52% (Guideline only)
Bladder	Max dose	42 Gy
	$D_{10\%}$	36 Gy
	$D_{50\%}$	20 Gy
Bladder trigone	Max dose	38 Gy
Urethra	Max dose	42 Gy
	$D_{1\ cc}$	40 Gy
Femoral heads	Max dose	31 Gy
	$D_{10\ cc}$	21.6 Gy
Skin	Max dose	32.4 Gy
Penile bulb	Max dose	40 Gy
	$D_{3\ cc}$	21.6 Gy
Large bowel	Max dose	29 Gy
Small bowel	Max dose	25 Gy

justification for further dose escalation to that area [84, 85]. Several groups have evaluated the use of multi-parametric MRI imaging and intensity modulated external beam monotherapy to identify and boost the radiation dose to the dominant lesion [12–15, 86]. Four of these studies boosted the dominant lesion under a conventional fractionation paradigm with doses ranging from 80 Gy in 40 fractions to 95 Gy in 35 fractions. Aluwini et al. [86] used the CyberKnife technology to perform an extreme hypofractionated regimen of 38 Gy in four fractions to the entire prostate and a boost of up to 11 Gy (total dose = 49 Gy) to the MRI-identified dominant tumor. The study was comprised of 50 patients with dominant lesions identified in 14. Although the dosimetric constraints imposed in the study were achieved for most patients, 30% had minor deviations, highlighting the technical challenges in this aggressive approach. All investigators concluded however that boosting the dominant lesion was technically feasible and resulted in toxicity profiles similar to those of whole-prostate conventional fractionation approaches.

Multi-parametric MR imaging has been the predominant imaging method evaluated for the purposes of differentiating tumor from surrounding normal prostatic tissue and segmenting the dominant lesions targeted for focal therapy. Specifically, T2-weighted imaging for localization based on anatomic visualization and diffusion-weighted (DWI), perfusion (DCE) and spectroscopic MRI for localization based on functional characteristics have all been fairly extensively studied. Although spectroscopy exhibits good specificity, the spatial resolution remains inadequate for planning purposes and it is used infrequently. On the other hand, specificity and sensitivity can be improved by including the complementary information from a combination of T2, diffusion and perfusion imaging. Groenendaal et al. [87] have studied the

congruence between tumor segmentations with diffusion and perfusion imaging using receiver operating curve (ROC) analyses and applying one or the other of the imaging sequences with multiple threshold values as the reference. Although excellent area under the curve (AUC) values were obtained for select patients, the average AUC value was only 0.6 with single imaging datasets, demonstrating a relatively low overlap between the two imaging methods and the possible advantage of using combined data.

Validation of MR-based localization through comparison with gold-standard pathology is technically challenging. Groenendaal et al. [88] segmented tumor tissue on T2, diffusion and perfusion imaging for five patients prior to prostatectomy and subsequently registered those delineations to tumor tissue delineated on the whole mount hematoxylin-eosin stained (H&E) sections. Congruence between the two methods was only 45–89% but addition of a 5 mm margin on the MR-based segmentations increased this to 85–100%. Only 2–3 mm of the MR margin was felt to be related to the MR-to-pathology registration uncertainty.

Several groups have pointed out the need to better understand the relationship between the parameters extracted from diffusion and perfusion imaging and the underlying structure and physiology of the prostate tissue. Doing so should strengthen our interpretation of the information provided by each and allow us to establish appropriate thresholds or other methods for classifying individual voxels as tumorous. Several studies have looked at the overall relationship between apparent diffusion coefficient and cell density within the prostate [89–92] with the results showing moderately strong correlations. Researchers from the University Medical Center Utrecht [93] investigated the voxel-level relationship between the apparent diffusion coefficient (ADC) and tissue features including cell density and presence of glandular tissue. They concluded that, at the voxel level, there exists significant heterogeneity of cell density and glandular tissue within normal prostate tissue and tumors that is reflected in the heterogeneity of the ADC map. Furthermore, for small tumors specifically, ADC values did not adequately reflect the histopathological features, perhaps due to partial volume effects, leading the authors to conclude that small tumors or parts of tumors might be missed on an ADC map.

In further recognition of the fact that T2, diffusion and perfusion imaging may be providing complementary information valuable for segmentation of the prostatic tumor, some groups are attempting to build quantitative models based on a voxel-level determination of tumor-bearing probability and to use those models to inform dominant lesion segmentation [36, 94–98]. For example, Groenendaal et al. [96] developed a logistic regression model using local statistics obtained from parameters from diffusion and perfusion imaging on 87 radiotherapy patients to predict tumor presence on a voxel level. After validation using prostatectomy patients, a method was also developed to stratify voxels into gross tumor volume (GTV), high risk clinical target volume (CTV) and low risk CTV based on tumor probability. Viswanath et al. [97] used texture features extracted from T2-weighted images. Dinh et al. [98] used over 30 features from multi-parametric MR, each patient's biopsy map and a population-based tumor probability atlas to create a model that was validated on a voxel level against pathology. Their results demonstrated an AUC of 0.78 when all features were combined and evaluated on patients from two institutions.

Although, as described above, the use of multi-parametric MRI alone or in combination with other features to automatically guide tumor segmentation for focal prostate radiotherapy is promising, it must still be considered investigational. Therefore, most ongoing clinical studies evaluating the role of focal irradiation of index lesions, are utilizing multi-parametric MR imaging with expert radiologist evaluation to define the tumor region [13, 14, 16].

At MSKCC, a Phase I study evaluating the feasibility of radiotherapy to the prostate and dominant intra-prostatic lesion using extreme hypofractionated, MR-guided SBRT is underway. The specific aims of this study are to assess the feasibility and toxicity of such treatment for

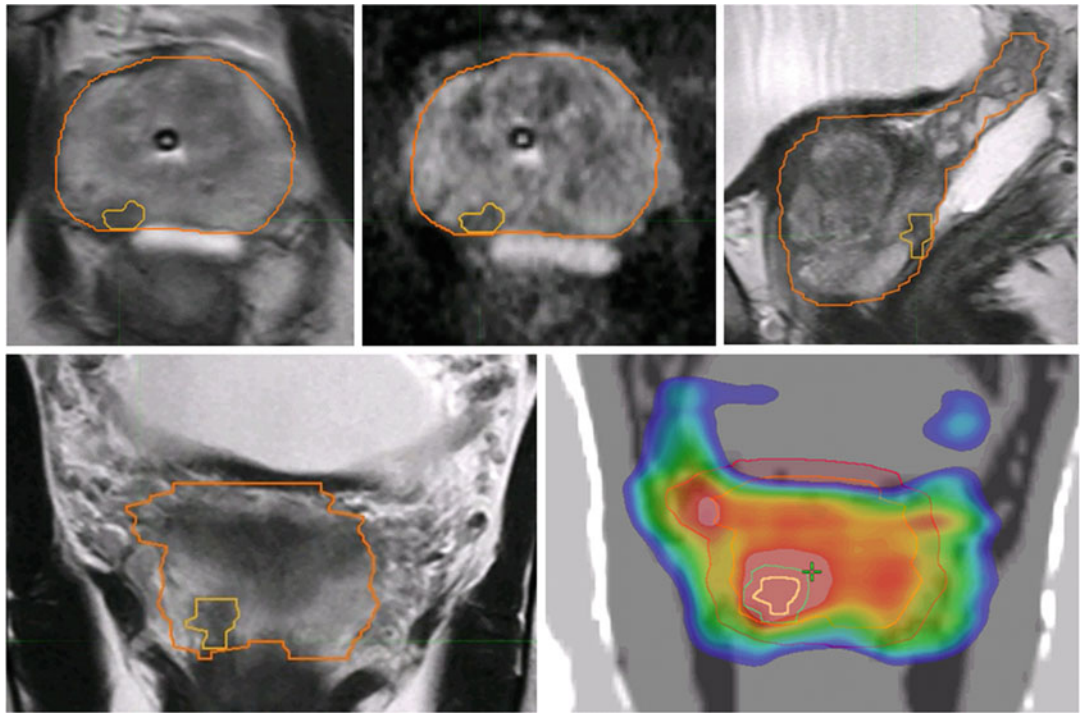


Fig. 2.12 (Top panel) Axial and sagittal T2-weighted images and axial DWI ADC map for a patient undergoing extreme hypofractionated SBRT with a simultaneous boost to the intra-prostatic dominant lesion (DIL). (Lower panel) Coronal T2-weighted image and corresponding synthetic CT image with overlaid VMAT dose distribution designed to deliver 40 Gy in five fractions to the prostate and 45 Gy in five fractions to the DIL. The colorwash isodoses range from 30 Gy (blue) to 45 Gy (red). For all panels, the DIL and prostate and seminal vesicles are shown in yellow and orange, respectively. The PTVs for the DIL and prostate are shown in green and red

intermediate risk patients with a regimen that consists of 45 Gy in five fractions to the dominant lesion and 40 Gy to as much of the remaining prostate as possible given strict normal tissue constraints to the bladder, bladder trigone, penile bulb and neurovascular bundles. Several weeks prior to the simulation, the patient undergoes a single procedure during which gold seed fiducials and a rectal spacer are implanted to aid with later image-guided treatment delivery and reduction of the rectal dose. Patients then undergo multiparametric MR imaging and MR-only simulation as described in the previous sections. A radiologist and radiation oncologist jointly review the MR images to define the dominant lesion PTV and a VMAT plan is then developed using methods similar to those described in Sect. 2.3. At the time of treatment, patients are set up using on-board, fiducial-guided kilovoltage imaging. Correct positioning, bladder and rectal filling are confirmed with cone beam CT (CBCT) registered to the synthetic CT and/or source MR images. Simultaneous megavoltage and kilovoltage imaging during treatment is used to track the prostate position from the gold seed fiducials with treatment interruption if positional shifts of >1.5 mm/10 s are observed [55]. An example of MR images and the VMAT plan incorporating DIL irradiation for one patient is shown in Fig. 2.12.

2.4.2 Adaptive Planning and MR-Guided Treatment Delivery

As discussed earlier, the combined use of MR-only treatment planning and image guidance for patient setup and monitoring of motion during treatment has allowed us to decrease the margin

around the prostate target and facilitated extreme hypofractionated treatment approaches. Further technological progress in the near future will support on-line adaptive re-planning and MR-guided delivery. Dose delivery at each session will be able to conform to the prostate and normal tissue "position-of-the-day" and treatment delivery gated using real-time MR-guidance will ensure that the high dose region adheres to an increasingly tight margin around the target.

Several groups have investigated the feasibility of on-line adaptive prostate radiotherapy using approaches such as plan libraries [99, 100] and MLC segment shape and weight modification [101–105]. Plan library approaches generate a series of plans a priori to reflect the most likely anatomical configurations between the prostate and other relevant tissues including the pelvic lymph nodes, rectum and bladder. At each treatment session, the most appropriate plan is then selected for delivery based on a measure of similarity between the simulation and treatment image sets such as mutual information. Qi et al. [99] evaluated the dosimetric advantages that could be expected by being able to select at each treatment session from any of nine available plans designed to accommodate typical changes in the superior–inferior and anterior–posterior position of the prostate with respect to the pelvic lymph nodes. Compared to the typical approach which merely shifts the isocenter based on the daily image-guided setup, a library-based adaptive approach maintained coverage of the prostate but improved coverage of the pelvis. Although the dosimetric results with full online re-optimization were still better, an a priori plan library approach can potentially be implemented with fewer resources and/or changes to the record and verify system or linac treatment console. MLC segment modification approaches have been proposed that rely on deformable registration between the images acquired at simulation and treatment [101] or more simply, a comparison of the target structure outlines [105] to determine the information necessary to morph the MLC segments to better conform to the treatment day geometry. Such approaches can, in theory, more accurately account for rigid body translations and rotations and deformations than a plan library approach albeit with additional effort at the treatment machine.

Although approaches for adaptive radiotherapy have been proposed, clinical implementation has been lacking due to the challenges of providing robust and efficient software functionality on standard linear accelerators and the relatively poor image quality of cone beam CT (CBCT). With the advent of MR-guided radiotherapy delivery systems (MRgRT) however, these challenges are being addressed and on-line adaptive radiotherapy is becoming increasingly feasible [106]. The superior pre-treatment imaging afforded by MRgRT systems should ultimately facilitate daily plan adaptation not only to the position of the prostate but to the dominant lesion as well. MRgRT systems will also support gated delivery based on real-time imaging, thereby further mitigating dose delivery inaccuracies resulting from intra-treatment motion. In the first version of such a system, the ViewRay MRIdian[11] system is able to monitor motion in a sagittal plane at approximately 4 Hz, perform the necessary deformable image registration, segment the structure and gate delivery based on user defined thresholds combining distance and time criteria. Further development of such systems and their integration with MR-only simulation and planning workflows will most certainly be a major factor in the further adoption and advancement of adaptive hypofractionated SBRT techniques.

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Organ Motion Considerations and Tracking During Prostate SBRT

3

Laura Happersett and D. Michael Lovelock

3.1 Introduction

The environment in which the prostate is located is spatially very dynamic; the varying volumes of stool and gas in the rectum, filling of the bladder and respiratory motion can all contribute to displacement of the prostate gland and seminal vesicles with respect to the bony pelvis. In particular, the use of the Calypso system with which electromagnetic transponders implanted into the prostate can be monitored in real time has revealed that the prostate may have a complex trajectory during the treatment session. For example, see the dynamic prostate trajectory in Fig. 3.1. Both slow drifts in position of more than 5 mm, and transient shifts of more than 10 mm lasting 20–30 s are commonplace. Average displacement also increases with time; Langen et al. [1] reported that 5 min after patient alignment, 16% of the 17 patients studied had displacements >3 mm, at 10 min the percentage had doubled. This is an important factor given the longer treatment times associated with SBRT.

The goal of accurate target positioning, both at pre-treatment setup and during treatment, via imaging or electromagnetic transponders, is to reduce the uncertainty with which the target and possibly the critical structures are positioned with respect to the radiation isocenter. An immediate benefit is the reduction of the PTV margin required for target dose coverage. This results in lower dose to critical structures, making possible the planned increase in the biologically effective dose. Prostate positioning has traditionally been accomplished with skin marks, radiographic bony pelvis alignment, and more recently in prostate SBRT, alignment of implanted fiducial markers prior to treatment fraction. Using measured displacements of implanted fiducials, the PTV margins required using the van Herk formulation [2] have been estimated to be reduced from 4.5 to 4.3 mm in the SI and AP directions using only pre-treatment Image guided setup to 2.9 and 2.8 mm respectively when a single mid treatment intra-fractional correction is made [3].

The use of image guidance has been reported to result in improved biochemical tumor control and reduced rectal toxicity in treatment using conventional fractionation [4]. It is assumed that this arises from the improved dose coverage to the target and a reduction in dose to the rectal wall. In the setting of prostate SBRT where target positioning is done only once prior to dose delivery, the time that elapses between the final pre-treatment imaging session and the beginning of dose delivery should be minimized [1, 5]. Such

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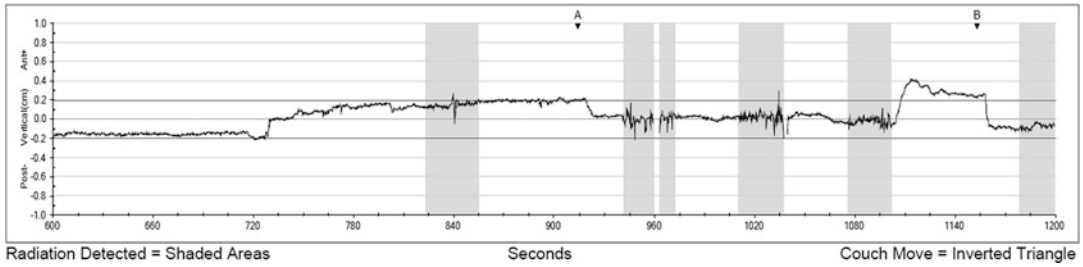

Fig. 3.1 Prostate motion during a treatment session. A Calypso trace of the target motion in the Ant/Post direction is shown. A tolerance of ±2 mm in all directions was used. Therapists were instructed to halt the beam and correct couch position if the tolerance was exceeded. Evident is a slow drift in the anterior direction (750–900 s interval), and more rapid anterior shifts at 725 and 1100 s. The couch position was corrected twice between beams (A and B Triangles). The therapists also held the beam at 960 s because the SI tolerance was exceeded (not shown) but the mis-positioning resolved itself in a few seconds

image-guidance has been achieved with various technologies, including volumetric imaging of the prostate [6], orthogonal radiographs of implanted fiducial markers [7], and electromagnetic transponders [1].

Given the higher dose per fraction, and tighter target margins associated with SBRT, the spatial accuracy of dose delivery is of key importance. The dynamic motion of the prostate during radiotherapy indicates that a single imaging procedure used to position the prostate prior to dose delivery may be insufficient. Intra-fractional monitoring and correction of the prostate position may be necessary. In the rest of this chapter, we review reports on the dosimetric benefit intra-fractional monitoring and correction. We define Manual Tracking as online monitoring with manual correction, and Dynamic Tracking as corrections made automatically via the MLC, couch or robot arm. Bowel preparation and other interventions taken to minimize prostate translations and rotations are also discussed.

3.2 Patient Setup and Preparation

3.2.1 Prone Versus Supine Setup

Compared with supine setup, the prone setup position for prostate patients has been found to decrease the rectal wall average dose, and the V95 (volume of wall receiving at least 95% of the prescription dose), especially near the seminal vesicles [8]. The use of real-time tracing of prostate position using electromagnetic transponders has revealed that although the average displacements are small, the supine position results in significantly less prostate respiratory motion in the AP and SI directions [9]. Patients are setup supine at MSKCC.

3.2.2 Immobilization Molds

Immobilization molds, in use for many years in prostate patient setup, have been shown to reduce setup error, based on bony anatomy. Techniques generally include use of either vacuum lock or alpha cradle cushion placed under the patient, or an overlying thermoplastic sheet molded to the patient shape. Studies comparing these two methods have resulted in different conclusions. Malone et al. [10] all have shown the thermoplastic technique had less setup error compared to the vacuum lock cushion, while White et al. [11] had shown the opposite. Whichever method that is chosen, it is recommended that the device is be locked on the couch at the same index position for each treatment. This permits record and verify systems to alert therapists to possible setup errors.

3.2.3 Bowel and Bladder Preparation

Bladder, rectal and bowel preparations are very important. Bladder filling during treatment will

displace the prostate in the posterior/inferior direction, while the distension due to rectal gas can result in large rotation of the prostate. Although such patient preparations will not eliminate motion, they are expected to reduce the frequency of intra-fractional correction. The instructions given to the patient must not be too onerousness to cause noncompliance. In a review, Clemente et al. [12] report that the most frequent reported rectal and bladder conditions were full bladder and empty rectum. Instructions for bladder filling range from drinking 250 to 500 ml 1–2 h before treatment. Cramp et al. [13] reported the use of an ultrasound bladder scanner to quantify the rate of bladder filling after drinking. The results were used to generate patients with customized instructions on when to drink prior to treatment. Patients with individualized bladder instruction needed 17% less intervention post CBCT compared to those patients that were given a standard time. Ideally patients are treated with an empty rectum. Instructions given to patients at MSKCC are listed Table 3.1.

3.2.4 Effects of the Endorectal Balloon, an Immobilization Device, and Hydrogel Spacer on Prostate Motion

The use of an endorectal balloon (ERB) both helps to stabilize prostate position by pushing it anteriorly, thereby improving target coverage, and by displacement of the posterior rectal wall away from the high dose region, in part sparing this normal tissue. Researchers at UT Southwestern [14] report intra-fractional prostate AP motion to be about half that of earlier reports, and they attribute this to their use of an ERB. Other groups have reported that the daily use of an ERB reduced intra-fractional prostate motion in patients receiving RT with conventional fractionation. Using electromagnetic transponders, Smeenk et al. [15] observed large reductions in AP displacements with the use of an air-filled ERB. Both et al. [16] observed that with the use of a water filled ERB, prostate displacement still increased with time, but if treatment could be completed within 6 min, a 3 mm PTV margin would be feasible. We note however, that the ERB has not been found to reduce the need for image guidance [17, 18]. Nor has it been found to always reduce rectal dose [19]. A device that stabilizes the prostate position more directly has been developed; Nicolae et al. [20] have described a novel endorectal immobilization system developed in house consisting of a rectal probe that is fixed to the treatment couch. In a prospective study of 20 SBRT patients, they reported all pre to post treatment 3D shifts seen in CBCT scans to be less than 3 mm. More recently, hydrogel spacers have been used to increase the separation between the prostate and the anterior rectal wall. Picardi et al. [21] discuss the possible reduction in prostate motion as being analogous to the reduction due the presence of an ERB. In this analysis of 20 moderately hypofractionated patients, they found no significant difference in inter-fractional prostate motion.

3.3 Dosimetric Benefits of Tracking

In a study of 28 patients planned with seven to nine IMRT fields with a posterior PTV margin of 3 mm, and 5 mm elsewhere, a study from the Duke Medical Center [22] found small dosimetric gains from tracking. Patients were treated to 37 Gy in five fractions and corrections were made only between beams. For the CTV, the

Table 3.1 Instructions to prostate patients being treated with hypofractionated radiotherapy at Memorial Sloan Kettering Cancer Center

Bowel/ Rectum	• Mix 1 rounded teaspoon of psyllium (Metamucil) powder in 8 ounces of water and drink every morning. Drink it 2 h before or 2 h after you take your other medications. • Do a Fleet enema 3 h before simulation and each treatment.
Bladder	• You will be treated with full bladder. In general, the steps are to void, then take 8 ounces of water 45 min before simulation and each treatment.

delivered dose distribution parameters Dmin, D99, and Dmean were all less than 1.4% lower than the planned, for the PTV, D1cc and D99 were within 0.2 Gy of that planned.

Eighty nine patients accrued to a prostate dose escalation protocol at Memorial Sloan Kettering Cancer Center [5] were treated to between 32.5 and 40 Gy in five fractions with beam arrangements and PTV margins similar to those used by Duke. Target position was monitored continuously using electromagnetic transponders; therapists were instructed to stop treatment and to correct the setup both between beams and during beam delivery if the displacement exceeded 2 mm in any direction. As in the Duke study, little prostate motion was found for the typical patient, and the PTV margins were adequate. However, by looking at the distributions of displacements that would have existed by the end of treatment had no corrections been made, it is evident that prostate motion occurred in a significant proportion of treatments. For approximately 18% of the treatment time, the target would have been at or beyond the tight 3 mm posterior margin. Similarly for anterior motion assuming the anterior rectal wall remained in contact with the posterior aspect of the prostate, the rectal wall would have been displaced $\geq$3 mm anteriorly into the high dose region 6.4% of the time. Dosimetric consequences of the intra-fractional corrections were estimated on a subset of patients by computing the dose distributions that would have been delivered had no corrections been made. Sixteen of 89 patients had beams that would have been delivered in part with a posterior target displacement of 4 mm or more. For these patients the delivered dose for the entire treatment course was computed by accumulating dose as a function of target position. For nine of these patients, the PTV D95 was less than 90% of the prescription dose. Thus approximately 10% of SBRT prostate patients in this protocol would have had a delivered dose distribution that would not have met the treatment planning coverage requirements if tracking had not been used. Improvements in dosimetric coverage metrics have also been reported in a multi-institutional Australian trial of prostate tracking during VMAT delivery, although results are limited at this early stage [23, 24].

3.4 Monitoring and Tracking Techniques

3.4.1 Electromagnetic Transponders

The Varian Calypso® system can monitor the position of the prostate gland in real-time by localizing three electromagnetic transponders implanted into the prostate. A radiolucent coil array positioned above the patient excites each of the transponders and their resonant response is detected by the array, allowing the positions to be determined with respect to the array. Localization with respect to room isocenter is achieved by continually monitoring the position of the coil array with respect to isocenter using a set of room mounted infra-red emitters and cameras. Using the transponders as a surrogate, the system updates the position of a target reference point, typically the isocenter, 15 times per second, thus monitoring is effectively continuous.

Transient shifts in position can be managed by setting tolerances in each direction on the displacement of the prostate from its planned position and automatically gating the dose delivery off when the displacement is exceeded [25]. When connected to the Varian Truebeam® treatment machine, the time between the target displacement exceeding the tolerance and the beam being gated off is less than 100 ms. Slow drifts are readily apparent to the therapists from the real-time display of prostate displacement. These can be corrected by the therapists stopping the beam if necessary, electronically transferring the Calypso generated couch correction from the Calypso system to the Linac, enabling the couch adjustment to be implemented on the Linac, and then restarting the beam. This can be done in about 30 s. A cautionary note: implanted Calypso transponders will produce a volume of null signal in MR scans several centimeters in diameter, precluding the use of MR imaging in followup. This factor needs to be incorporated into the clinical workflow [26].

3.4.2 The Cyberknife

The Accuray Cyberknife® is unique in that it is the only commercially available treatment system that dynamically tracks the prostate during dose delivery [27], automatically correcting beam alignment in response to shifts or rotations in prostate position during dose delivery. The Linac, including the beam generation and collimation system is mounted on a large robotic positioning arm. The prostate position is monitored throughout treatment by acquiring orthogonal radiographs using dual in-room kV imagers. Triangulation of four implanted gold fiducial markers is used to determine rotations or translations of the prostate from its planned position. The Cyberknife system uses the robotic arm to reposition the beam to compensate. Imaging frequency is adjusted automatically depending on the motion observed. For prostate tracking, the initial frequency is once every 60 s, dropping to once every 5 s when necessary. The latest version of the Cyberknife, the M6 as illustrated in Fig. 3.2, is equipped with an MLC maximum aperture of 10 × 11 cm, and is capable of dose rates up to 1000 MU/min. This maximum field size is large enough to make possible the selection of a single target point for prostate treatment. At the NYU Winthrop Cyberknife Center in New York, a typical SBRT prostate plan involves the use of a single target reference point, and 20 nodes, or non-coplanar robot positions. Each node has an individual fixed MLC aperture.

3.4.3 The BrainLab ExacTrac Imaging System

The ExacTrac is an in-room mounted kV imaging system that can be added to a vault and is compatible with the major treatment machine vendors. It consists of dual kV imagers arranged such that they are orthogonal and the central axis of each imaging system is aligned with the radiation isocenter of the Linac. In order to minimize the blocking of the imagers lines of sight, the kV sources are offset from the plane of gantry. Prostate localization is done using implanted fiducial markers. Once a pair of radiographs is acquired, the system uses proprietary automatic 2D/3D registration software to determine the three translational and three rotational corrections needed to align implanted fiducial markers. The corrections can be manually applied to a robotic couch top. When the gantry position is within a few degrees of the 0, 90, 180 and 270, both kV imagers have clear lines of sight thus enabling the 6D registration. During a 360 VMAT delivery arc, there are

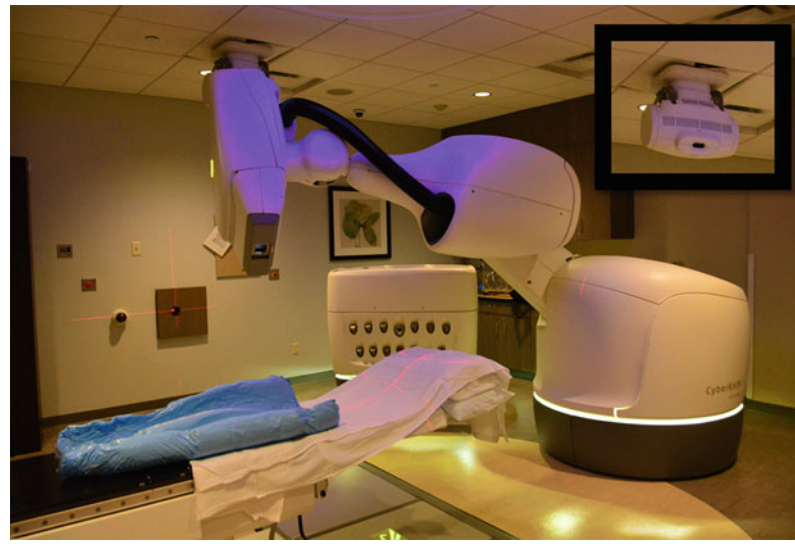

Fig. 3.2 The MLC equipped Cyberknife. The Linac mounted on the robotic arm with the MLC collimator attached. The inset shows one of the two ceiling mounted kV sources. The imaging panels are concealed below floor level. In the center background is the accessory console which holds the MLC, a circular collimator of variable radius and the fixed diameter cones. Image courtesy of NYU Winthrop Cyberknife Center in New York City

four opportunities for the therapists to determine prostate position and rotation. Additionally, a single image and resulting 2D registration, called Snap Verification, can be used to verify prostate position at any time. If used, this monitoring process has been estimated to significantly reduce necessary prostate PTV margins [28, 29].

3.4.4 Varian Intrafraction Motion Review (IMR)® and Auto Beam Hold (ABH)®

The Varian Truebeam® radiotherapy machine allows the kV imaging system to be deployed during IMRT or VMAT dose delivery. When equipped with the Advanced Imaging option, kV images can be acquired during treatment by triggering in several ways, such as by time interval or by gantry rotation interval. The outline of contoured or marker structures with user defined tolerance margins can be projected onto the kV images as they appear at the image reviewing screen during dose delivery. By carefully watching the radiographs, the therapists can visually check that the structure or fiducial marker in the image lies within the projected outline. Departmental guidelines must be setup that indicate when the therapist is to intervene and what tolerance margin to use. See Fig. 3.3 for an example and discussion of departmental procedures at MSKCC. Note that treatment has to be stopped, and an orthogonal image pair acquired to determine the 3D couch correction needed to return the target to its planned position.

Auto Beam Hold [30] is an extension of this functionality. When ABH is activated, the fiducial markers are localized within the image automatically, and if they fall outside of the tolerance, the dose delivery is gated off.

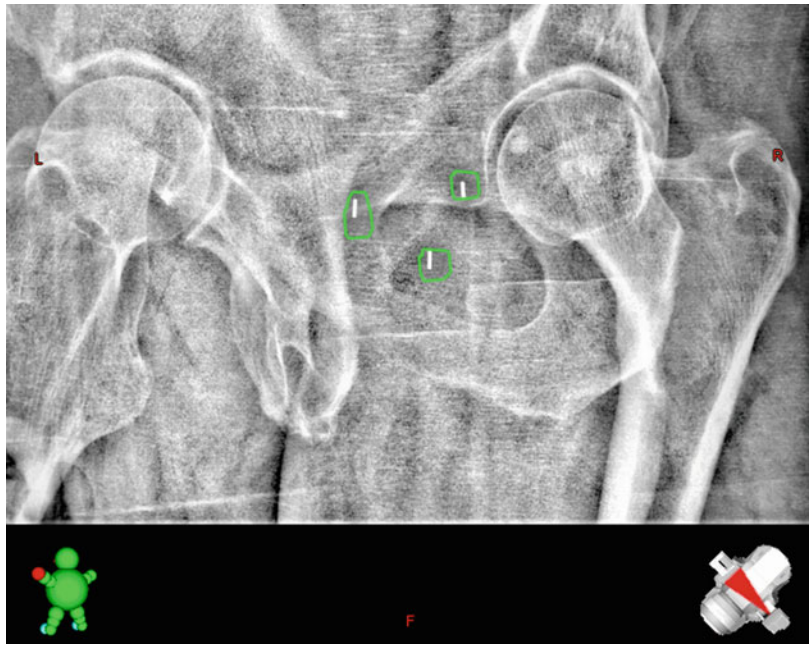

Fig. 3.3 A kV image acquired during a VMAT arc using intra-fractional Motion Review. Therapists visually inspect the images to ensure the implanted fiducial markers fall within the projected outline. At MSK, for prostate patients being monitored using IMR, structures are created by contouring each fiducial marker and expanding it 2 mm. kV images are acquired every 20° of gantry rotation for VMAT, or every 10 s for IMRT. If one fiducial marker moves outside of the contour for two consecutive kV images, the treatment is interrupted and an orthogonal kV pair taken. Once shifts are made the treatment is resumed

3.4.5 The Elekta Clarity® Autoscan Ultrasound System

The Elekta Clarity is an ultrasound (US) system that can provide real-time monitoring of the prostate position during dose delivery. An automated scanning transperineal US (TPUS) device mounted on the linac couch acquires images of the prostate during treatment. The position of the scanner is monitored in real-time with an in-room infrared tracking system, allowing the system to compute the prostate position with respect to isocenter. TPUS imaging has can provide a clearer image of the prostate than trans abdominal US because it is not shadowed by the pubic symphysis, reduces the concern of prostate displacement due to probe pressure and does not interfere with treatment delivery. A second Autoscan device is used to provide an intramodal reference image at the time of CT simulation. This registration process has been found to be quite accurate. In a study [31] comparing the intramodal US registration with CT-CBCT registration accuracy of patients implanted with fiducial markers, the mean discrepancies were all sub-mm. We note that at the time of writing, however, we could not identify reports of this interesting system being used to monitor and correct intra-fractional errors.

3.4.6 Non-Commercial Systems

Neither the KIM project, nor the MV-kV project described below, are commercially available. They are, however, of particular interest because they make efficient use of standard equipment that many centers already have, that is a modern C-arm gantry Linac equipped with on-board kV and MV imaging. Such projects, if adopted by the equipment vendors and the radiotherapy community, would make possible the near real-time monitoring of prostate position during treatment, bringing the possibility of treatments with an improved therapeutic ratio to a larger number of prostate patients.

3.4.6.1 The Kilovoltage Intrafraction Monitoring (KIM) Project and the SPARK Trial

KIM operates by acquiring a set of kV images from the on-board imaging system as the gantry rotates during VMAT dose delivery. kV images are pulled from the imager in real-time by using a dedicated frame grabber and computer [23]. This frame grabber system picks off images being sent from the imaging system without affecting operation of the Linac. The implanted markers are localized within the plane of the image with in house software. The conversion of marker coordinates obtained from a rotating monoscopic 2D imaging system to the 3D marker trajectory in room coordinates system is based on the work of Paulsen [32]. In outline, the method requires prior information on the marker locations which could be obtained from a CBCT, or a shorter imaging arc of 120° taken just prior to treatment. From this prior information, 3D Gaussian probability distributions are generated for each marker. After each marker location is determined in the rotating 2D image, the 'depth' coordinate is calculated using a best match with the 3D PDF using a maximum likelihood estimator. The tracking accuracy has been verified clinically with a ten prostate patient prospective study [33]. Comparison of the KIM coordinates with coordinates generated by triangulation from simultaneously acquired orthogonal kV and MV images; the mean and standard deviation of the differences in 3D position were 0.46 ± 0.58 mm.

The KIM process is also capable of tracking the target rotation. In a first-treatment report [23], the rotation was compared to that calculated using MV-kV triangulation. The mean and standard deviation of the difference in pitch was $0.3 \pm 3.3°$. Rotation determined using the CBCT projections prior to beam delivery was corrected manually prior to treatment by the therapists if the rotation about any axis exceeded 15°.

The information from KIM can used to correct target positioning errors in real-time. In an earlier effort lead by Keall, a MLC leaf tracking

technology was developed and implemented in the clinic using real-time target location from calypso transponders [24]. The leaf motion was modified dynamically to adapt to changes in target position as the dose was being delivered. More recently, the MLC tracking technology has been adapted such that it can be driven by the KIM signal [34]. In a prospective study of 15 prostate patients treated using conventional fractionation with VMAT arcs, intra-fractional shifts of prostate position were automatically corrected for in real-time by dynamic modification of the mlc leaf trajectories. Note that this was accomplished on a C-series Varian Linac with a modified MLC controller.

The KIM process is now being used in a prospective phase II multicenter trial for prostate patients in Australia. The SPARK (Stereotactic Prostate Adaptive Radiotherapy using KIM) trial will accrue 48 prostate patients who will receive SBRT [35]. Depending on the Linac type, prostate motion will be managed either by MLC tracking during the IMRT or VMAT dose delivery, or by couch correction. If couch correction is implemented, treatment is interrupted if the prostate is displaced by more than 2 mm for more than 5 s. A couch correction, determined using the KIM process, is applied. Tighter tolerances are allowed at the discretion of the treatment team. During MLC tracking, adjustment for prostate displacement is essentially continuous.

3.4.6.2 Simultaneous MV-kV Acquisition for Intra-Fractional Motion Monitoring: The MSKCC MV-kV Technique

The MSKCC MV-kV process [36] is a method to monitor 3D prostate position for SBRT prostate patients treated with VMAT arcs. As with KIM, this approach uses a frame grabber to pick off, in real time, images being acquired without affecting linac operation. The MV images are acquired at a frequency of a 9.5 Hz, while kV images are triggered at 20° gantry intervals. Short-arc digital tomosynthesis (SA-DTS) images centered on gantry angles orthogonal to the kV images are created to blur overlying and underlying anatomy and sharpen fiducial markers. These SA-DTS images are paired and registered to the corresponding kV image. To insure fiducial marker visibility on MV image, the leaf motion files generated by the Varian Eclipse® treatment planning system are modified. At gantry angles corresponding to triggered kV images, low dose MV imaging control points are inserted with MLC positions that are the identical to the previous treatment control point except for particular leaf positions that have been adjusted in order to expose one of the fiducial markers as shown in Fig. 3.4.

The imaging dose is subtracted from the treatment dose and the modified plans are recalculated in Eclipse® and renormalized to meet planning criteria. During treatment, an in-house program,

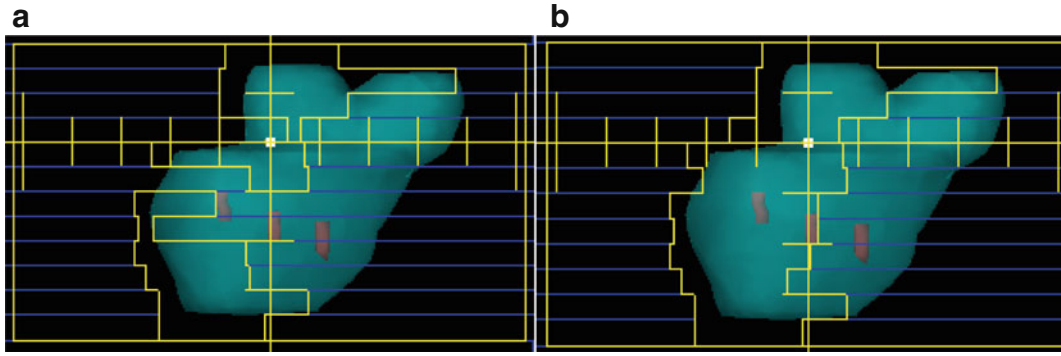

Fig. 3.4 Comparison of treatment control point to imaging control point. Prostate and fiducial markers are projected in cyan and red, respectively. (**a**) Treatment control point—All three fiducial markers are blocked by MLC. (**b**) Imaging control point—MLC changed to expose one fiducial marker

Sequence-Reg, registers the kV and MV DTS image to reference images created from a 3D model of the fiducial markers. The accuracy of the MV-kV auto-registration [36] has been compared to manual registration; the mean deviations were between 0.12 and 1.4 mm. The shifts from the initial setup position of the day are displayed and plotted in real time as shown in Fig. 3.5. If the center of mass of the three fiducial markers tracks off by more than the user specified amount in any direction, for two kV image acquisitions, Sequence Reg gives an audio alarm to alert the therapists. The therapists then halt delivery, acquire an orthogonal 2D pair using the linac's software, correct the patient position, then resume treatment. Sequence Reg is used to monitor prostate position for the remainder of treatment. Currently at MSKCC, a tolerance of 1.5 mm is used. To date, over 100 hypo-fractionated prostate patients have been treated with this monitoring and correction procedure. It is now standard of care at MSKCC. This intra-fractional monitoring technique has the advantage in that the kV imaging dose is comparatively very low. In addition, it offers straightforward accurate method of registering two simultaneously acquired 2D image sets to obtain a 3D match. Note that this was accomplished on a Varian Truebeam® Linac.

3.5 Summary

Although clinical data from prospective trials is sparse, the results can perhaps be summarized by noting that while measures of target coverage for the typical patient show only small improvements, there can be large improvements in coverage for patients who have atypical prostate motion. In the setting of SBRT, unusual prostate motion involving large displacements will not be 'averaged out' because the number of fractions is low. In effect, tracking makes the

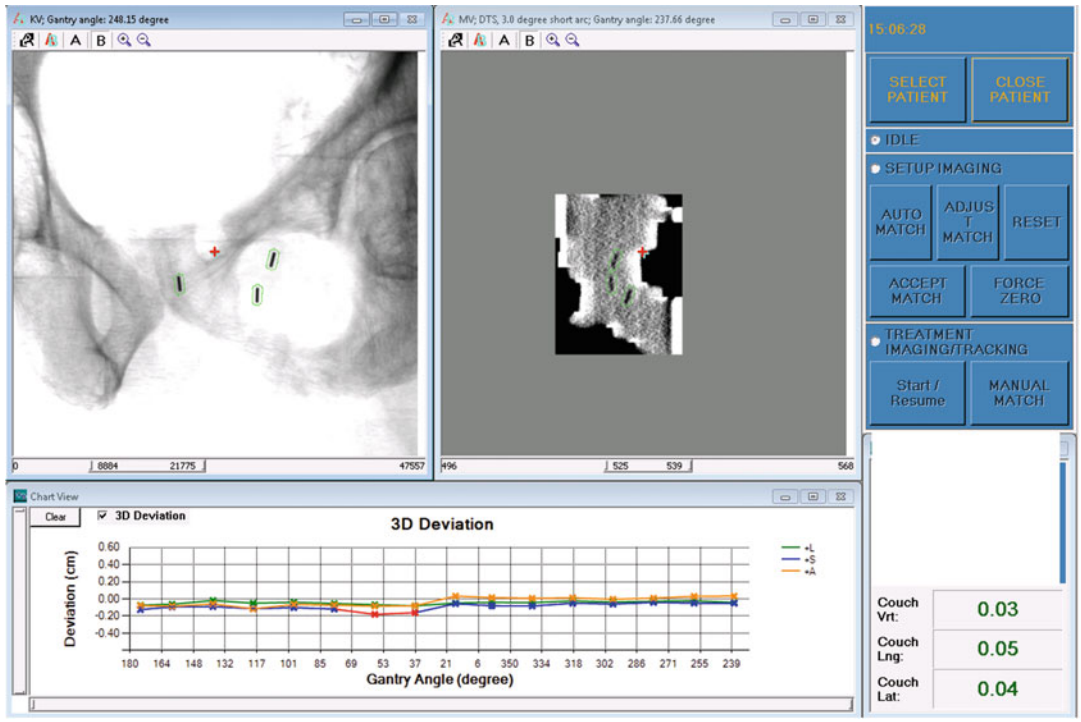

Fig. 3.5 Example of Sequence Reg used for monitoring: kV image on left and MV DTS image on right. Patient trace and shifts displayed. At approximately gantry angle 55, fiducial marker COM was out of tolerance for two control points. Beam was turned off; MV-kV images on demand were taken. After shifts applied treatment was restarted and patient did not track off again

clinical delivery process much more robust, with a much higher likelihood of delivering the planned dose distribution to all patients, including the those patients with outlier prostate motions. We have presented both commercial and developmental systems for prostate intra fractional monitoring and correction. If the necessary hardware is not available, periodic intra fraction imaging is encouraged and can still be incorporated into the workflow.

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Imaging and Anatomic Considerations for Prostate and Pelvic Organs Contouring

4

Tomer Charas, Alberto Vargas, and Michael J. Zelefsky

4.1 Introduction

Radiotherapy techniques are becoming more sophisticated and allow delivery of better radiation treatments with increased accuracy and precision. The ability to treat volumes more accurately is reliant on the radiation oncologist's ability to properly define and contour the volumes. Prostate cancer radiotherapy specifically poses a challenge as high doses of radiation are being delivered, and with the increasing interest in ultra-hypofractionated protocols, correctly defined target volumes and normal tissues becomes crucial. Currently, most oncological institutions use CT-based simulation and planning, and this chapter will include a section dedicated to the practical considerations for CT based contouring. MR imaging offer exquisite detail of the prostate and the male pelvis anatomy, and most of this chapter will focus on introducing the different structures needed to be recognized by the radiation oncologist using MRI for contouring. We aimed at providing useful information and helpful tips for successful contouring when treating prostate cancers with SBRT.

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4.2 CT Based Contouring: Practical Considerations

CT based treatment planning has been the cornerstone in prostate radiotherapy treatments in the last decades, and today it remains the main modality in treatment planning. CT simulation includes acquisition of a set of images with electron density values that are used by the treatment planning systems for dose calculation, plan optimization and digitally reconstructed radiographs (DRRs) generation. An additional goal would be contouring the target and the organs at risk based on the detailed anatomy. The CT should be performed in a reproducible fashion, and provide accurate information about patient geometry and tissue composition. After CT images are acquired and delineation of volumes have taken place, dose calculation will be performed by using voxel-based electron density maps [1].

Prostate target and pelvic contours, based on CT scans have been published and widely accepted [2, 3]. Online tools are accessible [4, 5] and have been evaluated and found to allow contouring harmonization and allow assessment of radiotherapy centers [6].

When delineating the prostate and the surrounding tissues, MRI images are often used in parallel to CT images to provide better volume definition [7]. It is worthwhile noting that accurate outlining of the structures, especially the prostate, is difficult on CT due to its limited soft-tissue contrast.

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Several studies showed high variability in prostatic apex, prostatic base and the base of seminal vesicles delineation [8]. This variability can be considerable and was reported to be 1.5–9% for the same user (intra-observer) and even higher—10–18%, among different users (inter-observer) [9]. The correct definition of the target volume becomes increasingly important when new, sophisticated, more conformal treatments and higher doses are given; Hence the incorporation of MRI into the routine use of volume definition can greatly increase treatment quality.

4.3 Image Fusion

Intermodality registration of CT and MR images will allow the users to benefit from the highly detailed anatomy presented on MRI images, while facilitating treatment planning systems to function optimally using the CT acquired data. Compared with MRI, CT based user defined volumes overestimate prostate size by 35% [3]. CT–MRI image fusion-based treatment planning allows more accurate target volume identification in prostate cancer patients than CT alone. When fusing the image sets, a prostate-to-prostate local registration is recommended; registration of the pelvis (i.e, boney anatomy) may be insufficient due to external (positioning) or internal (bladder and bowel filling states) variations that are difficult to control and reproduce. Matching exact pelvic position is therefore not required, but should be approximated [10]. MRI fusion and MRI simulation techniques are discussed in detail in a different section of this book.

4.4 Equipment, Techniques and Protocols for MRI Imaging of the Prostate

Prostate MRI can be performed on 1.5 and 3 Tesla systems; most modern 1.5 Tesla systems provide sufficiently high image quality even without the use of an endorectal coil. A standard diagnostic prostate MRI protocol consists of the following sequences:

- Wide field-of-view (FOV) T1-weighted images without fat saturation from the aortic bifurcation through the pelvis allow for the evaluation of pelvic lymph nodes, the bony pelvis, and possible post-biopsy changes (e.g. hemorrhage) in the prostate gland.
- T2-weighted images with 3–4 mm slice thickness and a prostate-focused narrower FOV (i.e. 140–230 mm, depending on prostate size) in the axial, coronal, and sagittal planes provide the basic anatomic information at the high spatial resolution. As a time-saving alternative, T2-weighted images can be acquired as a three-dimensional axial sequence with reconstruction of coronal and sagittal images during post-processing. In contrast to many other oncologic MRI applications, fat-saturated T2-weighted sequences have no role in prostate MRI.
- Diffusion-weighted images (DWI) in the axial plane provide functional information about water diffusivity, which increases diagnostic precision.
- Dynamic contrast-enhanced (DCE) sequences, which used to be routinely acquired, do not seem to increase the diagnostic precision over combined T2 + DWI sequences in the setting of untreated prostate cancer. For the evaluation of recurrent cancer (e.g. after surgery, radiation, focal ablation, or hormonal therapy), DCE sequences are essential as a diagnostic component and should be routinely acquired.

MRI simulation scans will include T2-weighted imaging with wide or narrow FOV, depending on the target to be treated (i.e pelvic lymph nodes or prostate only). For diagnostic MRI, artifacts caused by bowel motion can be reduced by using anti-peristaltic medications (e.g. glucagon) or by bowel preparation (i.e, fleet enema), but this is not commonly done for MRI simulation.

4.5 Prostate Zonal Anatomy on MRI

The prostate is located in the pelvis and sits within the levator sling. The normal zonal anatomy of the prostate is best demonstrated on T2-weighted imaging (Figs. 4.1, 4.2 and 4.3). The main components, their locations, MRI appearance and relevant details are described in

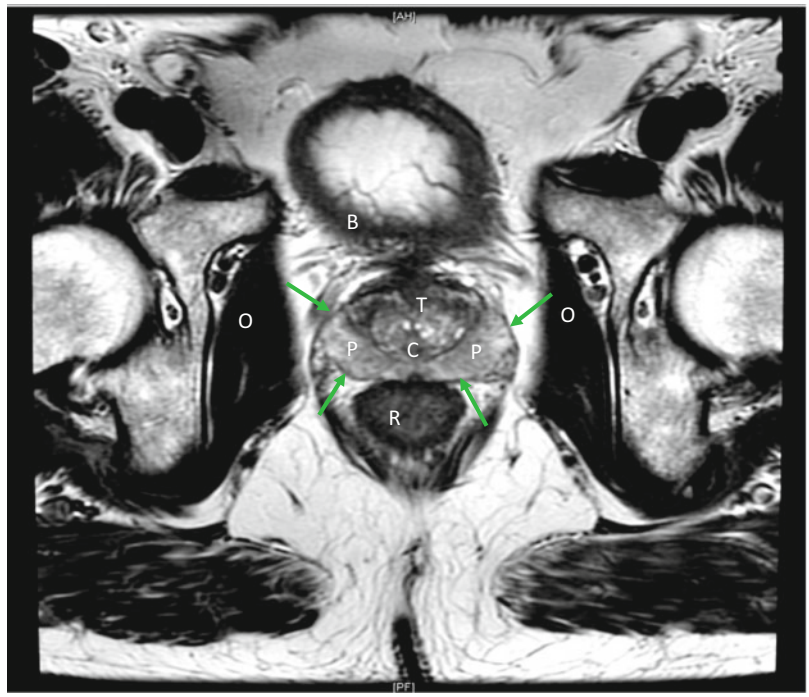

Fig. 4.1 T2WI of prostate base, axial view. Central zone (C); Transitional Zone (T); Peripheral zone (P), bilateral; Capsule (green arrows); Obturator internus muscles, bilateral (O); Rectum (R); Bladder wall (B)

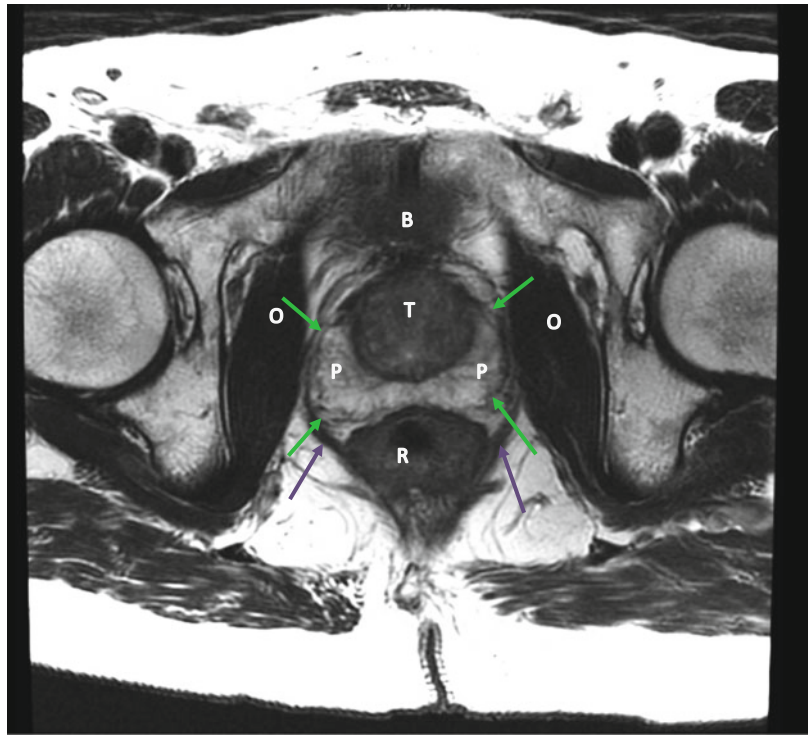

Fig. 4.2 T2WI of prostate midgland, axial view. Transitional Zone (T); Peripheral zone (P), bilateral; Capsule (green arrows); Obturator internus muscles, bilateral (O); Rectum (R); Inferior bladder wall (B); Levator ani muscles (purple arrows)

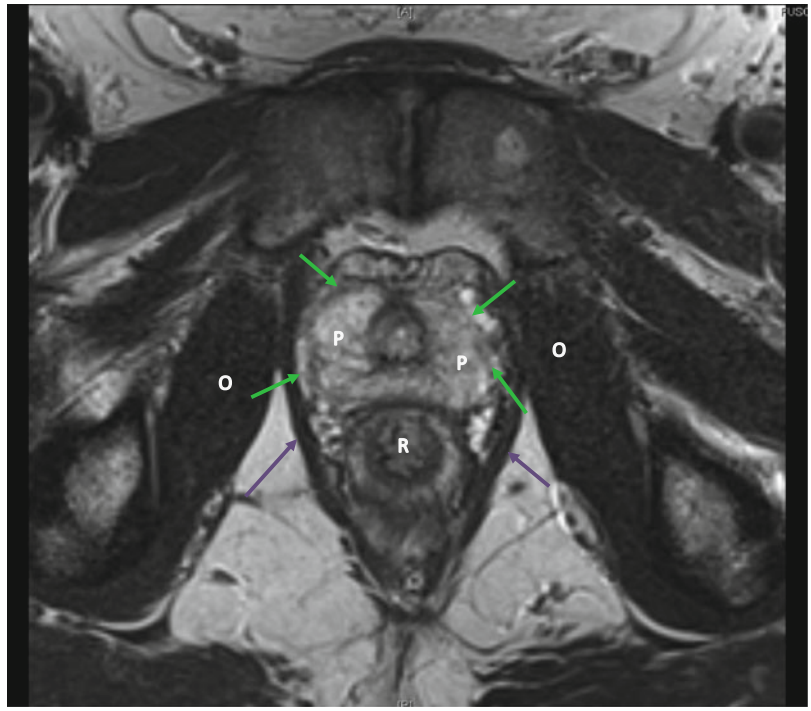

Fig. 4.3 T2WI of prostate apex, axial view. Peripheral zone (P), bilateral; Capsule (green arrows); Obturator internus muscles, bilateral (O); Rectum (R); Levator ani muscles (purple arrows)

Table 4.1 Prostate zones

Component	Location	T2WI appearance	Cancer arising (%)	Remarks
Central zone	Midline and posterior to the urethra, base to midgland/verumontanum	Low signal	5–10%	
Transitional zone	Anterior, base to apex	Low signal	10–20%	Enlarged with BPH
Peripheral zone	Posterior, base to apex	High signal	70–80%	Half crescent appearance
Capsule	Surrounding the glandular stroma	Low signal	–	Thin band appearance

Table 4.1. Lateral to the prostate, the obturator internus muscles form the pelvic sidewalls.

4.6 MRI Prostate Contouring

MRI images provide a detailed anatomic presentation of the prostate and adjacent organs, with enhanced tissue contrast. This improved tissue definition has been shown to better match the target volume size, when compared to CT [11]. Patients with treated MRI-defined target volumes have been shown to have comparable outcomes, with similar PSA relapse-free survival and overall survival, but with reduced side-effects [12]. Here we will detail the approach to such MRIs. Where applicable, the discussed structure will include a table with the relevant borders and landmarks for contouring.

4.7 Helpful Tips for Prostate Gland Contouring on MRI

– Get familiar with the different appearance of the anatomical zones of the prostate. While this seem to be a trivial advice, even experienced physicians who are used to CT-based-contouring, might find the abundance of details (i.e, zonal differences) confusing.

- Start contouring at mid-gland level where the gland is best visualized both on the lateral aspects and at the anterior-posterior aspects; commonly, at the midgland the capsule is easily defined.
- Avoid "over-contouring" on the lateral aspects, which may result in including the levator ani muscles, obturator internus muscles or venous plexuses.
- Use the sagittal and coronal planes to better define the apex and base of the gland; use "back and forth" approach—scrolling to previous and next images might help to better understand apex tapering inferiorly and base/bladder neck borders.
- Avoid big changes between adjacent images/cuts; The prostate is a smooth structure, and the contour should be the same. Dramatic differences between contiguous levels (usually 2–3 mm apart) may represent incorrect identification of structures.

4.8 Seminal Vesicles

Positioned superiorly and laterally to the prostate gland, on T2WI these thin walled, fluid-filled tubules like organs will normally appear white or light grey (hyperintense) and will be usually well defined and easily contoured by the experienced radiation oncologist (Table 4.2). The Vas Deferens is located medially to the seminal vesicles (SVs) at their proximal end (closer to the prostate base) and will appear darker (hypointense) (Fig. 4.4). On MRI imaging the posterior aspect of the SVs is well visualized, and bordered by the mesorectal fascia (Figs. 4.4 and 4.5).

4.9 Prostatic Urethra

The entire male urethra length is about 20 cm. It's proximal (posterior) part originates at the bladder neck (see below), ending at the external urinary sphincter (EUS, see below). It consists of a prostatic segment and a membranous segment (where the urethra transverse the urinogenital diaphragm). The distal (anterior) part continues as the bulbous urethra and the penile urethra, ending at the external meatus.

The prostatic urethra is the major component of the proximal urethra, beginning at the bladder neck (see below) and extends distally towards the urogenital diaphragm (see below). This segment of the male urethra, which is surrounded by the prostate, is rarely visualized on MR images unless a Foley catheter is placed [13]. On Axial images, the urethra is most commonly positioned centrally, but considerable variability exists. The authors recommend Foley insertion on simulation for accurate delineation of the urethra (Table 4.3).

4.10 Bladder Neck

The bladder neck is the area described as the lower urinary bladder segment, immediately proximal to the prostatic urethra (Fig. 4.6). The bladder neck has been reported to be of an importance in RT related GU toxicity [14, 15].

Bladder neck contouring can be somewhat challenging due to several reasons: it is highly variable anatomically, it is not easily identifiable on axial views and it is not a true anatomical structure; Nonetheless, when CT based contouring was used, the researchers defined the bladder neck as a volume located 5 mm around the urethra immediately inferior to the catheter

Table 4.2 Borders and landmarks for seminal vesicles contouring

Border	Landmark for contouring	Remark
Anterior	Follow seminal vesicles outline	
Posterior	Follow seminal vesicles outline	Does not go beyond mesorectum
Lateral	Follow seminal vesicles outline	Avoid going into venous plexuses
Superior	Follow seminal vesicles outline	
Inferior	Inserts into the prostate base	Will include Vas Deferens medially

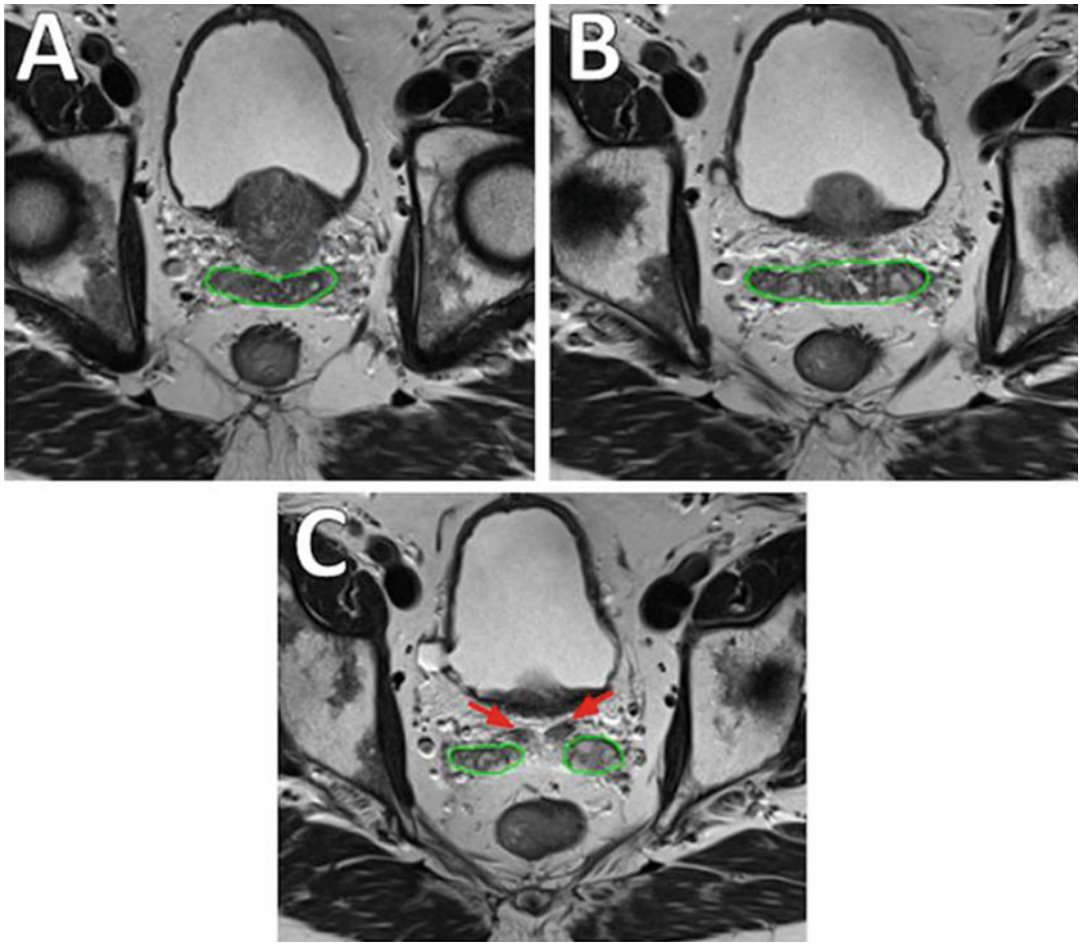

Fig. 4.4 Seminal vesicles contour, Axial view. Presented from proximal (panel A) to distal (panel C). SVs (green). Note the medial location of the Vas Deferens (red arrows) on the superior cut (Panel C). Both SVs and Vas Deferens are included in the volume as they join proximally

balloon and superiorly to the prostatic urethra [15]. MRI images allow better visualization and definition of the bladder neck, specifically at the bladder wall/prostate interphase, where the prostate base can be identified with glandular isointense signal, and the bladder wall will appear hypointense. As a rule of thumb, the authors use the anterior-posterior (AP) length of the prostate gland to define the bladder neck AP margins (see Table 4.4), best viewed on sagittal view (Fig. 4.7).

4.11 Neurovascular Bundle

The neurovascular bundle (NVB) contains the cavernous nerves and the prostatic neurovascular supply prostate [16]. It lies along the posterolateral aspect of the PZ, bilaterally, at the 5 and 7 o'clock positions (Fig. 4.8).

The NVB is best visualized at mid-gland level (Figs. 4.9 and 4.10); More superiorly the vessels and nerves are often displaced anteriorly and form a "curtain" like distribution along the lateral aspect of the capsule (Table 4.5).

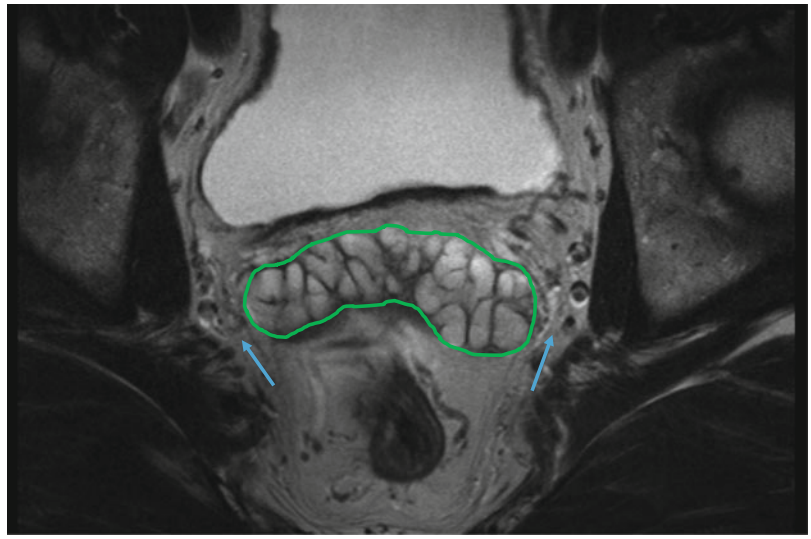

Fig. 4.5 Seminal vesicles contour, Axial view. SVs (green). Note the tubular shape, hyperintense SVs. The contour does not include the bilateral venous plexuses (blue arrows), and it does not go posteriorly beyond the mesorectal fascia

Table 4.3 Borders and landmarks for urethra contouring

Border	Landmark for contouring	Remark
Ant/Post/Lat	Outer margin of the Foley	Hypointense on T2WI
Superior	Immediately below the bladder neck	
Inferior	Most superior aspect of the penile bulb	

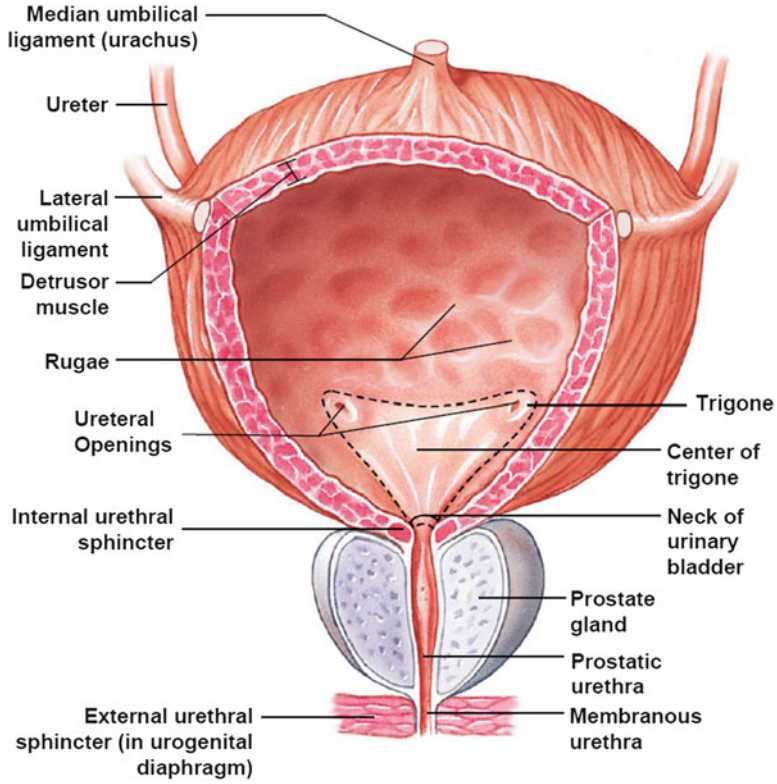

Fig. 4.6 Illustration of the organs responsible for the conduction and storage of urine. Note the location of the bladder neck, distally to the trigone and ureteral openings, and its proximity to the internal urethral sphincter. From Martini, Frederic H.; Timmons, Michael J.; Tallitsch, Robert B., Human Anatomy, 7th, ©2012, reprinted by permission of Pearson Education, Inc., New York, New York

Table 4.4 Borders and landmarks for bladder neck contouring

Border	Landmark for contouring	Remark
Anterior	Anterior aspect of the prostate	
Posterior	Posterior aspect of the prostate	
Lateral	3–5 mm beyond the lateral aspect of the prostate	Commonly does not reach the lateral bladder wall proper
Superior	Include the entire bladder muscle layer	
Inferior	Above upper most prostate base cut	

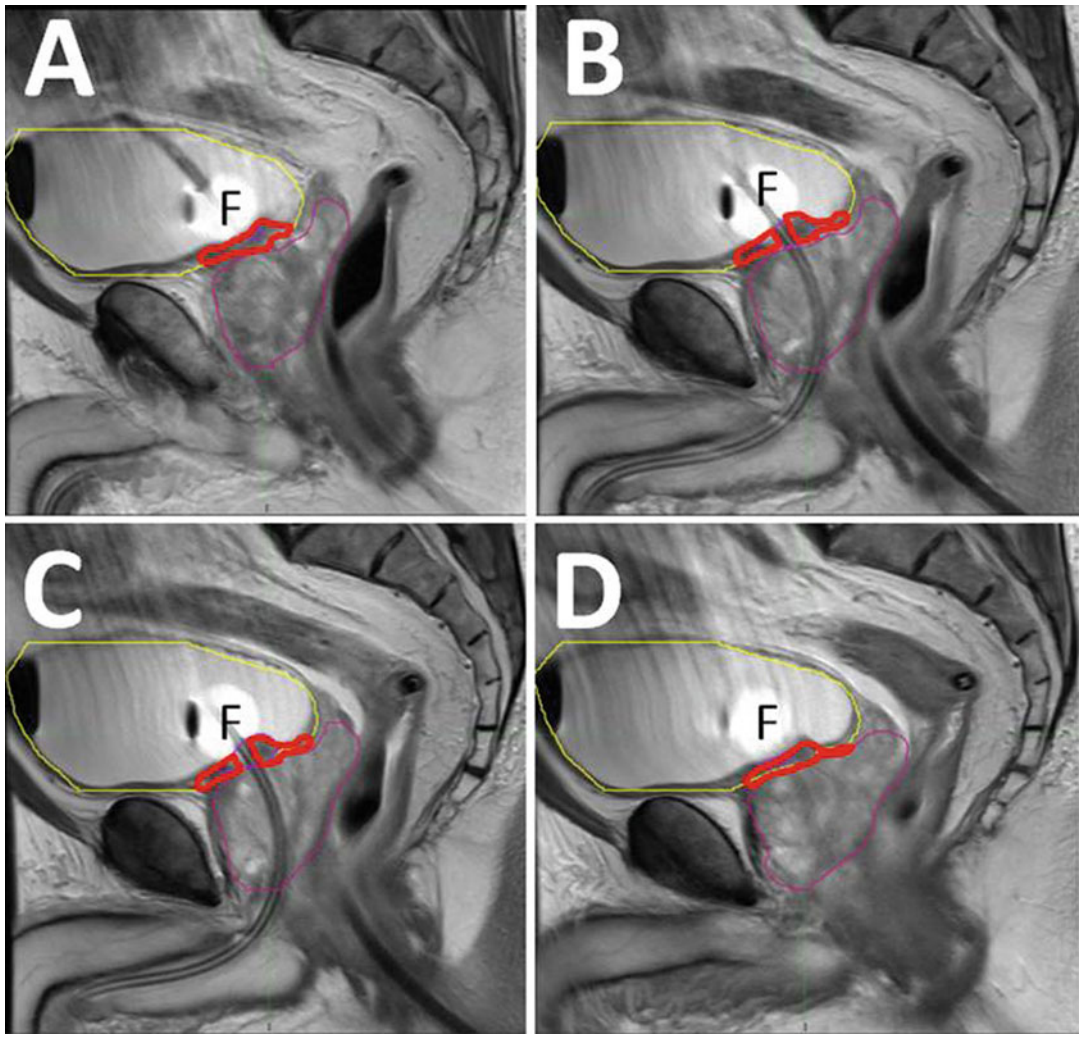

Fig. 4.7 Bladder neck contour, sagittal view. Presented from right (panel A) to left (panel D). Bladder neck (red); Prostate and SVs as CTV (purple); Bladder (Yellow); Foley catheter balloon (indicated with F). Notice the traversing Foley catheter creating a contour "separation". The bladder neck includes the entire muscular layer/wall, immediately superior to the prostate base

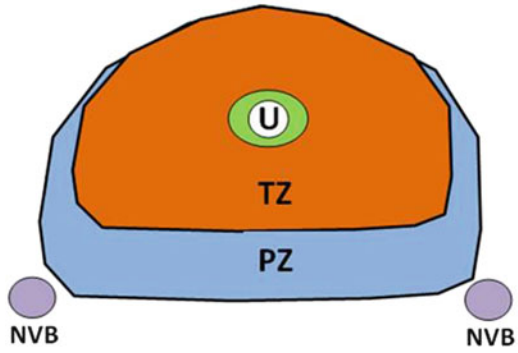

Fig. 4.8 NVB illustration. *PZ* Peripheral Zone (blue area), *TZ* Transitional Zone (orange area); *U* Urethra (green area), *NVB* Neurovascular Bundle (purple)

4.12 Urogenital Diaphragm and External Urethral Sphincter

The urogenital diaphragm (UGD, often termed Genitourinary diaphragm) is a deep pelvic muscular layer, and while its actual definition is questioned by some researchers [17], this anatomical and radiographic landmark should be well recognized by radiation oncologists. The UGD components are the striated urethral sphincter muscles and the deep transverse perineal muscle, covered by the perineal fascia media [18] (Figs. 4.11 and 4.12).

It has been noted that on CT scans the UGD tend to cause overestimation of the prostate gland size [19]. Recent evaluation of the UGD using MRI with endorectal coil demonstrated mean cranio-caudal length of 15.3 mm [20], longer than previously described, supporting the notion that properly identifying and contouring the UGD is challenging (Table 4.6).

The external urethral sphincter (EUS), which provides voluntary control of urine release into the distal (membranous) urethra, is made up from striated muscle fibers, originating from the inferior part of the ischiopubic ramus, and as they extend medially they surround the urethra, and insert on the other side [21]. From contouring perspective, the EUS should be contoured as a circular structure (Figs. 4.11 and 4.12).

4.13 Anterior Fibromuscular Stroma

The anterior fibromuscular stroma (AFMS) is composed of fibrous tissue and muscular fibers, and is located, as its name implies, at the convex anterior external surface of the prostate, and is separated from the pubic symphysis by Santorini's venous plexus (draining the dorsal veins of the penis) and adipose tissue located in the Retropubic space (also known as Retzius' space). The AFMS is thicker at mid-gland level,

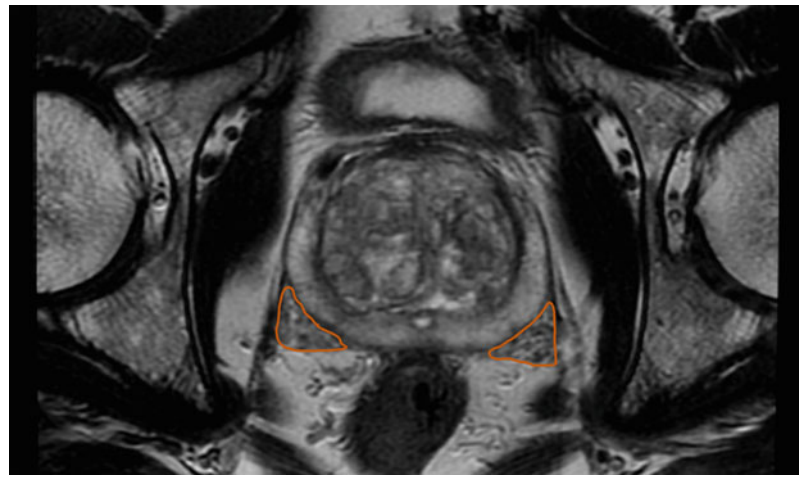

Fig. 4.9 Neurovascular bundle contoured, axial view. Bilateral NVB (orange) at midgland level. Note the posterior aspect of the NVB is confined by the mesorectal fascia

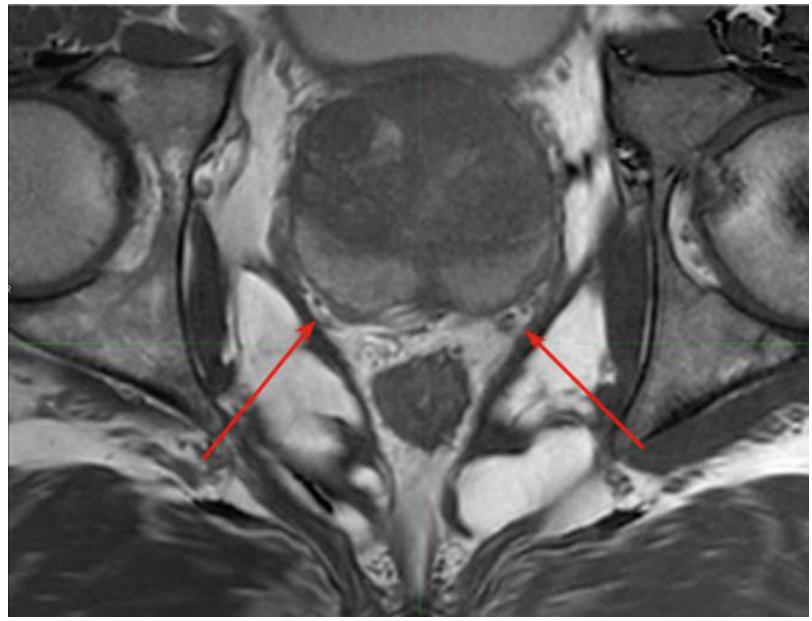

Fig. 4.10 Neurovascular bundle indicated, axial view. Bilateral NVB (red arrows) at prostate base level. Note the lateral aspects of the NVB is confined by levator ani muscles

Table 4.5 Borders and Landmarks for neurovascular bundle contouring

Border	Landmark for contouring	Remark
Anterior	Posterolateral aspect of prostate capsule	Towards the prostate base might be positioned more anterolaterally, along the prostate capsule
Posterior	Mesorectal fascia	
Lateral	Levator ani muscles	
Superior	Prostate midgland/base	Not always visualized at the base
Inferior	Prostate apex	

and as it extends laterally it thins out; inferiorly it blends into the muscular fibers of the UGD. It is relatively low in signal intensity on T2WI [22]. It is important to note that the AFMS is not a true capsule component [23], and it might appear thicker in patients with benign prostatic hyperplasia (BPH) [24] (Fig. 4.13, Table 4.7).

4.14 Penile Bulb and Bulbous Urethra

The penile bulb is well visualized on T2WI as a hyperintense, oval/drop-like midline structure, which is located immediately inferior to the UGD [25]. Due to reported relationship between erectile toxicities and radiation doses to the penile bulb, it is worthwhile considering contouring this structure, and evaluating the planned dose to it. The bulb, which is the most proximal end of the Corpus Spongiosum, which is attached superiorly to the UGD (Fig. 4.14) (Table 4.8).

The distal (anterior) urethra consists of a bulbous segment and a penile segment. The bulbous urethra is located between the inferior margin of the UGD and the penoscrotal junction; it is a hypointense midline tubular structure within the bulb of the corpus spongiosum. The penile urethra extends from the penoscrotal junction to the external meatus. As with the prostatic urethra, sagittal and coronal T2WI views may assist in demonstrating the urethral course at the different segments.

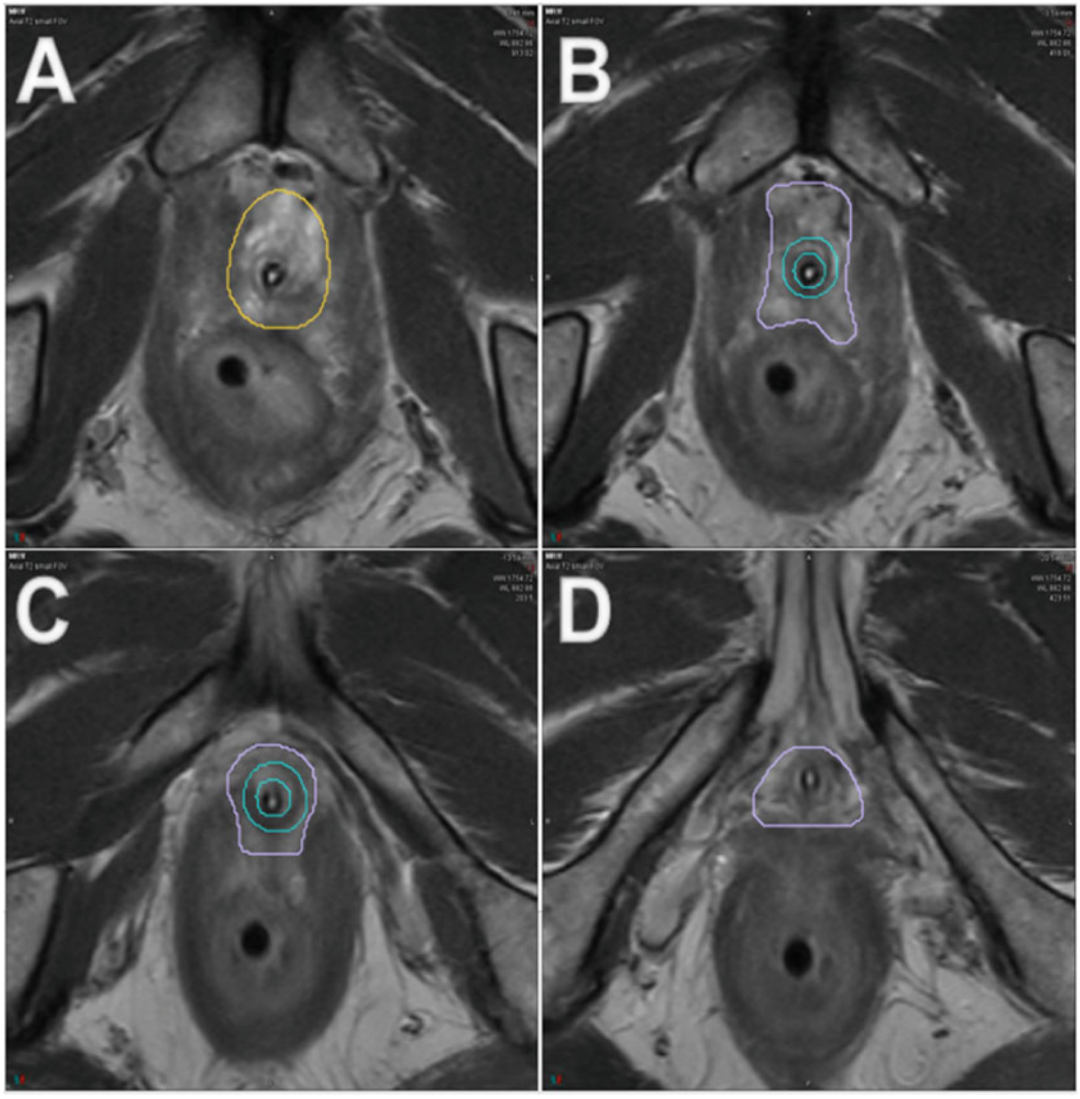

Fig. 4.11 Urogenital diaphragm, axial view. Presented from superior (panel A) to inferior (panel D). Prostate apex (orange); UGD (purple); external urethral sphincter (Cyan). Note that panel B is immediately below the prostatic apex, panel C is 1 cm below the apex and panel D is immediately above penile bulb (not shown)

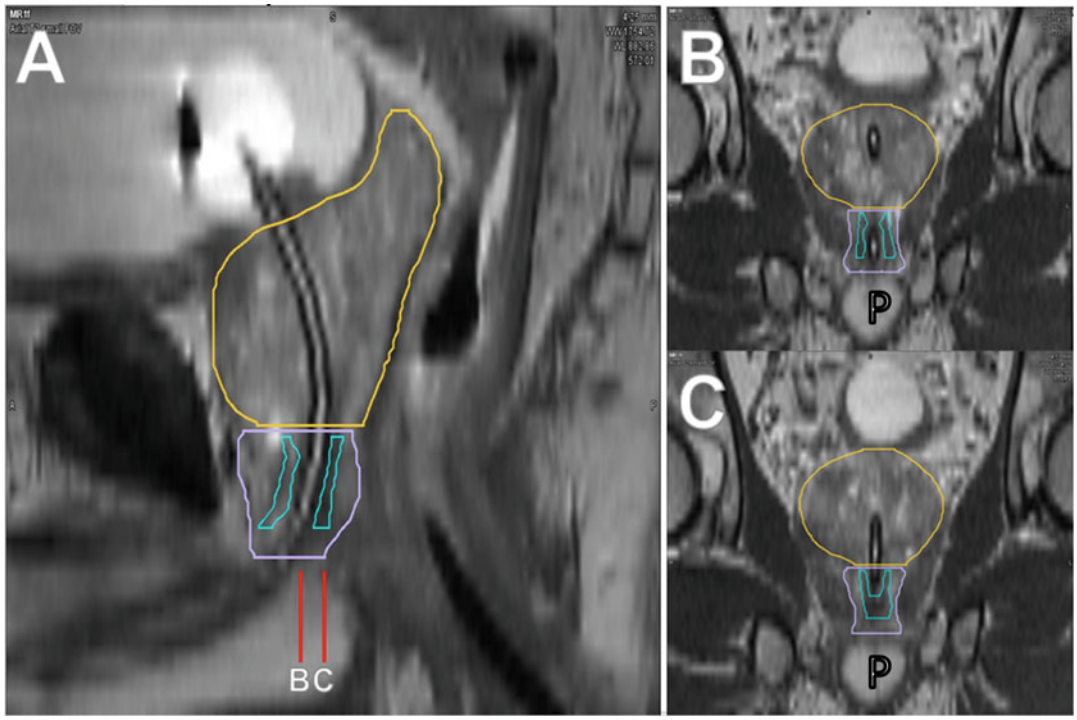

Fig. 4.12 Urogenital diaphragm, sagittal view (panel A) and coronal views at 2 levels (panels B and C). Prostate (yellow); UGD (purple); external urethral sphincter (Cyan; Penile bulb (indicated with P). Red lines on panel A indicate levels of coronal views of panels B and C

Table 4.6 Borders and Landmarks for urogenital diaphragm contouring

Border	Landmark For Contouring	Remark
Anterior	Pubic symphysis	Superiorly avoid including vessels in the retropubic space
Posterior	Rectum	
Lateral	Levator ani muscles/crus penis	
Superior	Prostate apex	
Inferior	Penile bulb	

4.15 Dominant Intraprostatic Lesion Contouring

While most commonly described by the radiologist using the PIRADS [26], the different aspects of dominant intraprostatic lesion (DIL) appearance on MR imaging should be recognized by the radiation oncologist. When using MRI based planning, the DIL must be properly incorporated into the CTV, and currently several clinical trials are assessing the role of increased dose to the DIL. It is also important to recognize that some DILs might abut the capsule, or present with radiographic extracapsular extension, as this might affect target definition.

Reviewing the entire PIRAD system is beyond the scope of this chapter, however, as presented below, assessing the T2 weighted imaging and diffusion weighted imaging (DWI) for hypointensities can indicate a presence of a lesion (Figs. 4.15. and 4.16).

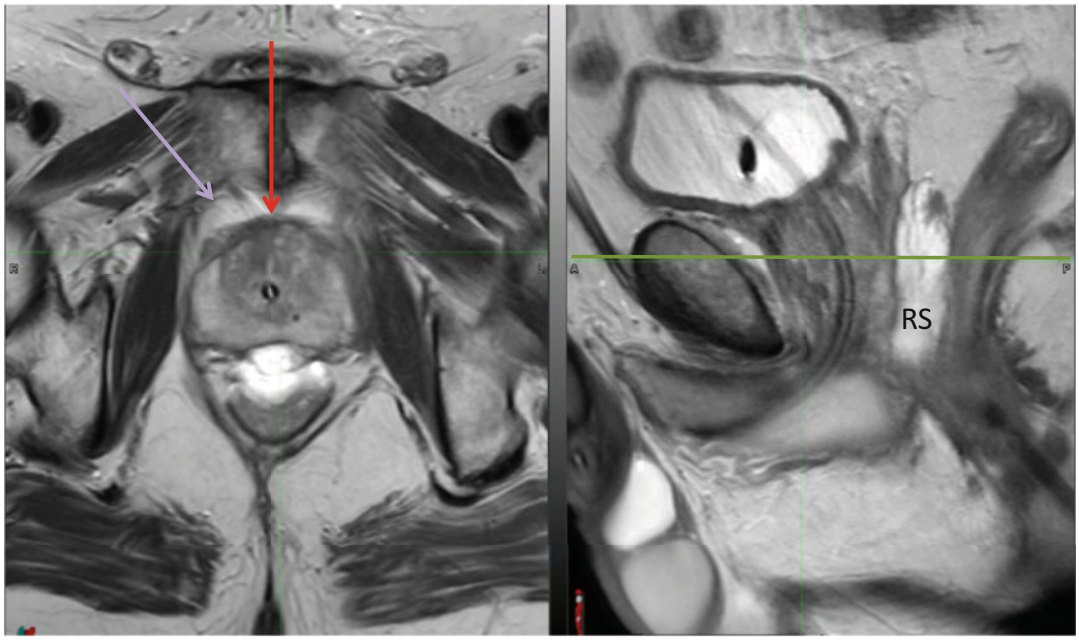

Fig. 4.13 Anterior Fibromuscular stroma on axial and sagittal views. AFMS (red arrow); retropubic space (purple arrow); Rectal Spacer (RS, see Sect. 4.17). The AFMS appears as a capsular "thickening" anteriorly. The green line on the right panel represents level of axial view

Table 4.7 Borders and Landmarks for anterior fibromuscular stroma contouring

Border	Landmark for contouring	Remark
Anterior	Retropubic space	
Posterior	Prostate transitional zone	
Lateral	Lateral/anterior prostate capsule	
Superior	Bladder neck/bladder wall	
Inferior	Prostate apex	

4.16 Pelvic Lymph Nodes Contouring

Pelvic lymph nodes contouring on CT images have been detailed by different radiation oncology groups, including Radiation Therapy Oncology group (RTOG) [2] and Royal Marsden Hospital (RMH) [27]. Generally, for prostate cancer, the term "pelvic lymph nodes" will include the lymphatic chains lined along the main vessels, which drain the prostate and the prei-prostatic fat. These include the external and internal iliac vessels, presacral venous plexus and obturator vessels. Although most guidelines still use boney anatomy landmarks, it is well recognized by most physicians that the vasculature anatomy may play a more critical role in defining the lymphatic target [28, 29], as the lymphatics are in close proximity to the vessels.

On MRI, the vessels are distinguishable from lymph nodes due to their different signal characteristics—vessels will have low signal on T2WI (as they contain fluids) while normal lymph nodes have somewhat variable signal on T2WI, but usually it is similar in intensity to parenchymal organ or muscle tissue. Normal (i.e, non- metastatic) periprostatic and presacral nodes are not routinely visible [30], so notable nodes are suspicious to be pathologic. As with CT definition, CTV will include the tissue surrounding the vessels, and will not include bowel, bladder, muscle or bone (Figs. 4.17 and 4.18).

4.17 Rectal Spacer

Several forms of interventions trying to reduce rectal dose have been evaluated, including mechanically increasing the rectoprostatic space

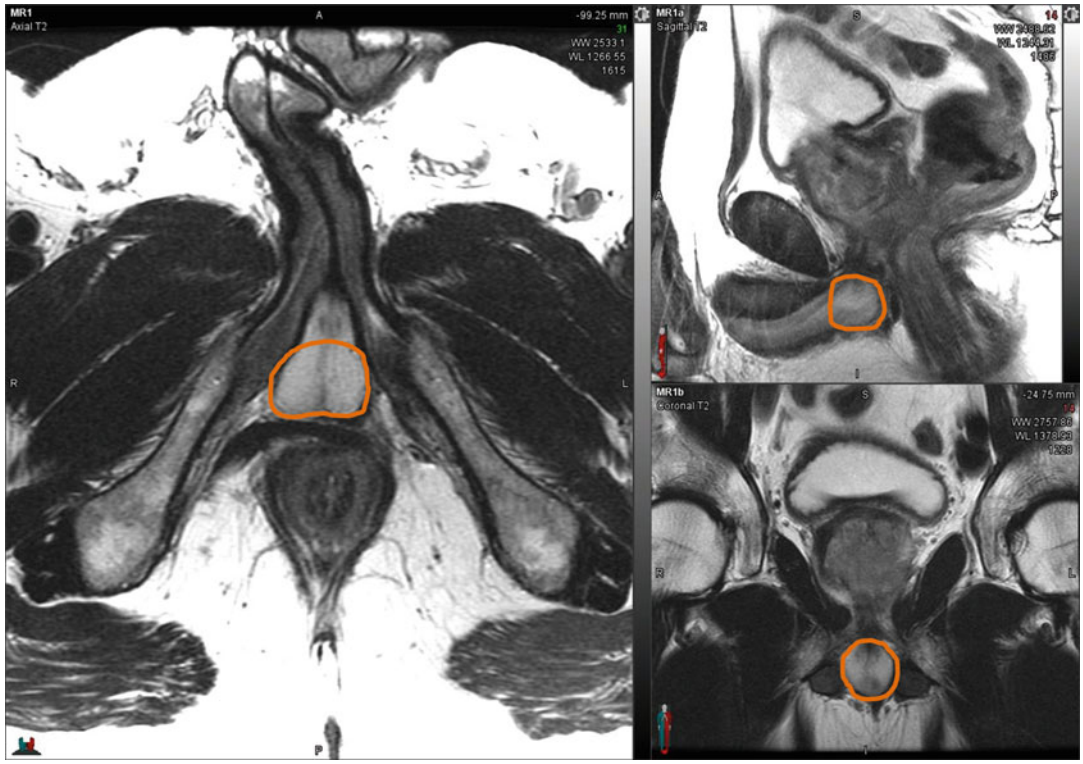

Fig. 4.14 Penile bulb on multiple views. Penile bulb (orange). Note on axial view (left panel) and the coronal view (bottom right) the crus of penis are on the lateral aspects of the bulb. The bulb's anterior border is the most posterior aspect of the pubic symphysis, as can be seen on sagittal view (top right panel)

Table 4.8 Borders and landmarks for penile bulb contouring

Border	Landmark For Contouring	Remark
Anterior	Pubic symphysis	Contour until most posterior aspect of pubic symphysis; beyond that considered corpus spongiosum
Posterior	Rectum/anus	
Lateral	Crus penis	
Superior	UGD	
Inferior	Perineal fat	

(Denonvilliers' fascia) by either injecting a rectal hydrogel spacer (SpaceOAR Augmenix, Inc, Waltham, MA, USA) or inserting and inflating a biodegradable balloon (BioProtect Balloon, BioProtect inc, Tzur Yigal, Israel) between the prostate and the rectum, or by the use of endorectal balloon, which is inflated in the rectal cavity, aiming at reducing rectal and prostate intrafraction motion [31].

SpaceAOR is currently the only Food and Drug Administration (FDA) approved absorbable hydrogel, that has been shown to reduce rectal dose, toxicity and QoL declines after prostate RT [32]. The authors routinely use it for patients undergoing prostate RT. The rectal hydrogel is clearly seen on MRI as hyperintense on T2WI (Figs. 4.19 and 4.20). To note, on CT scans the rectal hydrogel is not well distinguishable from

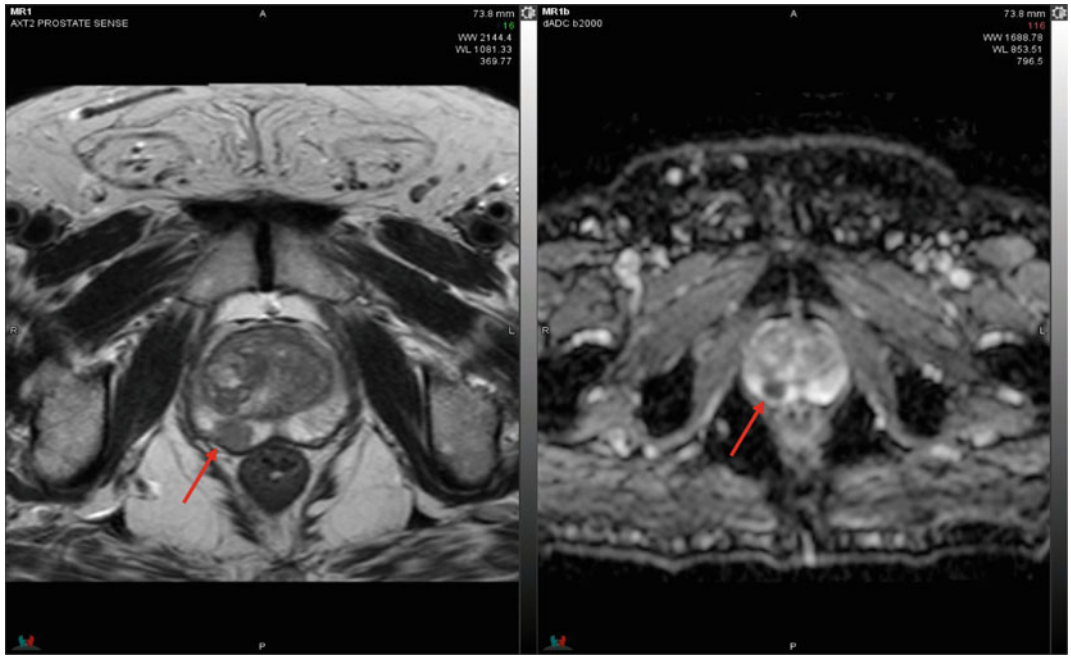

Fig. 4.15 Dominant Intraprostatic Lesion, axial views. T2 weighted imaging (left) with DIL indicated (red arrow) in the right posterior peripheral zone. Low signal is noted on DWI (right panel) in the same anatomical location

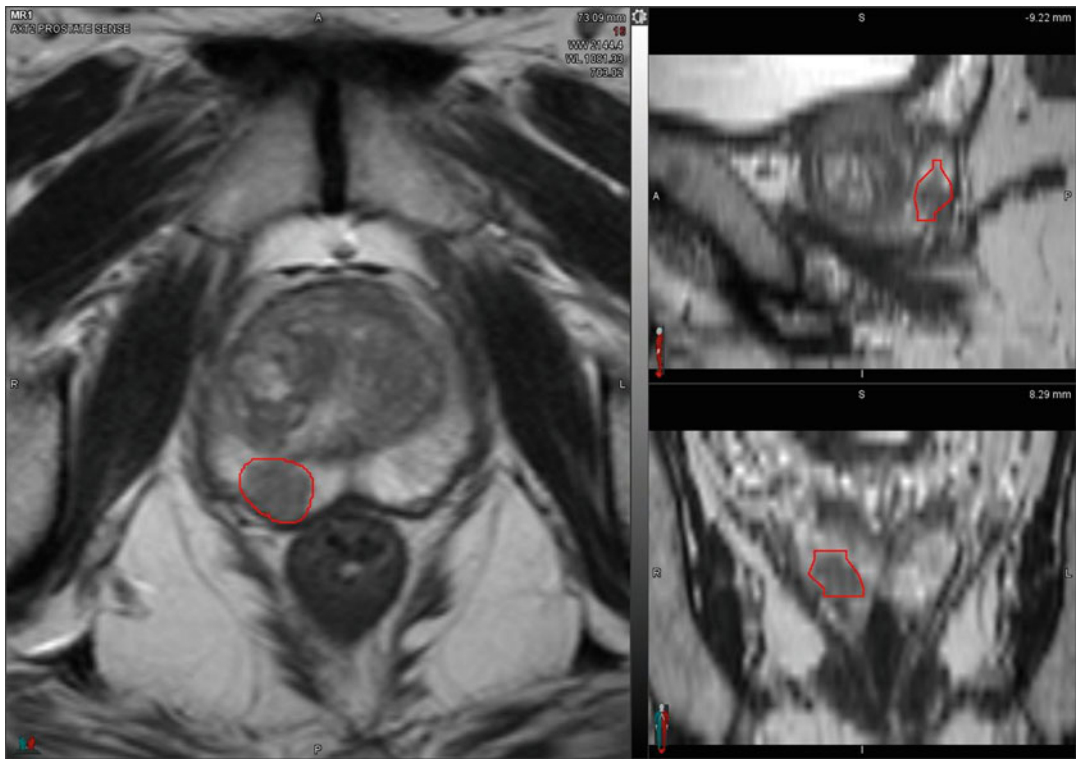

Fig. 4.16 Dominant Intraprostatic Lesion, multiple views. DIL (red) on T2WI on axial (left) sagittal (top right) and coronal (bottom right) views

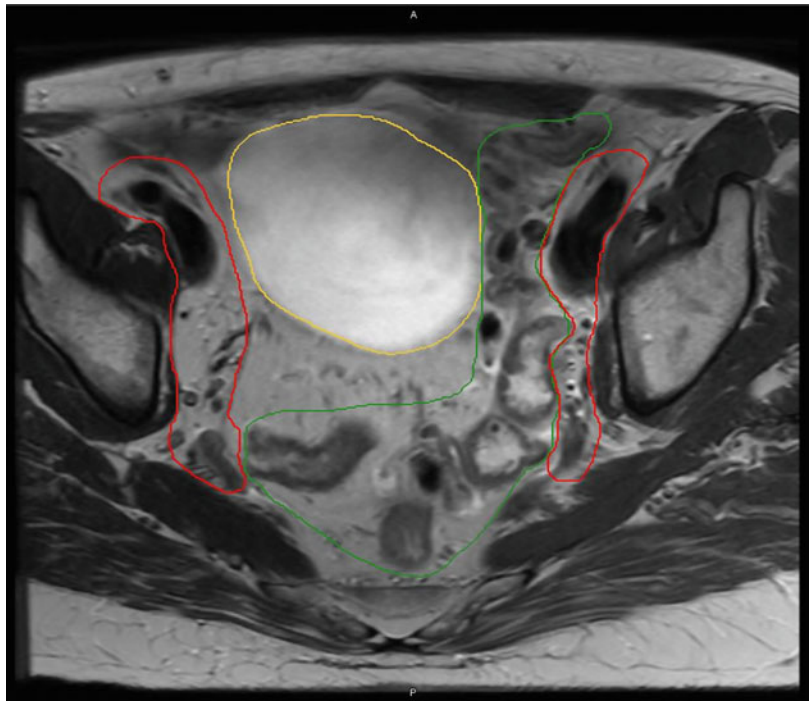

Fig. 4.17 Pelvis at level of acetabular roof, axial view. Lymph nodes CTV (red); Bladder (Yellow); Rectosigmoid (green)

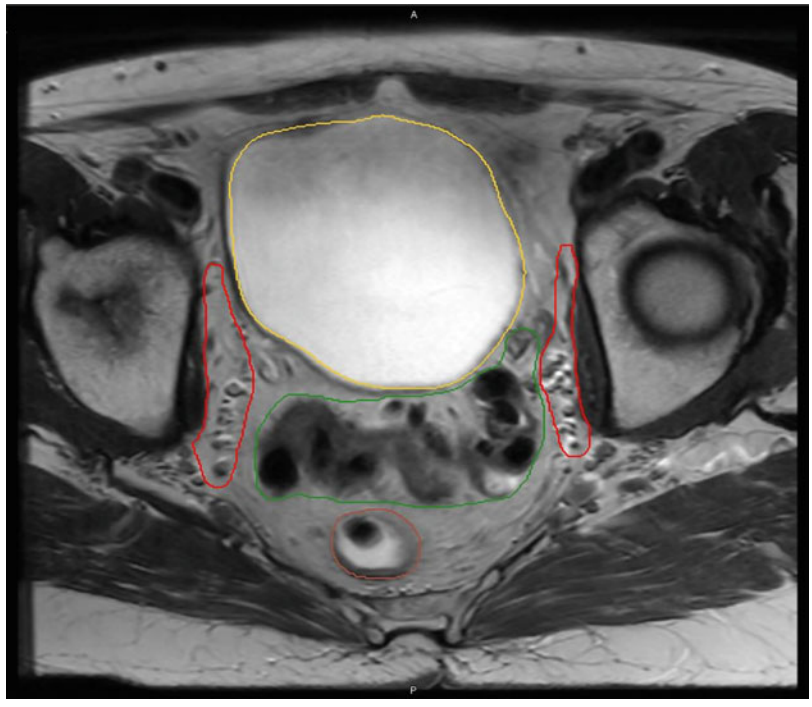

Fig. 4.18 Pelvis at superior level of femoral heads, axial view. Lymph nodes CTV (red); Bladder (Yellow); Rectosigmoid (green); Rectum (brown)

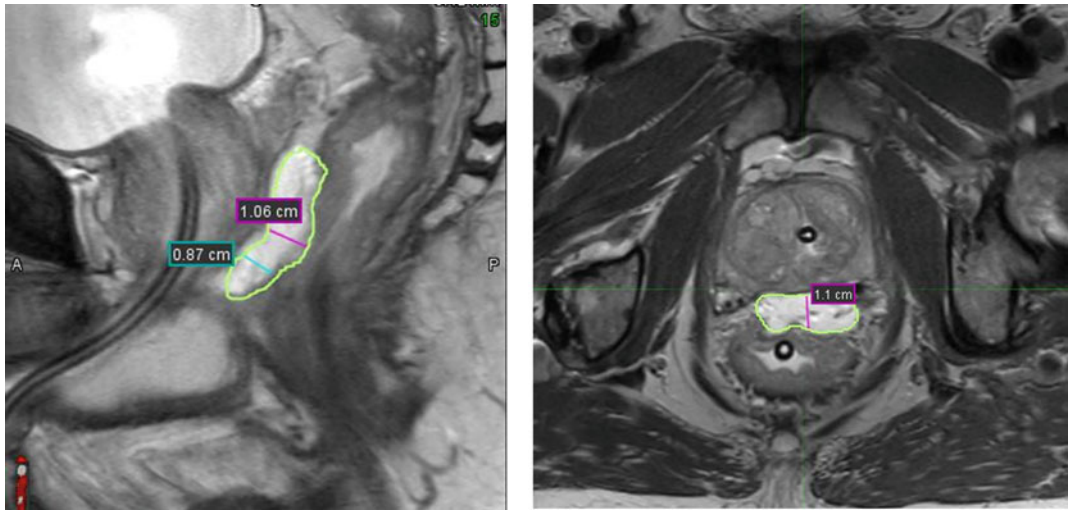

Fig. 4.19 Rectal hydrogel (SpaceAOR), sagittal and axial views. Spacer gel (light green). Note the measured distances between the prostate and the rectum created by the hydrogel, allowing dose reduction to the anterior rectal wall

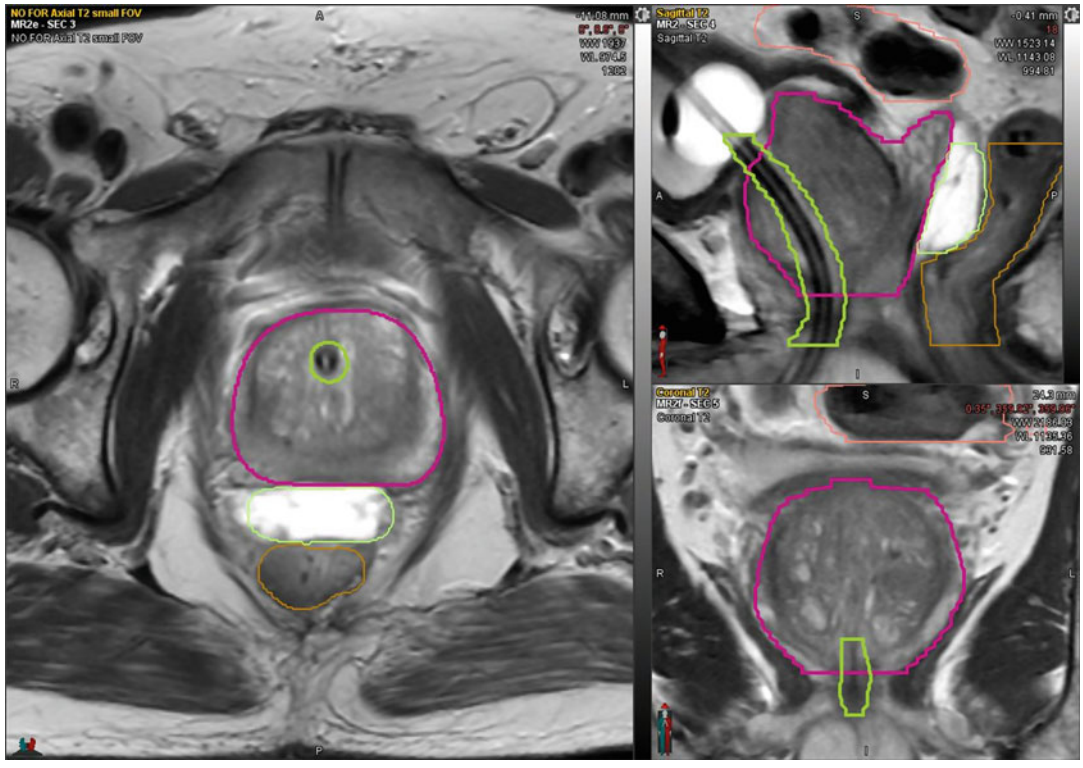

Fig. 4.20 Rectal hydrogel (SpaceAOR), multiple views. Prostate and SVs (pink); Spacer gel (light green); Rectum (brown); Urethra (bold green)

the (anterior) rectal wall and the (posterior) adjacent prostate aspect.

4.18 Summary

Prostate contouring on MRI requires understanding of the detailed pelvic anatomy and MRI techniques. Integrating MRI into prostate radiotherapy treatment planning allows for better target and organs at risk definition, more conformal radiation therapy treatments delivery and improved outcomes. MRI contouring requires profound knowledge, attention to details and clinical understanding. Radiation oncologists should become familiar with prostate MRI contouring as this challenging task is becoming widespread and more popular.

Disclosures Dr. Zelefsky serves as a consultant for Augmenix.

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5 Using Imaging to Design Dose Volume Constraints for Target and Normal Tissue to Reduce Toxicity

Rosario Mazzola and Filippo Alongi

5.1 General Aspects

The linear–quadratic model represents the basis for predicting the clinical effects of alternative fractionation schemes in radiotherapy. High fractionation-sensitivity seems to be an intrinsic property of prostate cancer [1]. From the clinical point of view, alpha/beta ratio of prostate cancer seems lower than that of dose limiting surrounding tissues (rectum, urinary bladder), allowing for safe dose/fraction escalation and improvement of the therapeutic ratio. The alpha/beta ratio for rectum and urinary structures is usually assumed to be 3 Gy and 5–10 Gy, respectively [2]. Apart from radiobiological basis, two kind of imaging are of paramount importance to guarantee the accuracy and safety when delivering high daily doses as well as in stereotactic body radiation therapy for prostate cancer. Firstly, multimodality imaging could be useful for clinicians to personalize clinical to planning target volume margins, allowing a better sparing of the organs at risk, and subsequently a reduction of the radiation-induced toxicity. Secondly, on-board image-guidance enables the verification of the target volume location before the treatment assuring a daily verification of the setup of the patient and of the target position taking into account setup errors [3].

5.2 Imaging and Geometrical Uncertainties for Target Volume

In the majority of the available studies regarding stereotactic body radiation therapy for prostate cancer [4–22], the co-registration of computed tomography images with prostate magnetic resonance imaging was performed to define the target volumes and organs at risk.

The importance to adopt the magnetic resonance imaging to define prostate gland is crucial to reduce the geometrical uncertainties in the delineation process. Using only computed tomography, the delineated volume could be imprecise, due to the low organ discriminating power based solely on differences of attenuation coefficients and the restriction to acquire images only in the transverse plane [23]. On the other hand, magnetic resonance imaging can better characterize soft tissues by providing higher soft tissue contrast on T2-weighted images [24]. Magnetic resonance imaging can therefore show with more details the internal prostatic anatomy and

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prostatic margins leading to more accurate delineations of prostate gland and subsequently improved target coverage [25, 26]. Of contrast, using computed tomography-based only delineation, three types of contouring errors with potential implications for planning target volume coverage can occur: definition of the gland apex, mid-gland and base regions of the prostate [27]. Studies have revealed that there are significant differences in prostate volumes estimated from magnetic resonance and computed tomography data. Roach et al. have shown that the Gross Tumor Volumes delineated on computed tomography images without contrast were 32% larger than those delineated on T1-weighted and T2-weighted fast spin echo magnetic resonance scans for prostate cancer [28]. The largest discrepancy was estimated in 7 mm (range 2–12 mm) between computed tomography and magnetic resonance, especially in the posterior region of the prostate. The prostatic apex was found to have the second largest discrepancy, averaging 4.5 mm (range 2–12 mm) [29].

Overall, despite the reduced inter- and intra-observer variability in magnetic resonance, computed tomography remains the modality for treatment planning calculation due to the lack of correlation between magnetic resonance voxel intensities and electron-density information. Computed tomography numbers are related to electron density values that are used in treatment planning to calculate dose to the patient and to correct for variations in tissue inhomogeneity by the calculation of a correction factor. Of contrast, using magnetic resonance there may be geometrical distortion due to magnetic field inhomogeneities, gradient non-linearities, susceptibility effects and chemical shifts [30].

5.3 Inter-fractions Prostate Deformation and Motion

Using multiple computed tomography scans, Deurloo and colleagues reported small shape variations along anterior–posterior direction ($\sigma \leq 0.9$ mm) and negligible variations along lateral and longitudinal directions ($\sigma \leq 0.5$ mm) [31, 32]. Larger shape variations was estimated for the seminal vesicles ($\sigma \leq 1.6$ mm). Prostate motion mostly depends by the rectal filling variations [32]. Quantitatively, vertical shift <3 mm at mid-posterior gland was observed in 90% of patients after 10 min and 2 min for, respectively, empty and full rectum.

Kerkhof et al. analyzed the potential impact of prostate deformation/shift by means of magnetic resonance in different rectal filling conditions [33]. An isotropic PTV margin of 4 mm from the prostate gland without seminal vesicles was considered. A significant increase in rectum D2 cc (mean: 8.3%; range: 2–15%) was observed depending on the rectal filling, while no significant reduction in target dose coverage (D95%) was detected. Therefore, for patients with empty rectum, if pre-treatment control with cone-beam computed tomography is performed and margins $\geq$4 mm for planning target volume are adopted, the prostate deformation could be considered negligible.

Of contrast, the rigid prostate model is inadequate when the target includes the seminal vesicles [31]. Generally, a negative correlation between the prostate and the seminal vesicles is observed for lateral rotations (pitch). This is likely determined by a full bladder condition, which pushes the seminal vesicles posteriorly and the prostate anteriorly [34].

5.4 Intra-fraction Prostate Motion

The mean prostate displacement increases over the intra-fraction time, for both supine and prone position. In particular, for supine positioning, an additional margin of 2 mm every 5 min should be added to the posterior margin [35, 36]. However, Ballhausen et al., utilizing 4D perineal ultrasound, demonstrated that intra-fraction shifts are small in most of the fractions, resulting in planning target volume overestimation with unnecessary healthy tissue irradiation if non-personalized margins are adopted [37–39]. Fixed target volumes margins should be personalized based on typical treatment duration. Otherwise, as alternatives to fixed planning target volumes margins, tracking systems for

intra-fraction couch correction should be considered for those patients who exhibit frequent and substantial prostate shifts.

5.5 Imaging for Intraprostatic Lesion Boost

Magnetic resonance imaging can be used to improve treatment planning for prostate carcinoma by providing information that not only helps to more accurately delineation of the prostate and seminal vesicles, but also to define a sub-target within the prostate that can be treated to a higher dose. Intraprostatic lesions detected combining magnetic resonance imaging and spectroscopy potentially could benefit from the administration of a focused higher radiation dose. Aluwini et al. explored the feasibility of stereotactic body radiotherapy with a focal boost to the magnetic resonance imaging-visible tumor as monotherapy for low- and intermediate-risk prostate cancer [4]. In all patients, four gold fiducials seeds were implanted in the prostate through ultrasound-guided trans-perineal pre-loaded needles. One week after fiducial implantation, computed tomography and magnetic resonance images were acquired. T1- and T2-weighted sequences were performed (1.5 T without endorectal coil) to elaborate the treatment plan after placement of a Foley catheter to delineate the urethra. Computed tomography and magnetic resonance images were matched on the markers and the Foley catheter. An integrated boost to the visible tumor at magnetic resonance imaging was planned up to 11 Gy/fraction which is 120% of the prescribed dose. Notably, in case of low-risk prostate cancer patient the visible tumor on the magnetic resonance was low.

In Table 5.1 are detailed the planning objectives and dose constraints adopted in the available studies on prostate stereotactic body radiation therapy.

5.6 Rectal Sparing

In stereotactic body radiation therapy for prostate cancer is crucial nearby organs sparing to guarantee acceptable safety profile. Some devices such as hydrogel spacers and endorectal balloons could reduce the rectal toxicity [3]. Spacers are injected into a perirectal space sitting between the Denonvilliers' fascia, anteriorly, and the rectal wall, posteriorly, in order to increase the distance between the prostate and the rectal wall, thus globally reducing the dose delivered to the rectum. The endorectal balloons is placed in the rectum and it is filled always with the same quantity of air of liquid: it obtains an immobilization of the prostate and a reduction of the dose delivered to the rectal wall (except for the anterior wall, which remains close to higher isodoses) at the same time. Both devices are visible at conventional morphological imaging for prostate gland.

In a dosimetric study [40] the increased near-maximum target dose after spacer insertion was associated with improvements in both target coverage and rectal sparing. Additionally, some evidences showed that the use of endorectal balloons reduce prostate displacement [41, 42], although not all reports were able to confirm these immobilizing capabilities [43]. Some issues concerning the reproducibility of the endorectal balloons position are reported in the literature. A mean intrafraction shift of the anterior endorectal balloon wall of 1.8 mm (maximum: 7.2 mm) was estimated, in particular in the posterior direction [44]. Wang et al. reported random errors in balloon positioning of up to 4.5 mm and maximum variations in balloon diameter of 2.8 mm [45]. For all these reasons, endorectal balloon cannot replace image-guided procedures. Measures to correct positioning errors remain necessary in stereotactic body radiation therapy for prostate cancer [46]. In fact, setup uncertainties could affect the target volume coverage, potentially leading to under-dosages [46–51]. Clinical

Table 5.1 Constraints adopted in the available studies on prostate stereotactic body radiation therapy

Region of interest (ROI)	Constraints	Reference (author year [reference])
PTV	$V_{100\%} \geq 95\%$; $D_{max} < 150\%$	Aluwini et al. [4]
	$V_{100\%} \geq 95\%$ (prescribed at the isodose of 70–90%)	McBride et al. [5]
	$V_{100\%} \geq 95\%$ (prescribed at the isodose of 77–80%)	Kang et al. [11] and Bolzicco et al. [14]
	$V_{100\%} \geq 95\%$ (prescribed at the isodose of 88–92%)	Freeman et al. [13] and King et al. [6]
	$V_{100\%} \geq 95\%$ (prescribed at the isodose of ≥75%)	Chen et al. [15], Arscott et al. [17], and Janowski et al. [19]
	$V_{100\%} \geq 95\%$ (prescribed at the isodose of 75–85%)	Oliai et al. [16]
	$D_{100\%} \geq 90\%$	Madsen et al. [8][a]
	$V_{100\%} \geq 95\%$; $D_{max} \leq 150\%$	Fuller et al. [18]
	$V_{100\%} > 95\%$	Lee et al. [21]
	$V_{95\%} > 99\%$; $D_{max} < 105\%$	Loblaw et al. [7]
	$V_{100\%} > 95\%$	Kim et al. [9] and Boike et al. [10][a]
	$V_{95\%} > 95\%$	Alongi et al. [12][a]
	$V_{95\%} > 95\%$ (prescribed at the isodose of 91–94%)	Ju et al. [20]
Rectum	$D_{max} \leq 38$ Gy (anterior rectal wall); $D_{1\ cm^3} \leq 32.5$ Gy (85% of the PD)	Aluwini et al. [4]
	$V_{36\ Gy} < 1\ cm^3$	McBride et al. [5] and Oliai et al. [16]
	ALARA; $D_{max} < 100\%$; $D_{50\%} < 50\%$	Kang et al. [11]
	$V_{50\%} \leq 50\%$; $V_{80\%} \leq 20\%$; $V_{90\%} \leq 10\%$; $V_{100\%} \leq 5\%$; $V_{36\ Gy} \leq 1\ cm^3$	Freeman et al. [13]
	$V_{50\%} \leq 50\%$; $V_{80\%} \leq 20\%$; $V_{90\%} \leq 10\%$; $V_{100\%} \leq 5\%$	King et al. [6]
	$D_{5\%} \leq 38$ Gy (mean 50 cm^3)	Bolzicco et al. [14]
	$V_{50\%} < 50\%$; $V_{75\%} < 25\%$; $V_{80\%} < 20\%$; $V_{90\%} < 10\%$; $V_{100\%} < 5\%$; $V_{36\ Gy} < 1\ cm^3$	Chen et al. [15] and Janowski et al. [19]
	$V_{36\ Gy} < 1\ cm^3$; posterior wall: $D_{max} \leq 50\%$	Oliai et al. [16]
	ALARA	Madsen et al. [8][a]
	$D_{max} \leq 100\%$; rectal mucosa[b]: $D_{max} \leq 75\%$	Fuller et al. [18]
	$D_{50\%} < 50\%$; $D_{100\%} < 5\%$	Lee et al. [21]
	$V_{28\ Gy} \leq 40\%$; $V_{32\ Gy} \leq 33\%$	Loblaw et al. [7]
	Anterior wall: $D_{max} \leq 105\%$; lateral walls: $D_{3\ cm^3} \leq 90\%$; posterior wall: $D_{max} \leq 45\%$	Kim et al. [9][a] and Boike et al. [10][a]
	$D_{50\%} < 18.1$ Gy; $D_{20\%} < 29$ Gy; $D_{10\%} < 32.6$ Gy; $D_{5\%} < 36.25$ Gy; $V_{36\ Gy} < 1\ cm^3$	Tree [2, 22]
	$V_{18\ Gy} < 35\%$; $V_{28\ Gy} < 10\%$; $V_{32\ Gy} < 5\%$; $D_{1\%} < 35$ Gy	Alongi et al. [12][a]
Bladder	$D_{max} \leq 41.8$ Gy; $D_{1\ cm^3} \leq 38$ Gy	Aluwini et al. [4]
	$V_{37.5\ Gy} < 5\ cm^3$	McBride et al. [5]
	$V_{37\ Gy} < 5\ cm^3$; $V_{100\%} < 10\%$; $V_{50\%} < 40\%$	Chen et al. [15] and Janowski et al. [19]
	$D_{10\ cm^3} \leq 37$ Gy	Oliai et al. [16]
	ALARA	Kang et al. [11]
	$V_{37\ Gy} \leq 10\ cm^3$	Freeman et al. [13]
	$V_{50\%} < 40\%$; $V_{100\%} < 10\%$	King et al. [6] and Chen et al. [15]
	$D_{5\%} \leq 40$ Gy	Bolzicco et al. [14]
	$D_{max} \leq 120\%$	Fuller et al. [18]
	$V_{32\ Gy} \leq 40\%$	Loblaw et al. [7]
	Outer 5-mm wall: $D_{max} < 105\%$; $D_{10\ cm^3} \leq 18.3$ Gy	Kim et al. [9][a] and Boike et al. [10][a]
	$D_{40\%} < 18.1$ Gy; $D_{10\%} < 36.25$ Gy; $V_{37\ Gy} < 10\ cm^3$	Tree [2, 22]
	$D_{1\%} < 35$ Gy	Alongi et al. [12][a]

(continued)

Table 5.1 (continued)

Region of interest (ROI)	Constraints	Reference (author year [reference])
Urethra	$D_{5\%} \leq 45.5$ Gy; $D_{10\%} \leq 42$ Gy; $D_{50\%} \leq 40$ Gy; $D_{max} \leq 45.6$ Gy	Aluwini et al. [4]
	$V_{49\ Gy} < 10\%$	McBride et al. [5]
	$D_{5\%\ or\ 2\ cm^3} \leq 40$ Gy	Bolzicco et al. [14]
	$V_{37\ Gy} < 50\%$	Arscott et al. [17][c] and Chen et al. [15]
	$D_{max} \leq 133\%$	Janowski et al. [19]
	$D_{max} \leq 120\%$	Fuller et al. [18]
	$D_{max} \leq 105\%$	Kim et al. [9][a] and Boike et al. [10][a]
	ALARA	Alongi et al. [12][a]
Femoral heads	$D_{max} \leq 24$ Gy	Aluwini et al. [4]
	$V_{40\%} < 5\%$	King et al. [6]
	$D_{25\%} \leq 25$ Gy	Bolzicco et al. [14]
	$V_{14.5\ Gy} < 5\%$	Tree [2, 22]
	ALARA	Alongi et al. [12][a]
Bowel/sigmoid	$D_{max} \leq 28.5$ Gy	Aluwini et al. [4]
	$V_{30\ Gy} < 1\ cm^3$	Chen et al. [15] and Janowski et al. [19]
	$V_{18.1\ Gy} < 5\ cm^3$	Tree [2, 22]
	ALARA	Alongi et al. [12][a]
Penile bulb	$V_{29.5\ Gy} < 50\%$	McBride et al. [5], Chen et al. [15], and Janowski et al. [19]
	$D_{25\%} \leq 29$ Gy	Bolzicco et al. [14]
	$V_{20\ Gy} \leq 90\%$	Loblaw et al. [7]
	$V_{29.5\ Gy} < 50\%$	Tree [2, 22]
	ALARA	Alongi et al. [12][a]
Testes	$D_{20\%} < 2$ Gy	Chen et al. [13] and Janowski et al. [19]

In the study by Boike et al. [10] an endorectal balloon was used
In the study by Alongi et al. [12] a spacer was injected before SBRT in some selected cases
Abbreviations: *ALARA* as low as reasonably possible, *PD* prescribed dose
DX% ⩽ Y%: The dose received by the X% of volume is ⩽ of the Y% of the prescription dose
DX% ⩽ Y Gy: The dose received by the X% of volume is ⩽ of Y Gy
DX cm^3 ⩽ Y%: The dose received by the X cm^3 of volume is ⩽ of the Y% of the prescription dose
DX cm^3 ⩽ Y Gy: The dose received by X cm^3 of volume is ⩽ of Y Gy
D_{max}: maximum dose
VX% ⩽ Y%: The X% of the prescription dose is received by ⩽ of the Y% of the volume
VX% ⩽ Y cm^3: The X% of the prescription dose is received by ⩽ of Y cm^3 of volume
VX Gy ⩽ Y%: The dose of X Gy is delivered to ⩽ of the Y% of the volume
VX Gy ⩽ Y cm^3: The dose of X Gy is delivered to ⩽ of Y cm^3 of volume
[a]LINAC based treatment, non-coplanar fields
[b]The rectal mucosa was defined as a solid structure formed by a 3-mm contraction of the rectal wall
[c]This constraint was applied to the membranous urethra, while no constraints were applied on the prostatic urethra

experiences confirmed a low incidence of grade 3 late rectal toxicity in patients treated with endorectal balloon, usually inferior to 3% [52–56], allowing to dose escalation studies for low- and intermediate-risk prostate cancer [10].

5.7 Urethral Sparing

Urethral toxicity has a significant impact on the quality of life in prostate cancer patients after irradiation. Contouring the male urethra on a computed tomography scan is difficult in the

absence of an indwelling catheter. Cystourethrography, retrograde urethrography or transrectal ultrasonography can help in assessing urethra. Unfortunately, these instrumental exams are invasive and present a limited field of view, making it difficult to appreciate the details of periurethral tissues. Magnetic resonance imaging studies demonstrated the capability of magnetic resonance to provide anatomical details of urethra as well as periurethral tissues [57]. Prostate adenocarcinoma tends to arise in a non-uniform anatomic distribution, with the majority (75–90%) of prostate cancers arising within the peripheral zone, while the transitional and central zones are involved in only 20–25% and 4–8% of cases, respectively [58]. Thus, given the proximal periurethral location of these low risk zones, the reduction of the dose to the intraprostatic urethra in selected prostate cancer patients would decrease urinary toxicity while maintaining high rates of disease control.

In the available clinical data, urethra is not equally defined. Specifically, in some cases, an additional computed tomography study was performed with an indwelling catheter and/or urethrogram, in other cases urethra was defined by means of MRI [4, 5, 9, 10, 12, 14, 17–19]. Due to the intrafraction organ motion, an urethral catheter could be useful. In the absence of catheter, a 2–3 mm of planning at risk volume of the urethra is reported [12].

5.8 Penile Bulb Sparing

Erectile disfunction represents a concern after radiotherapy for prostate cancer. Specific dose constraints for the erectile structures have not yet clearly defined. Due to the position in the caudal limit of the irradiation field, the penile bulb represents a critical organ sparing. The delineation of the penile bulb by means of computed tomography could have some limits mainly related to the low contrast in the pelvic area. Additionally, an inter-observer variability in contouring of the penile bulb on computed tomography for prostate cancer treatment planning is reported [59].

Of contrast, magnetic resonance imaging has been proposed as the most appropriate imaging modality for accurate localization of the penile bulb and a better sparing of the penile bulb due to a more precise delineation of the prostate apex [60–62].

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6 Expected PSA and Biochemical Control with Prostate SBRT Compared to Conventional Fractionated Radiotherapy

Josephine Kang and Alan Katz

6.1 Introduction

Prostate specific antigen (PSA) is a serum marker used to monitor biochemical control after treatment of prostate cancer. Per current guidelines, after definitive radiation therapy, patients should be followed with PSA every 6–12 months for 5 years, then annually [1]. Biochemical failure is defined using the Phoenix criterion of PSA nadir +2 ng/ml [2]. However, PSA kinetics after prostate stereotactic body radiation therapy (SBRT) can differ from standard external beam radiation (EBRT), with differences in expected nadir, PSA decay, and likelihood as well as magnitude and number of PSA bounce.

The use of a hypofractionated regimen to treat prostate cancer theoretically delivers a higher therapeutic ratio to tumor cells while sparing adjacent healthy tissue, as the α/β ratio for prostate cancer has consistently been reported to be 2.0 Gy or less, which is lower than the α/β ratio of surrounding normal tissues [3, 4]. Using an α/β of 1.5 Gy for prostate cancer cells, a total dose of 36.25 Gy in five fractions equates to an equivalent dose at 2 Gy per fraction (EQD2) of 91 Gy, above standard fractionation regimens.

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6.1.1 Biochemical Control

Biochemical control rates for prostate SBRT have been comparable to standard fractionation regimens, with disease control above 90% for low and favorable intermediate risk disease (Table 6.1) [17, 19–21]. Based on the favorable outcomes of emerging retrospective and prospective studies, the 2013 model policy from the American Society of Radiation Oncology (ASTRO) endorsed use of prostate SBRT in "select patients with low to intermediate risk disease" [22], and the National Comprehensive Cancer Network (NCCN) updated their guidelines to include prostate SBRT as a treatment option in "clinics with appropriate technology, physics, and clinical expertise" [23]. The majority of studies focus on low and favorable intermediate risk prostate cancer patients, and are summarized in Table 6.1.

The phase I–II SHARP study was one of the first prospective studies to report on prostate SBRT [8]. Forty patients with low-risk prostate cancer were treated to 33.5 Gy in five fractions, the equivalent of 78 Gy in 2 Gy fractions using an α/β of 1.5 Gy. The 4-year biochemical progression free survival (bPFS) was 90% using the nadir +2 ng/ml definition of failure. Subsequent prospective studies have demonstrated similarly promising clinical outcomes.

In 2013, King and colleagues published a multi-institutional pooled analysis of phase II studies [21] with over 1000 patients, majority

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Table 6.1 Biochemical control after prostate SBRT

Study	SBRT dose	FU (range)	# Pts	Risk categories	bPFS
Bolzicco et al. [5]	35 Gy/5 fx	36 months (6–76)	71	Low (41%), Int (42%), High (17%)	3 years 94.4%
King et al. [6]	35–36.25 Gy/5 fx	5 years (4.2–6.2)	41	Low, Favorable Int Risk	5 years 92.7%
McBride et al. [7]	36.25–37.5 Gy/5 fx	44.5 months (0–62)	45	Low	3 years 97.7%
Madsen et al. [8]	33.5 Gy/5 fx	41 months (21–60)	40	Low	4 years 90%
Vu et al. [9]	35–36.25 Gy/5 fx	24 months (18–78)	120	Low (58%), Int (32%), High (11%)	
Fuller et al. [10]	38 Gy/4 fx[a]	60 months (6–99)	259	Low (43%), Int (57%)	5 years Low 100%, Int 88.5%
Kim et al. [11]	45–50 Gy/5 fx	42 months (36–78)	47	Low (38%), Int (62%)	4 years 98%
Park et al. [12]	35–36.25 Gy/5 fx	53 months (IQR, 26–68)	39	Low (20.7%), Int (69%), High (10.3%)	5 years Low 100%, Int 83.9%, High 33.3%
Kishan et al. [13]	36.25–40 Gy/5 fx	35 months (3–93.4)	130	Low (53.1%), Fav Int (31.5%), Unfav Int (15.4%)	
Loblaw et al. [14]	35 Gy/5 fx	55 months (13–68)	84	Low	5 years 98%
Mantz [15]	40 Gy/5 fx	60 months	102	Low, Fav Int	5 years 100%
Chen et al. [16]	35–36.5 Gy/5 fx	2.3 years (1.4–3.5)	100	Low (37%), Int (55%), High (8%)	2 years 99%
Katz and Kang [17]	35–36.25 Gy/5 fx	72 months (0–96)	477	Low (68%), Int (32%)	7 years Low 95.6%, Fav Int 93.5%, Unfav Int 79.3%
Katz et al. [18]	35–0.25 Gy/5 fx	84 months (IQR, 60–96)	515	Low (63%), Int (30%), High (7%)	8 years Low 93.6%, Int 84.3%, High 65.0%
Katz [19]	35–36.25 Gy/5 fx	108 months (0–120)	230	Low	10 years 93%

Abbreviations: *FU* follow up, *Gy* gray, *Fx* fractions, *m* months, *y* years, *IQR* interquartile range
[a]Heterogeneous SBRT planning such that at least 1% of PTV receives ≥150% of prescription dose

treated to 35–36.25 Gy in five fractions. Outcomes were favorable, with 5-year bPFS rates for low, intermediate and high-risk patients of 95.2, 84.1 and 81.2%, respectively. Subsequently published prospective studies have similar positive rates of efficacy (Table 6.1), with 5-year bPFS rates ranging from 92 to 100% for low to intermediate risk disease, but long-term follow up is lacking.

Retrospective series have longer follow-up; the series by Katz et al. has the longest follow-up to date, and demonstrates 9-year bPFS of 94, 87 and 61% for low, intermediate and high risk patients, respectively, using a dose of 35–36.25 Gy [24]; this was recently updated for low-risk patients with 10-year outcomes with local control rates of 98.4% and bPFS of 93% [19]. There is no evidence to suggest that the addition of pelvic nodal RT or androgen deprivation therapy (ADT) improves SBRT outcomes, though this has not been rigorously analyzed in prospective randomized settings [25]. The body of evidence thus far suggests localized prostate SBRT compares favorably to standard EBRT and is an excellent option for patients with localized prostate cancer; as reference, the longest follow-up for patients treated to 81 Gy EBRT has relapse-free survival rates of 81, 78 and 62% for low, intermediate and high-risk patients, respectively [26].

The efficacy of SBRT in patients with unfavorable-risk (more than one adverse

intermediate risk factor or Gleason 4 + 3 disease) [25] or high-risk disease is less clear, as the data is sparse and majority of published studies focus on low- or favorable intermediate-risk disease outcomes. The data from Katz and colleagues shows a clear and significant distinction in outcome between favorable and unfavorable intermediate-risk disease (7-year bPFS of 95.2% vs. 68.2%, respectively), suggesting treatment intensification may be warranted for patients with unfavorable-risk features; but to date, no benefit for ADT or pelvic nodal RT has been established [18]. King et al. included 125 patients with high-risk disease in his consortium analysis; 38% received ADT. The 5-year bPFS was notably high, 81.2%, despite the limited use of ADT and lack of pelvic nodal RT. Katz et al. reported 8-year bPFS results of 65% for 38 patients with high-risk disease; only 55% received ADT [18]. Multivariate analyses showed no benefit of ADT addition. Mature results of ongoing studies examining the efficacy of prostate SBRT in higher risk patients are awaited, along with determination of the benefit, if any, of adding ADT, intensifying dose or targeting pelvic nodes. Until then, prospective studies with limited follow up and retrospective series suggest that biochemical outcomes after SBRT in unfavorable intermediate-risk and high-risk patient cohorts are likely comparable to rates achieved with standard EBRT [18, 20, 21].

6.1.2 PSA Nadir

PSA nadir is defined as the lowest PSA level PSA achieved after radiation therapy. After standard external beam radiation (EBRT), the PSA nadir value has been shown to predict for biochemical as well as distant failure [27–29], with nadir values of <0.5 ng/ml resulting in significantly lower 8 year distant metastases free survival (97% vs. 73–96%) and biochemical progression free survival (75% vs. 17–52%). The prognostic role of PSA nadir after SBRT, however, has not been validated due to relatively small number of patients on published reports, and overall low number of biochemical failures, rendering it difficult to correlate long-term biochemical control and metastasis free survival with degree of PSA nadir or other PSA metrics.

Studies show that nadir values after SBRT tend to be lower than standard EBRT (Table 6.2), suggesting clinical outcomes will also compare favorably [13, 30, 31]. A study from University of California San Francisco compared nadir after SBRT and standard EBRT, and noted lower 3-year PSA nadir value of 0.24 ng/ml vs. 0.60 ng/ml, respectively; $P < 0.005$) [13]. Similarly, Lee et al. demonstrated that SBRT to dose of 36.25 Gy in five fractions resulted in significantly lower PSA nadir values when compared to standard EBRT of 70.2–75.6 Gy (nadir 0.23 ng/ml vs. 0.37 ng/ml, respectively; $P = 0.01$). Kishan and colleagues compared PSA kinetics after prostate SBRT, HDR brachytherapy and standard EBRT, and noted a significantly greater percentage of patients after SBRT and brachytherapy achieved PSA nadir values of <0.5 ng/ml (76.2, 75.9 and 44.9%, respectively; $P < 0.0001$).

Reports demonstrate that low nadir values of 0.1 ng/ml are achievable over time after SBRT, and higher ablative doses result in lower PSA nadir and more rapid drop in value [10, 11, 19]. The retrospective series by Katz shows nadir of 0.1 ng/ml by 5 years followed by plateau in low risk patients, with follow up to 10 years [19]. Further studies with larger numbers and longer follow up are needed to confirm whether this lower PSA nadir corresponds to improved biochemical control.

6.1.3 PSA Bounce

Transient fluctuations in PSA have been documented to occur after radiation therapy (Table 6.2). Majority of studies define a PSA bounce as rise of ≥0.2 ng/ml above nadir, followed by subsequent drop to a new nadir. The biologic basis of PSA bounce is unknown, but it has been hypothesized that transient increases in PSA may reflect episodic prostatic inflammation, or sublethal damage transitioning to cell kill [32]. Initial reports were based on PSA

Table 6.2 PSA kinetics after prostate SBRT

Study	SBRT dose	FU (range)	# Bounce/total (%)	Magnitude of bounce (range)	Time to bounce (range)	Definition	PSA nadir	Time to reported nadir	PSA decay
Bolzicco et al. [5]	35 Gy/5 fx	36 months (6–76)	9/71 (12.6%)[a]	1.08 ng/ml	23 months (18–30)	PSA rise and subsequent decline to nadir	0.62 ng/ml[a]	3 years	1 years 0.93 ng/ml 2 years 0.87 ng/ml 3 years 0.62 ng/ml[a]
King et al. [6]	35–36.25 Gy/5 fx	5 years (4.2–6.2)	12/41 (29%)	0.39 ng/ml	18 months	≥0.2 ng/ml	0.32 ng/ml (0.03–2.65)	33 months	
McBride et al. [7]	36.25–37.5 Gy/5 fx	44.5 months (0—62)	9/45 (20%); 4/45 (9%) w/2 bounces; 1/45 (2%) w/3 bounces	1.07 ng/ml (0.4–2.8)	11.6 moths (7.2–18.2)	≥0.4 ng/ml	0.2 ng/ml (0–1.5)	44.5 months	1 year 0.91 ng/ml
Madsen et al. [8]	33.5 Gy/5 fx	41 months (21–60)					<0.5 ng/ml (32%); 0.5–1.0 ng/ml (40%); 1.0–2.0 ng/ml (23%)	18 months (3–36)	
Vu et al. [9]	35–36.25 Gy/5 fx	24 months (18–78)	34/120 (28%)	0.5 ng/ml	9 months	≥0.2 ng/ml			
Fuller et al. [10]	38 Gy/4 fx[b]	60 months (6–99)					0.1 ng/ml	5 years	
Kim et al. [11]	45–50 Gy/5 fx	42 months (36–78)	24/47 (51%); 5/47 (10%) w/2 bounces; 1/47 (2%) w/3 bounces	0.5 ng/ml	9 months	≥0.2 ng/ml	0.1 ng/ml	36 months	
Park et al. [12]	35–36.25 Gy/5 fx	53 months (IQR, 26–68)	14/39 (39%)	0.4 ng/ml (IQR, 0.34–2.54)	11 months (IQR, 6.0–18.5)	≥0.2 ng/ml	0.31 (IQE, 0.12–0.67)	23 months	
Kishan et al. [13]	36.25–40 Gy/5 fx	35 months (3–93.4)	40/130 (30.8%)	0.53 ng/ml (0.2–3.6)	14.8 months (3.6–43.3)	≥0.2 ng/ml			
Loblaw et al. [14]	35 Gy/5 fx	55 months (13–68)							
Mantz [15]	40 Gy/5 fx	60 months	15/102 (14%)		12–24 months				
Chen et al. [16]	35–36.5 Gy/5 fx	2.3 years (1.4–3.5)	31/100 (31%)	0.5 ng/ml (0.2–2.2)	15 months (3–21)	≥0.2 ng/ml	0.49 ng/ml (0.1–1.9)	2 years	

Katz and Kang [17]	35–36.25 Gy/5 fx	72 months (0–96)	16%	0.5 ng/ml (0.2–5.29)	36 months (3–60)	≥0.2 ng/ml	0.11 ng/ml	48 months (3–84 months)	
Katz [19]	35–36.25 Gy/5 fx	108 months (0–120)	21%			≥0.2 ng/ml	0.1 ng/ml	48 months	

Abbreviations: *FU* follow up, *Gy* gray, *Fx* fractions, *m* months, *y* years, *IQR* interquartile range
[a]SBRT monotherapy patients
[b]Heterogeneous SBRT planning such that at least 1% of PTV receives ≥150% of prescription dose

changes after prostate brachytherapy and standard EBRT [13, 32]. PSA bounce is a common occurrence after prostate SBRT as well, with studies suggesting a greater likelihood of multiple bounces, and higher bounce values.

6.1.3.1 Number of Bounces

Multiple bounces have been reported to occur after SBRT. In the phase I multi-institutional trial reported by McBride et al., it was noted that 20% of all patients had a bounce; 9% had two bounces and 1% had three bounces. The authors defined PSA bounce as a PSA increase of ≥0.4 ng/ml between any two consecutive measurements followed by subsequent decline; had they used more commonly applied definition of ≥0.2 ng/ml, the reported bounce frequency and number of bounces may have been greater.

A phase 1–2 trial using doses of 45–50 Gy in five fractions and a bounce definition of ≥0.2 ng/ml reported a PSA bounce in 51.1% of all patients with 10 and 2% of all patients exhibiting two and three bounces, respectively, at a median follow up of 42 months.

6.1.3.2 Duration of Bounce

According to studies reporting bounce duration, most patients return to PSA nadir by 6 months [17], but there are reported instances of longer bounce durations lasting as long as 11 months. The phase 1/2 study by Kim et al. report a median initial bounce duration of 3 ± 2.3 months, and second bounce duration of even longer; 6 ± 5 months.

6.1.3.3 Degree and Timing of Bounce

In general, the first PSA bounce occurs around 9–36 months [6, 10, 13], though late bounces many years after SBRT have been observed in our experience.

Most PSA bounces are below 2.0 ng/ml, but there are cases where the PSA bounce exceed this value, technically meeting criteria for biochemical failure if using the Phoenix definition, but demonstrating subsequent drop to a new PSA nadir after the bounce [7]. Thus, conservative management is recommended after prostate SBRT in patients who meet criteria for

biochemical failure, as a subset of these patients will be exhibiting a PSA bounce and not a true failure. In the phase I trial reported by McBride et al., it was noted that one patient who failed at 9 months using the Phoenix criteria (nadir +2 ng/ml) subsequently had decrease in PSA to a new nadir value. Similarly, a prospective phase 1/2 trial by Kim et al. found at least 1 out of 91 patients to meet criteria for failure using nadir +2 ng/ml, with subsequent drop in PSA over time [3]. We suggest using clinical judgment and close observation for at least 6 months in patients with rising PSA after SBRT before classifying a patient as a definite biochemical recurrence.

Though the Phoenix definition of biochemical failure is not reliable, it does appear to be more accurate than the former ASTRO definition of failure of three consecutive PSA rises; according to one study on prostate SBRT outcomes, the 4 year freedom from biochemical relapse with ASTRO definition was only 70%, versus 90% using the Phoenix definition; the authors note confounding due to late PSA bounces [8].

6.1.3.4 Predictors of Bounce

Two series report patients who exhibit a PSA bounce are significantly younger compared to those who do not [9, 17]. In multivariate analyses, factors including Gleason score, pre-treatment PSA, T-stage, and risk group were not found to be associated with likelihood of bounce.

A separate study noted that smaller prostate size (<30 ml) was associated with a significantly decreased likelihood of bounce; and enlarged prostates had a higher likelihood of having multiple bounces [11, 32]. According to one study, patients exhibiting very low PSA nadirs (<0.1 ng/ml) had a significantly lower likelihood of exhibiting a PSA bounce [11].

6.1.3.5 Is It Prognostic?

Though some studies suggest PSA bounce corresponds to improved biochemical progression free survival after standard EBRT or brachytherapy [33, 34], there is no definitive evidence to suggest that the PSA bounce is prognostic after SBRT [5].

6.1.4 PSA Decay

At 1 year follow up, the median percent PSA decline reported across various studies is approximately 80% [7, 12], suggesting a rapid initial drop followed by a more gradual decline that typically continues for years. A retrospective comparison of patients treated with 36.25–40 Gy of five-fraction SBRT, 81.0 Gy of IMRT or 43.5 Gy in six fractions of HDR showed PSA decay rates to be similar among all three modalities for the first 1000 days of follow up [22]; however, After 1000 days, IMRT treated patients had a plateau in PSA decay with a slope approaching 0, whereas SBRT and HDR treated patients continued to exhibit declines in PSA values, resulting in a lower PSA nadir at year 3 compared to conventional EBRT [31]. This is consistent with results reported by Katz et al., where patients after SBRT experienced a long, continued decline in PSA even out to 8 years, with ultimate nadir of 0.11 ng/ml [17]. Similarly, King et al. also reported in nadir values of 0.2 ng/ml by 3 years [10], which is lower than that reported after conventional 81 Gy EBRT at 0.6 ng/ml at 23 months [20]. Clearly, PSA outcomes after SBRT are distinct from conventional EBRT, implying larger, hypofractionated doses of radiation have a different impact on prostate cancer cells and subsequent PSA production.

Studies suggest that higher doses of SBRT result in lower PSA values at 3 years. Helou et al. report a significant ($P < 0.001$) difference in 3-year PSA values after 35 and 40 Gy in five fractions, with PSA of 0.64 and 0.27, respectively [35]. However, given short follow up, it is unknown whether the lower PSA nadir/higher dose results in better biochemical control; and given the higher incidence of GU toxicity with higher dose regimens, longer follow up is awaited to determine whether higher doses are justified.

6.2 Conclusions

In conclusion, biochemical control after prostate SBRT is comparable to standard fractionation external beam radiation. However, up to 50% of patients can exhibit a PSA bounce, which can exceed the current definition of nadir +2 ng/ml as biochemical failure. Given that a PSA bounce can last longer than 6 months in duration, and spuriously appear to be a biochemical failure before subsequent drop to a new nadir, caution should be taken before initiating salvage in such patients [8, 11].

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7 Overview of Tumor Control Outcomes with Prostate SBRT for Low and Intermediate Risk Prostate Cancer and Comparison to Other Treatment Interventions

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Learning Objectives and Outline

1. To understand radiobiology of prostate cancer and role of higher dose per fraction in its treatment
2. To summarize clinical outcomes of patients treated with
   a. Prostatectomy
   b. Conventional fractionated EBRT
   c. Moderate hypofractionated EBRT
   d. Brachytherapy (HDR and LDR)
   e. Proton beam therapy
   f. Extreme hypofractionation aka SBRT
3. Conclusion

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7.1 Radiobiological Consideration in Prostate Cancer and Support for Hypofractionation

Probability of cell kill from radiation is estimated based on ratio of intrinsic radiosensitivity to repair capacity of a particular tissue. Linear quadratic model is the most widely accepted model that fits probability of surviving fraction of cells after a given dose of radiation. Alpha (α) and beta (β) are the constants that represent intrinsic radiosensitivity and repair capacity and can be derived by fitting linear quadratic model to function of cell survival probability plotted against the radiation dose. The actual values of alpha (α) and beta (β) are difficult to ascertain, therefore, based on best fit model a ratio of α/β is reported, where early responding tissues are generally characterised by a high α/β ratio and late responding tissues are defined by a low α/β ratio. Tumors, generally are considered early responding tissues with α/β ratio of >8, while normal tissue complication probability is calculated based on assumption that α/β ratio for normal tissues is <4 and thus are considered late responding tissues. Radiobiological studies have shown as α/β ratio decreases, there is increased sensitivity to dose per fraction. Therefore, in most cancers, adjacent late responding tissues are more sensitive to increased dose per fraction than the tumors. For this reason, most radiation regimens utilize small daily fraction sizes (1–2 Gy) to maximize the therapeutic ratio,

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Table 7.1 Biological effective dose of various dose fractionation and treatment modalities

Total dose (Gy)	No. of fractions/dose per fraction (Gy)		BED ($\alpha/\beta = 1.5$) (Gy)	BED ($\alpha/\beta = 3$) (Gy)	BED ($\alpha/\beta = 10$) (Gy)
70	39	1.8	153.8	111.9	82.6
78	39	2.0	182.0	130.0	93.6
70.2	26	2.7	196.6	133.4	89.2
60	20	3.0	180.0	120.0	78.0
35	5	7.0	198.3	116.7	59.5
40	5	8.0	253.3	146.7	72.0
144 (LDR) Irradiation time 120 days	–	–	164.8	154.4	147.1
27 (HDR)	2	13.5	270.0	148.5	63.5
38 (HDR)	4	9.5	278.7	158.3	74.1

BED biological equivalent dose

with reduction in late complications without any compromise in tumor control.

Prostate cancer, on the other hand has unique radiobiology, first suggested by Brenner and Hall who observed that biochemical control was similar for 70 Gy given in 1–2 Gy fractions and I-125 brachytherapy using a prescription dose of 144 Gy [1]. Subsequent studies by others have demonstrated that the α/β ratio for prostate cancer ranges between 1.5 and 1.85 [2, 3]. This low α/β ratio predicts a greater capacity for repair between fractions, with an accompanying greater relative sparing with smaller fraction sizes. Therefore, a higher dose of radiation per fraction may be particularly effective in causing prostate cancer cell death. Table 7.1 illustrates biological effective doses for various dose fractionation regimens used in prostate cancer including low dose rate brachytherapy using iodine-125 (I-125) seeds.

In recent years it has become evident that hypofractionated radiotherapy regimens can provide excellent tumor control with limited toxicity to surrounding tissue, although the long-term results are yet to become available. In this chapter, we aim to summarize available tumor control data for various treatment modalities being employed for localized low- and intermediate-risk prostate cancer and compare those outcomes to early results with those obtained with extreme hypofractionated regimens also known as stereotactic body radiotherapy (SBRT).

7.2 Clinical Outcomes with Various Treatment Modalities

7.2.1 Surgery

Radical prostatectomy (RP) is considered one of the standards for men with low and intermediate risk prostate cancer. Last two decades has seen significant progress in RP methodology with introduction of laparoscopic RP in late 1990s [4] and robot assisted RP in early 2000s [5]. There are multiple older series that report clinical outcomes with RP, however, most of them are open procedures and include patients from prior to PSA-screening era. Selected publications, with large enough patient numbers from contemporary, post-PSA screening era with modern surgical techniques are summarized in Table 7.2. In these series, median follow-up ranged from 4 to 10 years. Biochemical relapse free survival (bRFS) for low-risk disease ranged from 79% at 5 years at University of Toronto [6] to 97% at 5 years from Johns Hopkins University [7]. Corresponding 10-year bRFS rates ranged from 64 to 95%. Whereas the bRFS for

Table 7.2 Outcomes with surgery

Author (location)	Population	Median follow-up (years)	bRFS	Notes
Roder et al. (Denmark) [8]	LR (n = 414) IR (n = 573)	4	82% at 5-years 76% at 10-years 70% at 5-years 60% at 10-years	
Mullins et al. (Johns Hopkins, US) [7]	LR (n = 2201) IR (n = 1019)	10	97% at 5-years 95% at 10-years 81% at 5-years 72% at 10-years	Includes only the post-PSA era patients from 1991–2011
Louis et al. (Toronto, Canada) [6]	LR (n = 812) IR (n = 1267)	–	79% at 5-years 59% at 5-years	
Diaz et al. (Detroit, US) [9]	LR (n = 250) IR (n = 197)	10	86% at 10-years 62% at 10-years	
Kane et al. [10]	N = 347, all LR patients eligible for AS	4	81% at 5-years 64% at 10 years	Only patients who would qualify for AS were included
Menon et al. [11]	LR (n = 705) IR (n = 479)	5	95.1% at 5-years 92.6% at 7-years 80.2% at 5-years 69.8% at 7-years	
Bhatta-Dhar et al. [12]	LR (n = 336)	5	87% at 6-years	Stratified patients according to PLND status—no difference

bRFS biochemical relapse free survival, *LR* low-risk, *IR* intermediate-risk, *AS* active surveillance, *PSA* prostate specific antigen

intermediate-risk disease ranged from 59% at 5 years at University of Toronto to 72% at 10 years from Johns Hopkins University.

Summary

Surgery is the oldest and most established treatment option for low- and intermediate risk prostate patients. With recent advances in surgical techniques and introduction of laparoscopic and robotic-assisted prostatectomy techniques, there has been some improvement in tumor control outcomes. Modern prostatectomy series report a 10-year median (range) biochemical relapse free survival of 86% (64–95%). Similarly, for intermediate risk patients treated with RP, median 10-year bRFS is reported to be 61% (59–72%).

7.2.2 Conventionally Fractionated Radiotherapy

Early studies reporting clinical outcomes of prostate cancer with conventional fraction were dismal. As the understanding of prostate cancer biology improved over the last three decades, the clinical outcomes improved as reported by multiple randomized control trials and institutional series, summarized in Table 7.3. Zelefsky et al. [13] reported on 1100 patients from Memorial Sloan Kettering Cancer Center (MSKCC) undergoing dose escalation with conventional fractionation. They found that with doses higher than 75.6 Gy there was statistically significant improvement in biochemical relapse free (bRFS) in both low and intermediate risk patients; 5-year bRFS was 90 and 70%, respectively. Results of four randomized control trials confirmed that the higher doses are required to achieve better tumor control outcome in localized prostate cancer [14–17]. Other institutional series further consolidated that higher dose delivered to the localized prostate cancer in conventional fractionation resulted in statistically significant improvement in bRFS [18–20].

Kalbasi et al. [21] performed a retrospective comparative effectiveness study of all prostate

Table 7.3 Outcomes with conventionally fractionated radiotherapy

Author (location)	Population	Dose	Follow up (years)	bRFS	Notes/toxicity
Zelefsky et al. (MSKCC) [13]	Total n = 1100 LR (n = 279) IR (n = 405)	≥75.6 Gy	5	LR: 90% at 5 years IR: 70%	
Zeitman et al. (PROG 95-09) [22]	Total n = 393 LR (n = 116) IR (n = 61)	79.2 GyE	5.5	LR: 80.5% at 5 years IR: 81%	
Zelefsky et al. (MSKCC) [18]	Total n=2047 LR (n=446) IR (n=849)	64.8 – 86.4 Gy	6.6	LR: 90% at 7 years IR: 72%	
Pollack et al. (MDACC, RCT) [14]	N = 305 All risk group patients	70 Gy 78 Gy	5.0	Low dose: 64% at 6 years High dose: 70%	Benefit most pronounced in IR and HR patients. A trend towards improved DMFS for IR and HR patients treated with 78 Gy
Peeters et al. (Dutch Multicenter RCT) [15]	N = 669 All risk group patients[a]	68 Gy 78 Gy ADT (n = 143) (6–36 months)	4.25	Low dose: 54% at 5 years High dose: 64%	SS benefit in IR patients, but not LR patients
Dearnaley et al. (UK MRC RT01 RCT) [20]	N = 843 LR[a] (n = 194) IR[a] (n = 264) HR[a] (n = 362)	64 Gy 74 Gy ADT all patients (3–6 months)	5.25	Low dose: 60% at 5 years High dose: 71%	Even high dose arm is lower than some of other trials and reported that >78 Gy is necessary for PCa
Kuban et al. Red (MDACC RCT) [16]	N = 301 All risk group patients	70 Gy 78 Gy	8.7	Low dose: 59% at 8 years High dose: 78%	
Heemsbergen et al. [17]	Total (N = 664) LR[a] (n = 119) IR[a] (n = 179)	78 Gy ADT (n = 193, mainly high risk)	9.2	61% at 10 years LR: 70% IR: 60%	

bRFS biochemical relapse free survival, *LR* low-risk, *IR* intermediate-risk, *HR* high-risk, *AS* active surveillance, *PSA* prostate specific antigen, *ADT* androgen deprivation therapy
[a]Risk groups based on Chism criteria for PSA failure

cancer patients registered in National Cancer Database (NCDB) from 2004 to 2006. Authors analysed 12,229 low-risk and 16,714 intermediate-risk patients and reported 7-year OS of 86 and 82%, respectively, for those treated with EBRT dose ≥75.6 Gy. In propensity score matched analysis, dose escalated EBRT (≥75.6 Gy) was associated with statistically significant improvement in OS for intermediate risk patients (HRs 0.84; $p < 0.001$), but not for low risk patients.

Summary

Multiple randomized trials and large institutional series have now confirmed that the higher doses of radiation are required to improve bRFS and OS for patients with localized low and intermediate risk prostate cancer. Traditionally, using

Table 7.4 Outcomes with Moderately hypofractionated radiotherapy

Author (location)	Population	Dose Gy/#fraction	Median follow up (years)	Outcome, bRFS in hypofractionated arm	Notes
Lee et al. (RTOG 0415) [23]	N = 1115, all LR	73.8/41 vs. 70/28	5.8	93.7% at 5 years	G2 or worse late toxicity in hypofractionated arm—GU (29.7%), GI (22.5%)
Dearnaley et al. (CHiPP trial, UK) [24]	N = 3216 LR (15%) IR (73%)	74/37 vs. 60/20 (or 57/19) ADT (97%)	5.2	LR: 96.6% and 90.9% at 5 years for 60/20 and 57/19 cohorts IR: 90.2% and 86.0%	G2 or worse late toxicity—GU (5%), GI (3%)
Pollack et al., US [25]	N = 303 IR (66%) HR (34%)	78/38 vs. 60.2/26 ADT (9.9% of IR patients, 35.1% of HR patients)	5.7	Overall 67.7% at 5 years	G2 or worse late toxicity in hypofractionated arm—GU (44.9%), GI (18.1%)
Aluwini et al. (HYPRO trial), Netherlands [27]	N = 820 IR (26%) HR (74%)	78/39 vs. 64.6/19 ADT (66% in hypofractionated arm)	5	No outcome results reported yet	G2 or worse late toxicity in hypofractionated arm—GU (41.3%), GI (17.7%)
Catton et al. (Canada) PROFIT trial [26]	N = 1206 all IR patients	78/39 vs. 60/20 No ADT	6	85% at 5 years	G2 or worse late tocixity in hypofractionated arm—GU (22.2%), GI (8.9%)

bRFS biochemical relapse free survival, *LR* low-risk, *IR* intermediate-risk, *HR* high-risk, *AS* active surveillance, *PSA* prostate specific antigen, *ADT* androgen deprivation therapy, *GI* gastrointestinal, *GU* genitourinary, *G2* grade 2

the conventional fractionation regimens, the higher doses were achievable only by increasing the number of fractions, which implies that patients would come for more than 8 weeks of daily treatments. These additional treatments are not only burdensome for the patient and family, but can also pose challenge for busy radiotherapy centers.

7.2.3 Moderately Hypofractionated Radiotherapy

Moderate hypofractionation for prostate cancer has cautiously been introduced into clinical practice, with the hope of reducing overall treatment time, while maintaining efficacy. Early institutional series laid the ground work for three randomized clinical trials that demonstrated that moderate hypofractionation results in excellent tumor control, acceptable toxicity and increased convenience to patients compared to standard fractionation. Thus, these regimens have been accepted as the new standard as a monotherapy option for favorable intermediate risk patients or as a part of combination with androgen deprivation therapy (ADT) for unfavorable intermediate or high risk patients undergoing treatment with external beam radiotherapy. Table 7.4 summarizes the key clinical trial and pertinent results from moderate hypofractionation series.

RTOG 0415 assessed the role of moderate hypofractionation in low-risk patients in a randomized control trial [23]. Total of 1115 patients were randomized to either receive 73.8 Gy in 41 fractions or 70 Gy in 28 fractions. At a median follow up of 5.8 years, there was no difference in disease free survival (85.3 vs. 86.3%) and acute toxicity between two arms. CHiPP trial is the largest randomized trial, that included 3216 men from the United Kingdom with localized prostate cancer that either received 74 Gy in 37 fractions, 60 Gy in 20 fractions or 57 Gy in 19 fractions [24]. Fifteen percent and 73% of them were low- and intermediate-risk patients, respectively. Five-year biochemical and clinical failure free rates were similar across all

three arms: 88.3% in 74 Gy group, 90.6% in 60 Gy group and 85.9% Gy in 57 Gy group. Although there was no difference in late gastrointestinal (GI) toxicity (11.9% vs. 13.4%), there was, however, a trend towards slightly higher genitourinary (GU) toxicity at 5 years with hypofractionated regimen 11.7 versus 9.1% (HR = 1.34, p = 0.07).

In trial by Pollack et al. [25] 303 men with localized intermediate- (66%) and high-risk (34%) disease were randomized to either receive conventionally fractionated RT (76 Gy in 38 fractions) or hypofractionated RT (60.2 Gy in 26 fractions) between 2002 and 2006; low-risk patients were excluded. The 5-year biochemical and clinical disease failure was similar in both arms, 21.4 versus 23.3% and there was no significant difference in acute or late GI or GU toxicity. In the Canadian PROFIT trial 1206 intermediate risk patients were randomly assigned to either receive 78 Gy (standard) or 60 Gy (short) course radiotherapy in 39 or 20 fractions, respectively [26]. Five-year bRFS rate was 85% for both arms (HR = 0.96). The investigators noted a significant increase in grade 2 of higher acute GI toxicity in short arm compared to standard arm, 16.7 vs. 10.5% (p = 0.003); conversely, for late grade 2 of higher toxicity occurred more frequently in standard arm versus short arm, 13.7 versus 8.9%, respectively (p = 0.006). Acute and late grade 2 or higher GU toxicities were similar in both arms. The authors concluded that short fractionation is not inferior to the standard fractionated radiotherapy for intermediate risk patients and is more convenient for patients.

Contrary to other trials, in HYPRO Trial, a phase three randomized non-inferiority trial that compared 78 Gy in 39 fractions to 64.6 Gy in 19 fractions in 820 intermediate and high-risk patients [27], the investigators reported a significantly higher grade 3 or worse late GU toxicity in hypofractionation arm (19.0 vs. 12.9%, p = 0.021). Late grade 2 or worse GI toxicity was similar between two arms at 17.7 and 21.9%. Nonetheless, the investigators could not reject inferiority because the hazard ratios for both GU and GI toxicity were higher than their initial hypothesis. Furthermore, due to high grade 3 or worse GU toxicity observed at 3 years, investigators concluded that non-inferiority of hypofractionation could not be confirmed. It is important to note that only one quarter of the patients in this trial were intermediate risk and remainder were high-risk patients that required long term ADT as well as inclusion of seminal vesicles in the treatment volume. Additionally, the hypofractionation dose in this trial was higher than other contemporary hypofractionation trials, which may explain higher incidence of toxicity. Lastly, the HR for non-inferiority was set much lower in this trial compared to others.

Royce et al. [28] recently conducted a meta-analysis of these 3 non-inferiority randomized trials that evaluated moderately hypofractionated regimens (2.4–4 Gy) compared to conventionally fractionated regimens (1.8–2 Gy). Sixty five percent of patients were intermediate risk (n = 3553). Based on random effects model, hypofractionated RT had significantly improved disease-free survival (HR 0.89, p = 0.047) compared to conventionally fractionated RT, however there was no difference in OS. Authors also noted that there was increased grade 2 or higher acute GI toxicity with hypofractionation (RR = 1.42, p = 0.002), but it did not translate into higher late toxicity. A trend towards an increase late G2 or higher GU toxicity was observed with hypofractionation (RR = 1.18, p = 0.08).

Summary

Randomized trials have now demonstrated that moderately hypofractionated radiotherapy regimens can provide excellent tumor control and are much more convenient for the patients, compared to conventionally fractionated radiotherapy regimens. The reported bRFS survival ranged from 90.9 to 93.7% 5 years for low-risk disease and 85–86% at 5 years for intermediate-risk disease.

7.2.4 Brachytherapy

Brachytherapy (BT) is an excellent treatment modality as monotherapy for low-risk patients as well as favorable intermediate risk patients.

Table 7.5 Outcomes with LDR monotherapy

Author (location)	Population	Intervention	Median follow up (years)	Outcome, bRFS	Notes
Zelefsky et al. (11 institutions, US) [29]	N = 2693 LR (n = 1444) IR (n = 960) HR (n = 192)	LDR monotherapy with either I-125 (68%) or Pd-103 (32%)	5.3	LR: 82% at 8 years IR: 70% HR: 48%	
Sylvester et al. (Seattle, US) [30]	N = 215 LR (73.5%) IR (20.6%) HR (5.1%)	LDR monotherapy with I-125	11.7	LR: 85.9% at 15 years IR: 79.9% HR: 62.2%	
Morris et al. Cancer 2013 (Vancouver, Canada) [31]	N = 1006 LR (58%) IR (42%)	LDR monotherapy with I-125 ADT (65%), 6 months	7.5	96.7% at 5 years 94.1% at 10 years	
Herbert et al. (Vancouver, Canada) [32]	N = 439 all IR	LDR monotherapy with I-125 ADT (94%), 6 months	5	94% at 5 years	
Kollmeier et al. (MSKCC) [38]	N = 236 LR (75%) IR (25%)	LDR monotherapy with I-125 (72% of patients)	6.9	LR: 97% at 8 years IR: 94%	G2 or worse late toxicity—GU (14%), GI toxicity (2.5%)
Sekiguchi et al. (Japan) [33]	N = 305 LR (57%) IR (43%)	LDR monotherapy with I-125 ADT (30.5%), 6 months	5.5	Overall 95.5% at 5 years LR: 94.2% IR: 97.3%	G2 or worse late toxicity—GU (8.9%), GI (1%)
Kittel et al. (Cleveland Clinic, US) [34]	N = 1989 LR (61.3%) FIR (29.8%) HIR (4.5%) HR (4.4%)	LDR monotherapy with I-125 ADT (18.2%), 6 months (1-48 months)	6.8	Overall 81.5% at 10 years LR: 86.7% LIR: 79.3% HIR: 80.9% at 5 years HR: 67.5% at 5 years	G3 or worse late toxicity—GU (7.6%) and GI (0.8%)
Cosset et al. (Paris, France) [35]	N = 675 LR (67%) FIR (33%)	LDR monotherapy with I-125 ADT (58%)	11	Overall 82% at 10 years LR: 87% IR: 71%	G3 or worse late toxicity at 10 years—GU (0.2%) GI (1.7%)
Prestidge et al. (abstract only) [36]	N = 292, FIR	LDR monotherapy with I-125 or Pd-103	6.7	86% at 5 years	RCT for EBRT + BT vs. BT alone for FIR patients
Frank et al. (MD Anderson, US) [37]	N = 300, FIR	LDR mono with I-125, Pd-103 or Cs-131	5.1	92.7% at 5 years	G2 or worse late toxicity—GU (3%), GI (1%)

bRFS biochemical relapse free survival, *LR* low-risk, *IR* intermediate-risk, *FIR* favourable intermediate-risk, *LIR* low-tier intermediate risk, *HIR* high-tier intermediate risk, *HR* high-risk, *AS* active surveillance, *PSA* prostate specific antigen, *ADT* androgen deprivation therapy, *GI* gastrointestinal, *GU* genitourinary, *RCT* randomized control trial, *EBRT* external beam radiotherapy, *BT* brachytherapy, *G2* grade 2

Furthermore, BT when combined with either EBRT or ADT (or both) is one of the standard treatment options for intermediate- and selected high-risk patients, especially after publication of ASCENDE-RT trial (Morris et al. Red Journal 2017). Tables 7.5 and 7.6 summarize

Table 7.6 Outcomes with HDR Monotherapy

Author (location)	Population	Dose Gy/# fractions	Median follow up (years)	Outcome, bRFS	Notes
Demanes et al. (UCLA and WBH, US) [39]	N = 298 LR and FIR	42/6 (2 implants 1 week apart); or 38/4 (single implant)	5.2	97% at 8 years	G2 or worse late toxicity—GU (28.9%), GI (<1%)
Barkati et al. (Australia) [40]	N = 79, favourable risk (T2c, GS $\leq$ 7, PSA $\leq$ 10)	30/3, 31.5/3, 33/5, 34.5/3 ADT (9%)	3.3	85.1% at 5 years	G3 or worse late toxicity—GU (20.6%), GI (0%)
Hoskin et al. (UK) [41]	N = 197 LR (4%) IR (52%) HR (44%)	34/4, 36/4, 31.5/3 and 26/2 ADT–IR (74%) and HR (93%)	5, 4.5, 2.8 and 0.5	Overall 91% at 4 years IR (95%) HR (87%)	G3 or worse late toxicity—GU (3–16%), GI (1%)
Zamboglou et al. (Germany) [42]	N = 718 LR (73%) IR (16%) HR (11%)	38/4 (1 implant, n = 121 or 2 implants, n = 351), and 34.5/3 (3 implants, n = 226)	4.4	94% at 5 years 90% at 8 years	G3 or higher late toxicity—GU (3.5%), GI (1.6%)
Ghadjar et al. (Germany) [43]	N = 36 LR (n = 28) IR (n = 8)	38/4 (single implant) ADT (n = 5)	6.9	97% at 5 years	G2 or worse late toxicity—GU (47%), GI (none)
Yoshioka et al. (Japan) [44]	N = 190 IR (42%) HR (58%)	48/8 (n = 7), 54/9 (n = 97) and 45.5/7 (n = 86); single implant ADT–IR (44%) and HR (94%)	7.7	Overall 85% at 8 years IR: 91% HR: 77%	G2 or worse late toxicity—GU (13%), GI (2%)
Jawad et al. (William Beaumont, MI) [45]	N = 494 LR (68%) IR (32%)	38/4 (n = 319, 1 implant), 24/2 (n = 79) and 27/2 (n = 96, 1 or 2 implants) ADT (14%)	5.5, 3.5 and 2.5	97%, 87% and 90% at 5 years for 3 dose levels, respectively	G2 or worse late toxicity—GU (23%) and GI (4/5%)
Hauswald et al. (UCLA, CA) [46]	N = 448 LR (n = 288) IR (n = 160)	42–43.5/6 (2 implants, 1 week apart) ADT (9.5%)	6.5	97.8% at 10 years	G3 or worse late GU toxicity 4.9%
Patel et al. (UCLA, CA) [47]	N = 190 all IR	43.5/6 (83%, 2 implants, 1 week apart) No ADT	6.2	90% at 8 years	G2 or worse late toxicity—GU (22.6%), GI (1.1%)
Strouthos et al. (Germany) [48]	N = 450 LR (n = 198) IR (n = 135) HR (n = 117)	34.5/3 (3 separate implants) ADT (12.8%)	4.7	5-year bPFS 95%; LR (96.1%), IR (96.1%) and HR (92.1%)	Late G2 or worse toxicity: GU (15%), GI (0.4%)
Prada et al. (Spain) [49]	N = 60 LR (73%) IR (27%)	19/1 ADT (33%)	6	66% at 6 years	No G2 or worse toxicity

bRFS biochemical relapse free survival, *LR* low-risk, *IR* intermediate-risk, *HR* high-risk, *AS* active surveillance, *PSA* prostate specific antigen, *ADT* androgen deprivation therapy, *GI* gastrointestinal, *GU* genitourinary, *RCT* randomized control trial, *EBRT* external beam radiotherapy, *BT* brachytherapy, *G2* grade 2, *G3* grade 3

contemporary series that report long term tumor control outcomes for patients treated with low dose rate (LDR) and high dose rate brachytherapy (LDR), respectively.

7.2.4.1 Low Dose Rate Brachytherapy

With improvement in brachytherapy approach using trans-rectal ultrasound (TRUS) in the 1980s and introduction of stable low energy radioisotopes, LDR brachytherapy became an established and popular treatment modality for low risk and favorable intermediate risk prostate cancer. Zelefsky et al. [29] reported long-term results of 2693 patients with localised prostate cancer treated with I-125 or palladium-103 (Pd-103) implantation by pooling data from 11 institutions across the US and Canada. At median followup of 5.3 years, 8-year bRFS was 82 and 70% for low- and intermediate-risk patients treated with LDR monotherapy alone. The Seattle group has the longest reported outcomes of low-, intermediate- and high-risk patients treated with LDR monotherapy with I-125 seeds [30]. At median follow up of 11.3 years, they reported 15-year bRFS of 85.9 and 79.9% for low risk (n = 158) and intermediate risk (n = 44) patients, respectively. Others have similarly reported excellent institutional results of patients treated with LDR brachytherapy with or without short term (6 month) androgen deprivation therapy [31–35]. The median (range) bRFS for low-risk patients treated with LDR brachytherapy with or without ADT is reported to be 87% (82–94%) at a median of 10 years (5–15 years) follow up. Outcome for intermediate-risk patients treated with LDR brachytherapy with or without ADT were 83% (70–97%) at median follow up of 6.5 years (5–15 years).

While the above reported results are from retrospective registries, only two prospective trials of LDR monotherapy for intermediate risk patients have been reported so far [36, 37]. Results from RTOG 0232 study, where selected IR patients were randomized to receive either EBRT+LDR BT or BT alone have been presented in abstract form only [36]. At median follow up of 6.7 years, they showed that 5-year bRFS for IR patients treated with LDR monotherapy was 86%. Similarly, Frank et al. [37] in a prospective phase 2 trial reported 5-year bRFS of 93% for favorable IR patients treated with I-125, Pd-103 or Cs-131 monotherapy.

7.2.4.2 High Dose Rate Brachytherapy

High dose rate (HDR) brachytherapy has most commonly been used in the boost setting with EBRT for unfavorable intermediate- or high-risk patients. Demanes et al. [39] were the first to report utilization of HDR brachytherapy as monotherapy for localized prostate cancer by pooling patients from California Endocurietherapy Cancer Center (CET) and William Beaumont Hospital (WBH). Patients either received 42 Gy in six fractions in two separate implants, 1 week apart (CET) or 38 Gy in four fractions in a single implant (WBH). All patients were low risk or favourable intermediate risk. At median follow up of 5.2 years, 8-year bRFS was 97% with minimal G2 or worse GI toxicity and favorable G2 or worse GU toxicity (29%). Barkati et al. [40] performed phase 1 dose escalation study of delivering 30 Gy, 31.5 Gy, 33 Gy and 34.5 Gy in 3 fractions in a single implant and reported 5-year bRFS of 85% in favorable IR patients treated with HDR monotherapy. They, however, observed a high rate late urinary retention due to urethral stricture (9%). Hoskin et al. [41] reported their dose escalation study from United Kingdom, that included mostly intermediate and high risk patients and majority of them received ADT. With favorable GI and GU toxicity profile, they reported 4-year bRFS of 95% for intermediate risk patients. Most importantly they reported feasibility of delivering HDR monotherapy in two fractions using CT and MRI based planning techniques. Zamboglou et al. has so far reported the largest series of men with localized prostate cancer undergoing HDR brachytherapy [42]. Eighty-nine percent were low- and intermediate-risk patients. They reported cumulative 5- and 8-year bRFS of 94% and 90%, respectively for entire cohort, with low grade 3 or worse late GI and GU toxicity.

In recent years there have been multiple institutional reports confirming favourable bRFS outcomes with acceptable GU and GI toxicity with HDR brachytherapy [43–49]. Most authors have reported bRFS of 97% (66–98%) for combined cohorts of low- and intermediate risk patients and at median follow up 6.0 years (5.0–10.0 years). Others, who stratified patients according to the risk grouping report 95% bRFS at 5 years for low risk disease and 93% (90–96%) at 6.5 years (4–8 years) for intermediate risk disease.

Summary

Brachytherapy has proven to be an excellent treatment modality for low- and intermediate-risk prostate cancer. While, LDR has proven record in low-risk disease with established dose, HDR practice still has significant heterogeneity in terms of total dose and number of fractions. Median 10- and 6.5-year bRFS in low- and intermediate-risk patients treated with LDR is reported to be 87% (82–94%) and 83% (70–97%), respectively. Corresponding rates with HDR at 5- and 6.5-years are 96 and 93% (90–96%) for low-and intermediate risk patients, respectively. Even, though both LDR and HDR options are available for this cohort of patients, they are, however, limited mostly to large academic centers. Furthermore, interest in brachytherapy has been declining, in part due to decline in trained radiation oncologists who can perform brachytherapy. Improvement in external beam technologies and advent of moderate and extreme hypofractionation have further reduced its utilization in most recent decade.

7.2.5 Proton Beam Therapy

There has been an increased interest in utilizing favorable dose profile of proton beam to treat prostate cancer. The rationale for using protons in radiotherapy arises due to the physics that account for the way that conventional high energy x-rays (photons) and protons deposit their energy in the patient. Unlike x-rays, for proton beam therapy (PBT) the energy deposited per unit distance increases markedly as the proton slows down, producing a sharp peak (the Bragg peak) of energy at the end of the proton range. Very little energy is deposited distal to the Bragg peak. The beneficial effect of the Bragg peak is utilized to decrease the dose deposited outside the prostate, especially in the rectum, thus potentially resulting in lower toxicity.

Zeitman et al. [22] first utilized protons for dose escalation trial (RTOG 95-09) in low- ($n = 115$) and intermediate-risk ($n = 68$) patients. They successfully increased the dose to 79.2 CGE using conventional fractionation and reported excellent bRFS at 10 years: 92.9% for low-risk and 69.6% for intermediate-risk. University of Florida Health Proton Therapy Institute has published their experience in treating prostate cancer with protons in a series of publications and report 5 year bRFS of 99% for low-risk patients and 93–99% for intermediate risk patients [50–52]. The rate of grade 3 or worse GI and GU toxicity was very low in their cohorts: 0.5–1.0% and 1.7–4.8%, respectively. Recently, Japanese investigators have reported 8-year bRFS of 95% for low-risk patients and 87% for intermediate risk patients treated with 74 CGE using PBT [53]. They also reported very low rates of GI and GU toxicity.

Summary

Proton beam therapy is an emerging treatment modality for localized prostate cancer. Although initial data suggest good biochemical control rates [98% (93–99%) for low-risk patients and 93% (70–99%) for intermediate risk patient at 5 years], additional studies with longer term follow up are required to validate these findings. Furthermore, the PBT is being delivered with conventional fractionation regimen, that provides the same logistic challenges as the conventionally fractionated radiotherapy discussed earlier. Hypofractionated PBT regimens are being studied, but to date there are no published data available (Table 7.7).

Table 7.7 Outcomes with proton beam therapy

Author (location)	Population	Dose	Median follow up (years)	Outcome, bRFS	Notes
Mendenhall et al. (Jacksonville, US) [50]	N = 211 LR (n = 82) IR (n = 82) HR (n = 40)	LR: 78 CGE IR: 78–82 CGE HR: 78 + Chemo	5	LR: 99% at 5 years IR: 99% HR: 76%	Late G3 or worse GU toxicity 4.8%; GI 1.0%
Zietman et al. (RTOG 95-09) [22]	N = 195 LR (59%) IR (35%)	79.2 CGE in 39 fractions	8.9	LR: 92.9% at 10 years IR: 69.6%	RCT of low dose (70.2 CGE) vs. high dose (79.2 CGE); no difference in OS
Bryant et al. (Jacksonville, US) [51]	LR (n = 512) IR (n = 527)	≥78 CGE in 39 fractions	5.3	LR: 99% at 5 years IR: 94%	Late G3 or worse GU and GI toxicity: 2.9% and 0.6%
Henderson et al. (Jacksonville, US) [52]	LR (n = 120) IR (n = 95)	LR 70 CGE in 28 fractions; IR 72.5 CGE in 29 fractions	5.2	LR: 98.3% at 5 years IR: 92.7%	Late G3 or worse GU and GI toxicity: 1.7% and 0.5%
Takagi et al. (Japan) [53]	LR (n = 249) IR (n = 602)	74 Gy RBE in 2 Gy RBE fractions	5.8	LR: 95% at 8 years IR: 87%	Late G2 or more GU and GI toxicity: 2.0% and 3.9%

bRFS biochemical relapse free survival, *LR* low-risk, *IR* intermediate-risk, *HR* high-risk, *AS* active surveillance, *PSA* prostate specific antigen, *ADT* androgen deprivation therapy, *GI* gastrointestinal, *GU* genitourinary, *RCT* randomized control trial, *G2* grade 2, *G3* grade 3

7.2.6 Extreme Hypofractionation Aka SBRT

Hypofractionated radiotherapy for prostate cancer has been studied since the 1960s [54]. Early experience using 36 Gy delivered in 6 Gy fractions reported minimal acute and long-term toxicity with this approach. This early experience utilized relatively crude planning techniques as compared with more modern approaches, however despite this; hypofractionated therapy appeared to be safe. Since this early experience, many subsequent studies have demonstrated that toxicity of hypofractionated regimens using brachytherapy or external beam radiation appear at least comparable if not more favorable to conventionally fractionated regimens [39, 55–59]. Extreme hypofractionation and stereotactic techniques were not routinely utilized in treatment of prostate cancer until mid 2000s when significant developments in radiation planning and delivery were introduced. A medline/pubmed search using MESH terms "prostate" and "stereotactic radiotherapy" yielded only 42 results between 1995 and 2004, whereas 305 publications were found with same MESH terms for years 2005–2014, indicating significant increase in number of publications and interest in prostate SBRT. Baker et al. (Cancer 2016) analysed the US National Cancer Database on utilization of SBRT and found that in 2012 there were approximately 7.6 and 3.2% of patients were being treated SBRT at academic and comprehensive cancer centers, respectively across US, compared to zero in 2004

There are several advantages of SBRT, that have resulted in adoption of this technique:

1. Low α/β ratio of 1.5 for prostate cancer indicates that potentially there may be higher effect of tumor control with hypofractionation compared to conventional fractionation.
2. Due to rectal α/β ratio higher than prostate (3 vs. 1.5), late rectal complications may be decreased for a given level of tumor control
3. Patient convenience and possibly improved quality of life with fewer fractions, compared to 7–9 weeks of treatments with conventional fractionation.

4. Potential benefit of cost efficiency for cancer center as the equipment utilization and staffing may be more efficient with fewer fractions.

7.2.6.1 Early Results

While earlier publications focused on feasibility and toxicity of SBRT, recently clinical outcomes of patients being treated with SBRT have been reported and these are summarized in Table 7.8. King et al. [60] from UCLA, reported outcomes in 67 low-risk patients treated with 36.25 Gy in 5 fractions using Cyberknife™ technology. At median follow up of 2.7 years, 4-year bRFS was 94% with only 2 PSA and biopsy proven local failures. At median follow up of 3.7 years Mcbride et al. reported 3-year actuarial bPFS of 97.7% in 47 low risk patients treat at 4 different cancer centers with doses ranging between 36.35 to 37.5 Gy in 5 fractions [61]. Aluwini et al. [62] from Erasmus Cancer Center included both low (60%) and intermediate-risk (40%) patients and increased the dose to 38 Gy to entire prostate with integrated boost of 55 Gy to the dominant intraprostatic lesion in 5 fractions. At median follow up of 23 months, 2-year biochemical control rate was 100% with acute grade 2 and 3 GI toxicity of 12 and 2% and late grade 2 higher GI toxicity of only 3%. Loblaw et al. reported results of prospective Phase I/II trial of delivering 35 Gy in 5 once weekly fractions in 29 days using linear accelerator-based treatment delivery systems [63]. The 5-year biochemical control in their low-risk cohort of patients was 98%. They also performed biopsies at 36 months from completion of treatment on all patients enrolled in the trial and found that 96% of the patients had negative biopsy.

Katz and Kang have published the largest SBRT series to date, that included 470 (324 - low-risk and 153 intermediate-risk) patients treated with 35–36.25 Gy in 5 fractions [64]. Eleven percent of patients received 6 months of neoadjuvant and concurrent ADT. They reported 7-year actuarial bPFS of 95.6 and 89.6% for low- and intermediate risk patients, respectively. They further stratified their intermediate cohort into low-tier and high-tier groups and found that there was statistically significant difference in bPFS (93.5 vs. 79.3%) between the two groups. Updated results of 230 low-risk patients treated with either 35 Gy/5 fractions of 36.25 Gy/5 fractions were recently reported [65]. With a median follow up of 9 years, 10-year bDFS was 95.8% without any difference between two dose levels. The only difference reported was in G3 GU toxicity: 4 vs. 15% in 35 and 36.25 Gy cohorts, respectively.

Hannan et al. included 36% low-risk and 64% intermediate risk patients from five cancer centers across the US in phase I/II dose escalation trial [66]. They delivered 45 Gy (n = 15), 47.5 Gy (n = 15) and 50 Gy (n = 62) in 5 fractions and reported 3- and 5-year actuarial freedom from biochemical failure rate of 100 and 98.6% for the entire cohort. They, however, observed 7% rate of grade 3 of higher GI toxicity at 5 years, which was indeed higher than that reported in contemporary prostate cancer literature. Kotecha et al. recently reported their results of phase II trial of integrated dose escalation for dominant lesion in 24 high tier intermediate and high-risk patients [67]. They treated the entire prostate to 36.25 Gy, while boosting the dominant lesion to 50 Gy in 5 fractions. Sixty seven percent of patients received ADT for a median of 6 months (range 4–30.5 months). Early results indicate, 2-year bRFS of 95.8% at median follow of 25 months, with only 2 relapses both occurring in high risk patients.

Summary

SBRT demonstrates excellent early outcomes for patients with low and intermediate risk disease. Follow up is short to have meaningful comparison with other modalities. Nonetheless, available data suggests bRFS of 97% (94–98%) at 4.5 years for low-risk patients, 90% at 8 years for intermediate-risk patients and 99% (96–100%) at 2 years for patient cohorts with mixed low- and intermediate-risk patients. Pooled analysis

Table 7.8 Outcomes with SBRT

Author	Population, sample	Dose Gy/# fractions	Follow up (years)	Outcome, bRFS	Notes
King et al. UCLA and Stanford, CA) [68]	N = 67, all LR (phase II)	36.25 Gy/5 (Cyberknife)	2.7	94% at 4 years	Very low rates of G2/3 GI and GU toxicities
McBride et al. (4 US cancer centers) [61]	N = 45, all LR	37.5 Gy/5 (n = 10) or 36.25 Gy/5 (n = 34) (Cyberknife)	3.7	97.7% at 3 years	G2 or worse late toxicity—GU (17%), GI (7%)
Aluwini et al. (Erasmus, Netherlands) [62]	N = 50 LR (n = 30) IR (n = 20)	38 Gy/4 (DIL boost to 44/4)	2	100% at 2 years	G2 or worse late toxicity—GU (20%), GI (3%)
Loblaw et al. (Toronto, Canada) [63]	N = 84, all LR (phase I/II)	35/5, once weekly over 29 days (LINAC)	4.6	98% at 5 years	G2 or worse late toxicity—GU (5%), GI (7%)
Katz and Kang (New York, US) [64]	N = 470 LR (n = 324) IR (n = 153)	35 Gy/5 (n = 154), 36.25 Gy/5 (n = 316) (Cyberknife) ADT (n = 51)	6	LR: 95.6% at 7 years IR: 89.6%	SS difference in FIR and UIR patients. G3 or worse late toxicity—GU (1.7%)
Hannan et al. (5 US centers) [66]	N = 91 LR (36%) IR (64%) (phase I/II)	45/5 (n = 15), 47.5/5 (n = 15) 50/5 (n = 62) ADT (16.5%)	4.5	Overall 98.6% at 5 years LR: 100% IR: 98%	G3 or worse late toxicity—GU (6%), GI (8%)
Katz, A [65]	N = 230, all LR	35/5 (n = 41) 36.25/5 (n = 190) CyberKnife	9	93.7% at 10 years; no difference between 2 dose levels	G2 or worse late toxicity—GU (12%), GI (4%)
Kotecha et al. (Cleveland, OH) [67]	N = 24 IR and HR patients (phase II)	36.25/5 (boost to 50/5 way from OARs)	2.1	95.8% at years	G2 or worse late toxicity—GU (8%), GI (8%)
King et al. [68]	N = 1100 LR (58%) IR (30%) HR (11%) Pooled analysis of phase I/II trials for localized prostate cancer	36.35 (35–40)/5	3	Overall 93% at 5 years LR: 95% IR: 84% HR: 81%	For patients with 5 year follow up: 5-year bRFS was 99% for LR and 93% for IR

bRFS biochemical relapse free survival, *LR* low-risk, *IR* intermediate-risk, *HR* high-risk, *AS* active surveillance, *PSA* prostate specific antigen, *ADT* androgen deprivation therapy, *GI* gastrointestinal, *GU* genitourinary, *RCT* randomized control trial, *G2* grade 2, *DIL* dominant intraprostatic lesion, *LINAC* linear accelerator

of multiple phase I/II trials also show 5-year DFS of 95 and 84% for low- and intermediate-risk patients respectively [68]. These are promising results when compared to other modalities as illustrated in Fig. 7.1. Furthermore, given the convenience conferred by the SBRT regimens

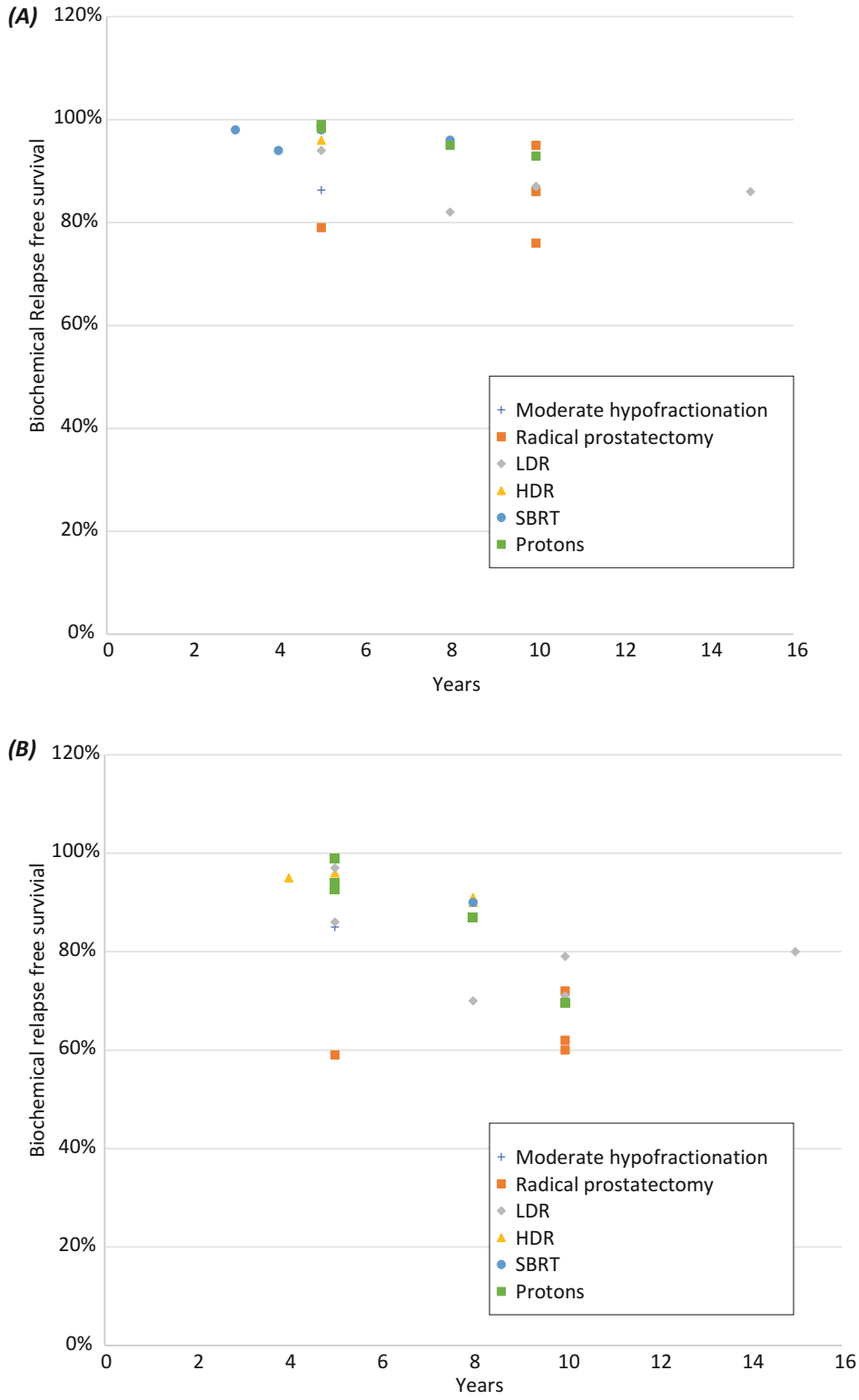

Fig. 7.1 Comparison of reported biochemical relapse free survival with various treatment modalities in series that reported low-risk patients (**a**), intermediate-risk patients (**b**) or both low- and intermediate-risk patients (**c**)

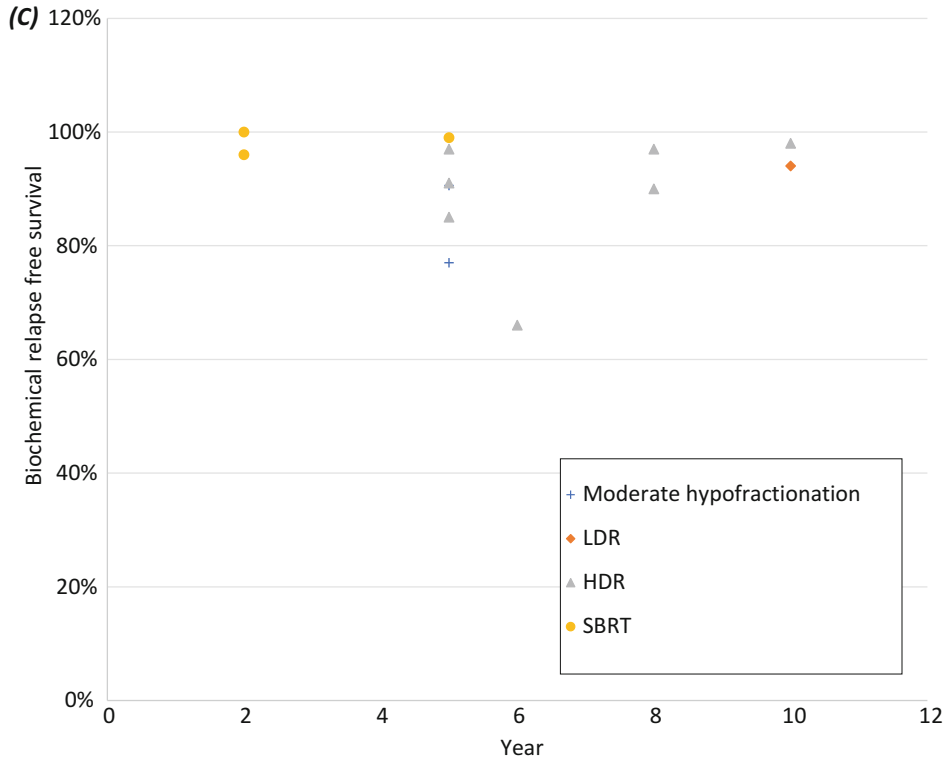

Fig. 7.1 (continued)

for patients and treatment centers it has become very attractive options. In the coming years, once more mature data is available, SBRT will become one of the standard treatment option as a monotherapy for low and intermediate risk patients.

Combination of external beam radiotherapy with brachytherapy has established as standard treatment option for intermediate prostate cancer as demonstrated in ASCENDE-RT randomized trial [69]. There is adequate emerging evidence that SBRT, as it is well tolerated by the patients may be better treatment option for low-tier intermediate risk patients as monotherapy, as well as for high-tier intermediate risk patients in combination brachytherapy. This later hypothesis has been tested in prospective manner by the MSKCC group, but the results have not been published yet (personal communication). Furthermore, SBRT may also have a role in treatment of patients in high risk category. Recently published, multi-institutional retrospective analysis of high risk patients (GS 9-10) has also confirmed that combination of EBRT and brachytherapy results in improved local and distant control as well as there may be an improvement in overall survival [70]. SBRT should be studied in a prospective randomized manner to evaluate its efficacy against conventional EBRT in the setting of combined modality treatment of high risk patients.

7.3 Conclusion

With advancement in image guidance and availability of protective measures such as rectal spacer, SBRT has become relatively easy to deliver and convenient treatment choice for patients, with

minimal toxicity. It is conceivable that in near future, SBRT would be the primary form of external beam treatment for prostate cancer patients.

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8 Overview of Toxicity Outcomes with Prostate SBRT and Comparison to Other Treatment Interventions (Urinary, Rectal and Sexual Outcomes)

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8.1 Introduction

Prostate cancer is the most common cancer diagnosis amongst adult males in the United States, with an expected 161,360 new diagnoses in the United States in 2017 [1]. Less than 10% of these patients will present with metastatic disease, and the vast majority of cases are considered curable at diagnosis. The prognosis with localized disease is typically excellent compared to other cancers, with 5 and 10 year cancer specific survival rates approaching 100%. The Prostate Testing for Cancer and Treatment (ProtecT) trial, a recently published large randomized study which compared radical prostatectomy, conventionally fractionated external beam radiotherapy (EBRT), and active surveillance in patients with low-risk prostate cancer failed to identify a difference in efficacy between surgery and radiation [2]. Consequently, the toxicity associated with each treatment and resultant effect on quality of life (QoL) are arguably more important in selecting an intervention strategy for prostate cancer than for other malignancies. Detailed QoL data collected from this trial reveals marked differences in these interventions [3].

Stereotactic body radiation therapy (SBRT) has gained acceptance for many disease sites over the past several years, but the concept is not entirely new in principle for prostate cancer. A retrospective study from the United Kingdom reported on the feasibility and safety of delivering 36 Gy in six fractions to patients over 20 years beginning in 1964 [4]. Despite the limited technology and lack of image-guided therapy, the authors nonetheless concluded that hypofractionation is not only an "economical use of scarce resources, but even more important, is less wearing for patients than daily fractionation." Even in light of these promising findings, the current movement towards extreme hypofractionation has only been possible with the development of

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advanced radiation techniques, precise image guidance, and a more refined understanding of the radiobiology of prostate cancer.

The development of modern SBRT techniques for prostate cancer has generally been a success, as most studies have demonstrated comparable rates of rectal, urinary, and sexual toxicity without a compromise in efficacy. However, identification of the appropriate dose and number of fractions has not been without setbacks, and the margin for error with extreme hypofractionation is almost certainly narrower than with conventional schedules [5]. In this chapter, toxicity following SBRT for localized prostate cancer is reviewed, with an emphasis on preventative measures, symptom management, and comparison of morbidity to that observed using other treatment strategies.

8.2 Genitourinary Morbidity

8.2.1 Profile and Etiology of Acute Genitourinary Morbidity

The most common acute side effects in patients treated with SBRT for prostate cancer affect the genitourinary system. The pattern of acute toxicity in these patients is well established, and similar in nature to patients treated with conventionally fractionated external beam radiotherapy techniques. Symptoms are most pronounced in the week following treatment, typically persist at 1 month, and resolve to baseline 3 months after treatment [6]. The severity of acute symptoms is similar to IMRT and may be less than brachytherapy (Table 8.1). The most common urinary symptoms patient's experience during SBRT are urinary frequency, weak stream, and dysuria while other symptoms such as incontinence and hematuria are not typically seen during and immediately following treatment. While acute morbidity does not appear worse with moderately hypofractionated therapy [14–16], medical management of urinary toxicity may be required more frequently during extremely hypofractionated treatment [17].

The etiology of acute urinary toxicity is not perfectly understood, though three factors are usually indicated: prostate size, urethral dose, and bladder dose. As with brachytherapy, multiple studies have associated prostate size with higher rates of acute urinary morbidity [18–20]. Nonetheless, one published series which

Table 8.1 Comparison of published AUA score changes following brachytherapy and SBRT

Study	*N*	Modality	Total dose (Gy)	Baseline AUA score	1 week AUA score	1 month AUA score	3 month AUA score	Long-term AUA score
Henderson [7]	255	LDR ±EBRT	145 (LDR) 110/45 (LDR/EBRT)	6	n/r	19 (6 weeks)	15	5 (2 years)
Van Gellekom [8]	127	LDR	D90 = 133.0 (mean)	7.3	n/r	19.8	15.2 (6 months)	10.4 (2 years)
Williams [9]	173	LDR	D90 = 136.5 (median)	5.5	n/r	17.1	14.4	8.0 (1 year)
Crook [10]	150	LDR	145	6	n/r	13	13	3 (2 years)
Meier (Abstract) [11]	295	SBRT	40	7.6	14.2	11.6	7.5	6.4 (4 years)
Tree [12]	51	SBRT	36.25	6	11 (1–3 weeks)	8 (4–6 weeks)	5 (7–12 weeks)	n/r
Rana [13]	102	SBRT	35–40	10.5	n/r	13.4	10.6	8.6 (3 years)
Repka [6]	102	SBRT	35–36.25	9.1	11.8	11.8	8.2	n/r

Adapted with permission [6]
Abbreviations: *n/r* not reported, *n/a* not applicable

included only patients with prostates >50 cc demonstrated acceptable rates of acute urinary morbidity, without need for catheterization or other invasive procedures [21]. Although urinary symptom scores may peak slightly higher in these patients, they tend to resolve by 3 months post-treatment and long-term outcomes are not notably worse than other patients.

The impact of radiation dose to the bladder and urethra on acute urinary morbidity is not well understood. In one recent study, prostate size and hot spots in the bladder wall were predictive of acute urinary morbidity, while no dosimetric indices related to the prostatic or membranous urethra were associated with toxicity [18]. Further research in this area is warranted, but given similar observations in patients undergoing low-dose rate (LDR) brachyterhapy, these findings are certainly intriguing [22].

Grade 3 or higher toxicity, such as urinary obstruction requiring catheterization, is generally rare during and immediately following prostate SBRT [23–25]. Although early pilot studies utilized urinary catheterization for planning and treatment in an attempt to mimic high-dose rate (HDR) brachytherapy [26, 27], most practitioners today avoid this invasive procedure, instead using MRI guidance to identify the location of the prostatic urethra.

8.2.2 Profile and Etiology of Late Genitourinary Morbidity

Unlike acute genitourinary toxicity, late urinary problems caused by radiation may not be self-limited, requiring medical or even surgical interventions to alleviate symptoms. Nonetheless, while short-term symptoms affect nearly all patients, the incidence of late toxicity is relatively rare. The vast majority of patients, following resolution of acute symptoms, can expect to return to baseline or even improved functional urinary levels [13, 23, 28, 29].

However, some proportion of patients may experience late urinary toxicity following SBRT. Most commonly, a late urinary flare syndrome has been described, where patients experience a second, often more bothersome increase in lower urinary tract symptoms [30]. This syndrome appears to affect approximately 10–20% of patients, and the incidence appears to peak approximately 1 year following completion of treatment (Fig. 8.1). A similar clinical syndrome is well described in patients treated with brachytherapy [10, 31, 32]. Fortunately, this syndrome appears to be self-limited, although medical management is often indicated. The etiology of this symptom flare is not well understood and there is scant data upon which to draw definite

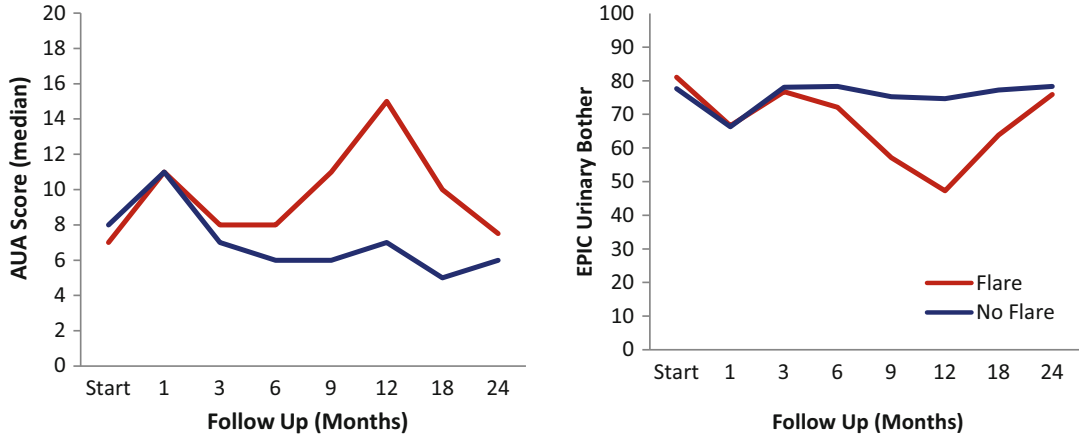


Fig. 8.1 Late urinary flare syndrome is defined as an IPSS increase of at least five points above baseline with a minimum score of 15 that returns to baseline with conservative management. Median IPSS values (left) and EPIC Urinary Bother scores (right) are presented in patients who experience the syndrome and those who do not

conclusions. One retrospective study using normal tissue complication probability (NTCP) modeling suggests that small volumes of the bladder receiving high doses (*e.g.* hot spots) is predictive of late urinary flare syndrome [33]. Another dosimetric analysis identified similar findings, with the increasing volume of bladder receiving high doses associated with more irritative urinary symptoms 1 year following treatment [20]. These reports are intriguing, as retrospective studies of patients treated with dose-escalated IMRT or low-dose rate brachytherapy have identified bladder neck (trigone) dosimetry as the most important predictor of late urinary toxicity [22, 34]. However, other studies have suggested that inhomogeneous plans, as well as high maximum point doses in the prostatic urethra, may also predispose patients to late toxicity [35].

Other, more severe symptoms following prostate SBRT are less common [36]. Hematuria occurs in approximately 20% of patients at some point following treatment, although it resolves in the vast majority of patients without intervention [37]. Unsurprisingly, the incidence of hematuria appears to be significantly increased in patients who have previously undergone a surgical procedure for benign prostatic hyperplasia (BPH) such as transurethral resection of the prostate (TURP) or simple prostatectomy (http://ascopubs.org/doi/abs/10.1200/JCO.2018.36.6_suppl.91). On cystoscopic evaluation, the most common late finding is hyperemia within the bladder neck and/or prostatic urethra. However, full cystoscopic evaluation of hematuria is usually required, as bladder cancer is the fourth most common cancer in men and metachronous cancers may be detected [1, 38].

Chronic obstructive and irritative symptoms are not typical following prostate SBRT, and indeed some patients may notice improvement in their overall urinary function following treatment. Irritative symptom scores in particular appear significantly improved over baseline at 3 years following SBRT, particularly in those patients with higher baseline IPSS values (Fig. 8.2) [39]. This may be due to the overall decrease in prostate size that can be expected in the years following SBRT, which may in turn ease urinary flow through the prostate. Overall, chronic symptomatic obstruction is rare in patients following prostate SBRT less than 10% of patients reporting obstructive voiding symptoms that they felt were a "moderate to big problem [25]." Urinary obstruction requiring invasive intervention, such as urinary catheterization or TURP is rare, with most studies reporting rates of <5% [13, 23–25]. As with EBRT, urinary

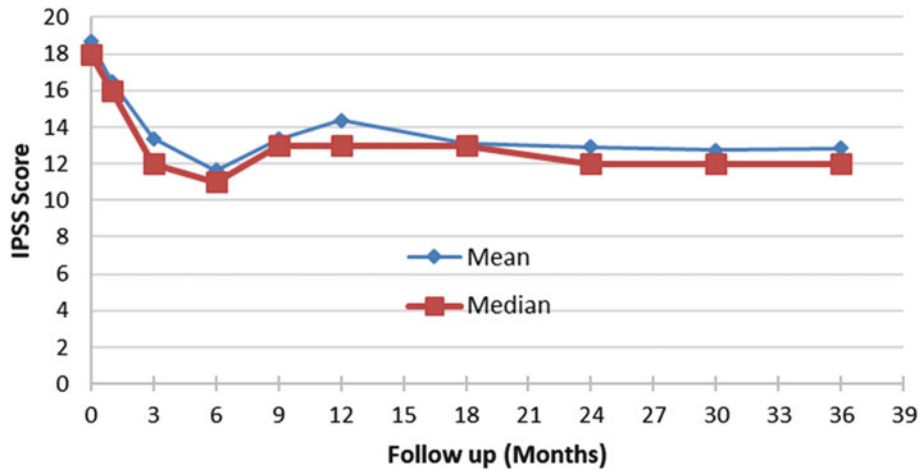


Fig. 8.2 Improvement in International Prostate Symptom Score (IPSS) following prostate SBRT in patients with pre-treatment IPSS > 15. Data presented at ASTRO 2017; reproduced with permission from the authors [39]

incontinence by any definition is uncommon following SBRT and likely related to comorbidities in this aging population [28, 36].

8.2.3 Management and Prevention of Genitourinary Symptoms

Acute urinary symptoms are typically self-limiting and resolve over time without medical intervention. Nonetheless, symptomatic management is often indicated to minimize patient discomfort and improve patient QoL during and after treatment. Management is similar to that of patients who are treated with conventional fractionation or brachytherapy, as urinary symptoms typically respond well to tamsulosin or other alpha-adrenergic antagonists. Indeed, many practitioners prefer prophylactic alpha-adrenergic antagonist use in an attempt to mitigate potential acute side effects associated with SBRT, although this has not been demonstrated to eliminate morbidity entirely [6]. Furthermore, there is some evidence that non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, may have a role in limiting treatment-induced edema and consequently limit radiation symptoms [40], although good data documenting their effect are lacking. Finally, in those patients who have significant urinary morbidity that is not responsive to standard treatments, a short steroid taper may be effective in providing relief [6, 30]. In particular, the steroid taper appears to be effective for symptom management in patients experiencing late urinary symptom flare.

Another method of limiting toxicity may be in adjusting the overall length of treatment time. Practice patterns in this regard vary, with some radiation oncologists preferring treatment on consecutive days while others may space out treatment over multiple weeks. Little comparative data is available to evaluate these regimens, although a small randomized trial has suggested a toxicity benefit to extending the overall treatment course. In this study, 152 men were randomized to receive LINAC-based SBRT to a total prostate dose of 40 Gy in five fractions over 11 or 29 days. While there was no difference in clinician-graded urinary toxicity, a higher percentage of patients in the 11-day arm experienced a minimally clinically important change (95.7 vs. 74.6%, $p < 0.01$) [41].

Patients who experience hematuria during treatment should undergo urinalysis to rule out an infection, as hematuria is not expected in the acute setting during or following SBRT. In the case where a patient notices hematuria months to years following treatment, or if hematuria does not resolve in the acute setting, cystoscopic evaluation and potentially imaging of the upper urothelial tract is required. While cauterization or fulguration of radiation-induced abnormal vasculature is not always necessary, these patients should be evaluated for the presence of a metachronous bladder cancer or other urinary abnormality.

Detailed attention to treatment planning and delivery may also result in lower acute and late urinary toxicity. Strategies may include shrinking planning target volumes, careful treatment planning, and intensive image-guided radiation therapy (IGRT). Specific recommendations for these approaches are detailed at the end of this chapter.

8.2.4 Comparison to Other Treatment Strategies

Unfortunately, no randomized data currently exist comparing oncologic or quality of life outcomes following SBRT to other standard treatments, such as radical prostatectomy, conventionally fractionated EBRT, moderately hypofractionated EBRT, brachytherapy, or proton beam therapy (PBT). Several randomized trials comparing SBRT to conventionally fractionated or moderately hypofractionated EBRT are underway (University of Miami HEAT Trial, NCT01794403) or under development (NRG-GU005, NCT03367702), but it will be several years before results are available. One notable trial based in the United Kingdom, the PACE trial (NCT01584258), will compare SBRT to radical prostatectomy. An overview of late toxicity

Table 8.2 Late GU and GI toxicity following prostate SBRT and other radiation modalities

Author	Technique	Dose (Gy)	Median follow-up (yrs)	*N*	Gr 2 GU (%)	Gr 3 GU (%)	Gr 2 GI (%)	Gr 3 GI (%)
Zelefsky [43]	IMRT/IGRT IMRT/no IGRT	86.4	2.8	186 190	10.4 20	– –	1.0 1.6	– –
Michalski [44]	3D-CRT IMRT	79.2	4.6 3.5	491 257	13.4 7.8	2.5 1.9	22 15.1	5.1 2.6
Hamstra [45, 46]	IMRT/No spacer IMRT/Spacer	79.2	3.1	73 149	7.0 7.0	0 0	5.7 0	1.4 0
King [47]	SBRT	36.25	2.7	67	8.8	3.5	2	0
Chen [28]	SBRT	35–36.25	2.3	100	31	1	1	0
Khor [48]	HDR boost + EBRT	19.5 + 46	5	344	16.8[a]	11.8[a]	–	–
Hoskin [49]	HDR boost + EBRT	17 + 35.75	7.1	110	31[b]	–	7[b]	–
Hsu [50]	HDR boost + EBRT	19 + 45	2.5	112	7.1	2.7	2.7	0.9
Rodda [51]	LDR boost + EBRT EBRT	115 78	6.5	198 200	32.8 20.6	18.4 5.2	31.3 20.2	8.1 3.2
Katz [52]	SBRT boost + 3D-CRT	19–21 + 45	5	45	4.6	2.3	13.3	–
Lin [53]	SBRT boost + VMAT	21 + 45	3.5	41	3–11[c]	0	0	0
Anwar [54]	SBRT boost + SIB	9.5–10.5 + 45	3.6	48	27	2	0	0
Paydar [42]	SBRT boost + IMRT	19.5 + 45–50.4	4.2	108	40	6	12	1

Adapted with permission [42]

Abbreviations: *IMRT* intensity-modulated radiation therapy, *IGRT* image-guided radiation therapy, *3D-CRT* 3D-conformal radiation therapy, *SBRT* stereotactic body radiation therapy, *HDR* high dose rate, *LDR* low dose rate, *EBRT* external beam radiation therapy, *VMAT* volumetric arc therapy, *SIB* simultaneous integrated boost

[a]Urethral stricture rates

[b]Severe toxicity per the Dische scale

[c]0–11% toxicity rates in late follow-up period with cumulative rates not reported

following a variety of approaches is presented in Table 8.2.

In the meantime, the best available comparative data originate from a secondary analysis of the PROSTQA study, which analyzed prospectively collected data from patients undergoing brachytherapy or intensity modulated radiation therapy (IMRT) [55]. In this analysis, these data were compared to outcomes in patients treated with prostate SBRT [29]. Investigators reported largely similar QoL outcomes between the different therapeutic strategies, although higher rates of obstructive urinary symptoms were noted in patients treated with brachytherapy at all time points analyzed from 6 months to 2 years. No differences in urinary incontinence were detected, and rates of hematuria were not reported. Furthermore, another retrospective study suggested that SBRT may be associated with lower rates of long-term genitourinary toxicity than moderately hypofractionated treatment approaches [56].

Nonetheless, studies have raised concern that SBRT may be associated with higher rates of high grade toxicity than conventional treatments. In particular, a population study identified higher rates of genitourinary billing codes codes suggestive of toxicity in patients treated with SBRT as compared to IMRT, and this finding was observed at multiple time points [57]. Interestingly, the patient populations identified in this study differed widely between the different treatments, as SBRT patients tended to be

younger, Caucasian, live in metropolitan areas, and have higher incomes than their IMRT counterparts. Although statistical matching was employed to create balance between the treatment arms, more than 90% of IMRT patients were excluded from the analysis. Furthermore, patients treated with SBRT in this era were predominantly treated on protocols that mandated frequent follow-up visits with lower thresholds for invasive intervention such as cystoscopy [58]. It may be that as SBRT becomes more routine, practitioners' technical ability will improve; this "learning curve" phenomenon has been observed in prostate brachytherapy centers [59]. Notably though, even accounting for the higher complication cost, SBRT was less expensive than IMRT in this population analysis.

There are limited data to illuminate potential QoL differences between patients treated with SBRT and PBT, and comparison currently requires hypothesis or extrapolation. However, given that the primary benefit for PBT in the definitive treatment of localized prostate cancer is the elimination of the "low-dose bath" associated with IMRT and photon-based SBRT techniques, it is unlikely that a clear improvement in urinary toxicity would be observed with PBT. Studies suggest that long-term urinary outcomes appear to be similar with PBT and IMRT [60], and given the lack of clear difference in outcomes between IMRT and SBRT, it stands to reason that neither PBT nor SBRT would offer significant urinary QoL advantage. However, these approaches have not been compared directly in a randomized trial.

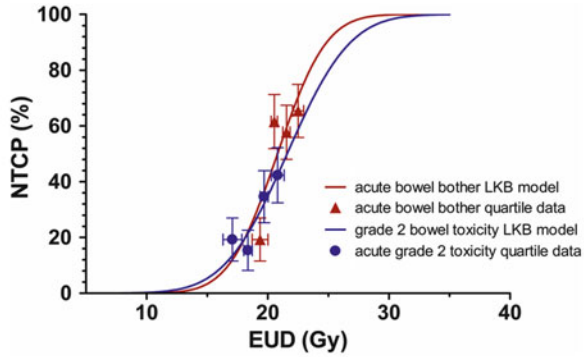
Until data from ongoing randomized trials becomes available, comparison between radical prostatectomy and SBRT also relies on non-randomized comparisons and extrapolation from other data-sets. In particular, the ProtecT trial obtained detailed QoL data on patients randomized to either 3D-CRT or surgery [3]. Surgical patients reported worse incontinence and were more likely to use $\geq$1 pad per day, although 3D-CRT patients reported higher rates of nocturia and more irritative symptoms as expected. The SBRT toxicity profile likely would compare similarly, but these findings have not been validated in the setting of a randomized trial.

8.3 Gastrointestinal Morbidity

8.3.1 Profile and Etiology of Acute Gastrointestinal Morbidity

Much like genitourinary toxicity, acute gastrointestinal morbidity in patients treated with SBRT is similar in pattern and intensity to that of patients treated with conventionally fractionated EBRT. Patients typically experience the most severe morbidity in the week following SBRT, with some improvement at 1 month, and return to baseline by 3 months [61]. Studies have demonstrated that bowel movement urgency, bowel movement frequency, incontinence, bloody stools, abdominal pain, and overall gastrointestinal bother are significantly worsened following SBRT. Urgency and frequency appear to be the most common treatment related acute gastrointestinal effects, and these symptoms tend to be the last to resolve in the months following treatment. Bloody stools are less common, and may frequently be secondary to increased irritation in patients with pre-existing hemorrhoids [62].

As with EBRT, the bulk of acute gastrointestinal symptoms experienced by patients can likely be attributed to rectal dosimetry. Given the intimate nature between prostate and rectum, separated only by the rectoprostatic (Denonvilliers') fascia, some high dose to the rectum is unavoidable. However, the dosimetric indices which best predict acute toxicity have not been fully elucidated. Data from one study, which employed an eight fraction treatment approach, suggests that the volume of rectum receiving $\geq$28 Gy may be predictive of acute gastrointestinal toxicity [63]. The authors recommended keeping the V28Gy under 15 cm^3, although the applicability of this strategy to a five fraction approach is unclear. Another study, which employed normal tissue complication probability (NTCP) modeling, identified the rectal V20Gy as an independent predictor of grade 2+ rectal toxicity 1 week following SBRT, with a 39% incidence in patients where this value exceeded 30.2% [64]. Furthermore, no patient or disease-related parameters were associated with acute toxicity, and predictive models using both



	m	TD50 (Gy)	n
Acute bowel bother	0.15 (0 – 0.30)	20.8 (15.1 – 26.5)	0.27 (0.01 – 0.53)
Acute grade 2 rectal toxicity	0.19 (0 – 0.38)	21.6 (15.9 – 27.3)	0.39 (-0.11 – 0.89)

Fig. 8.3 NTCP modeling and parameter estimates for acute bowel toxicity 1 week following completion of prostate SBRT

physician graded toxicity or patient reported outcomes resulted in similar model estimates. These data, along with estimated NTCP parameters, are presented in Fig. 8.3.

8.3.2 Profile and Etiology of Late Gastrointestinal Morbidity

Late gastrointestinal toxicity is a concern for patients treated with SBRT; however, due to tight treatment margins [65], image-guided therapy, and the favorable therapeutic ratio associated with hypofractionation, the incidence of high grade toxicity is quite modest. Although most follow-up remains relatively short in comparison to data from conventionally fractionated series, rates of late grade 2+ toxicity are reportedly less than 15% [23, 24, 66, 67], while grade 3+ toxicity is quite rare. Urgency and frequency, which can be pronounced acutely, are generally not present and do not reappear once the initial symptoms have resolved.

The most common late rectal toxicity following SBRT is hematochezia. The incidence of this adverse effect is not clear, as rates reported in the literature vary widely, which may be secondary to differences in toxicity reporting. Nonetheless, the rate of hematochezia requiring aggressive intervention, such as argon plasma coagulation (APC), is likely quite low, with one large series reporting an actuarial 2-year rate of 1.5% [37], which compares favorably to the EBRT and IMRT literature. However, another study, in which patients were treated using a strategy that prioritized target coverage over risk of toxicity, reported a high-grade hematochezia rate of 19.4%, although the investigators used a non-standard grading schema [68]. The rate of rectal bleeding requiring more than two sessions of APC in this study was 3.1%.

A more concerning adverse effect of SBRT, particularly in the setting of dose escalation, is loss of integrity of the rectal wall, including rectal ulcers or rectourethral fistulae. While these toxicities are typically not observed in patients treated with standard SBRT doses (35–40 Gy in five fractions), there are reports in the literature of high grade rectal toxicity requiring emergent cauterization or diverting colostomy [69]. In this study, 6.6% of patients treated to a total prostate dose of 50 Gy in five fractions experienced grade 3+ rectal toxicity. While retrospective analyses of the data suggest that high-grade toxicity may be limited by limiting the volume of rectal wall receiving 50 Gy below 3 cm^3 and keeping $<35\%$ of the rectal wall circumference to 39 Gy

[70], given the limited toxicity and excellent oncologic outcomes associated with lower dose-per-fraction regimens, extreme dose escalation is not recommended outside the context of a clinical trial.

8.3.3 Management and Prevention

Many practitioners take steps prior to simulation and treatment to limit radiation dose to the rectum in an attempt to minimize both acute and late gastrointestinal toxicity. For example, the use of an enema prior to CT simulation, as well as each treatment fraction, minimizes stool and gas in the rectum, which can improve set-up reproducibility and radiation targeting. Others may choose to use a rectal balloon, which can also provide excellent interfraction reproducibility, although it is more invasive and uncomfortable for patients. Additional steps may be helpful, such as instructing patients to adhere to a low-residue diet, which can minimize stool and gas in the rectum during treatment. Much like urinary toxicity, an alternative strategy may be extending the overall duration of treatment without changing the overall treatment dose or shrinking margins. In an early prospective trial of prostate SBRT, investigators switched from a daily schedule to an every-other-day schedule in an attempt to mitigate toxicity. While no decrease in urinary symptoms was observed, there was a statistically significant decrease in patient-reported bowel symptoms [71].

Nevertheless, the majority of patients do not require medical intervention for management of acute gastrointestinal symptoms during treatment. There are limited medical interventions available for patients with abdominal pain, and in many cases these symptoms may be related to radiation-related changes in their bowel habits. However, should increased gas production be identified as the culprit, anti-flatulence medications such as simethicone may be used to ameliorate patient discomfort. In patients with frequent loose stools, an anti-diarrheal medication such as loperamide may be useful for symptomatic relief, and it is useful to instruct patients on its use prior to undergoing therapy. Other symptoms, such as acute rectal bleeding, require further investigation on the part of the treating physician. Detailed history and anorectal evaluation are necessary to identify a potential source of bleeding; however, overall management is similar to patients treated with EBRT as topical steroid preparations are the mainstay of management in the acute setting. If a patient experiences severe pain with bowel movements and digital rectal examination, rectal fissure should be suspected and surgical evaluation may be warranted.

Late rectal bleeding is a concern following radiation therapy, and would typically be an indication for formal gastroenterology work-up. It is important to remember that the differential diagnosis for late rectal bleeding includes multiple potential etiologies which may not be related to the patient's history of radiation, such as diverticulosis. Full colonoscopic evaluation is useful, as it both evaluates for potential radiation changes in the rectal wall, as well as potentially identifies any underlying colorectal polyps or malignancies, particularly in those patients who have not been appropriately screened.

One approach to limiting rectal toxicity involves placement of a bio-absorbable hydrogel spacer between the prostate and the rectum. A randomized trial of patients undergoing IMRT with or without a peri-rectal spacer demonstrated improved rectal dosimetry as well as lower rates of clinician-graded toxicity and patient-reported QoL declines [45, 46]. Dosimetry studies suggest that spacer placement may improve target coverage or rectal dosimetry when treating with SBRT compared to either rectal balloon or no other intervention [72, 73]. This approach is particularly promising for patients with pre-existing rectal comorbidity, such as inflammatory bowel disease.

8.3.4 Comparison to Other Treatments

The same population based analysis which raised concern for higher rates of urinary toxicity in SBRT patients, also found significantly higher

usage of gastrointestinal diagnosis codes 6 months following treatment compared to IMRT [57]. However, in this case these differences were not observed at later time points, and rates were actually nominally lower in SBRT patients at 2 years. Furthermore, the PROSTQA study is again the most detailed source of comparative toxicity data for patients undergoing SBRT, IMRT, or brachytherapy, and results appear to suggest a benefit for SBRT compared to these other modalities [29]. In this study, patients treated with SBRT reported lower overall rates of gastrointestinal bother than patients treated with IMRT or brachytherapy at all time points measured following treatment. At 2 years, only 2% of SBRT patients reported "moderate-severe" problems with overall bowel function, compared to 10 and 7% in those treated with IMRT and brachytherapy, respectively.

No good data exist comparing gastrointestinal outcomes between SBRT and prostatectomy patients, but it is likely that patients treated with all forms of radiation experience more rectal toxicity than those undergoing surgery. Indeed, in the ProtecT trial, EBRT was associated with lower overall bowel function, higher rates of bowel bother, more frequent loose stools and fecal incontinence, incidence of bloody stools, and negative changes in bowel habits. The overall size of this effect in this study was relatively modest, and given that bowel toxicity appears lower with SBRT than with 3D-CRT, the magnitude of bowel QoL improvements in surgical patients is likely quite low. Nonetheless, patients considering radical prostatectomy or SBRT should be counseled on these potential differences.

Contrarily, given the greater uncertainties with treatment delivery, PBT is likely associated with similar or even higher rates of gastrointestinal morbidity. A population study which compared 3D-CRT, IMRT, and PBT for prostate cancer demonstrated higher rates of gastrointestinal diagnoses and procedures following PBRT as compared to IMRT [60]. Given the even tighter margins associated with SBRT treatment and apparently lower gastrointestinal toxicity, SBRT might result in even lower rates of late rectal toxicity. Nonetheless, this study is complicated by the fact that most PBT patients were treated with passively-scattered protons, a technique which achieves clearly inferior conformality at the prostatic-rectal interface compared to actively-scanned protons [74], which is the current standard of care.

8.4 Sexual Dysfunction

8.4.1 Profile and Etiology

Overall, SBRT is associated with an excellent toxicity profile in regards to male sexual health and well being. Nonetheless, given the physiologic function of the prostate, as well as location in close proximity to neurovascular structures [75], some detriment to normal sexual activity is possible. Patients do not typically experience acute toxicity, although a mild detriment in sperm count may be observed and patients should be cautioned about the risks of conception during and in the months following prostate SBRT secondary to scattered testicular dose. This risk may be slightly higher in patients treated with non-coplanar techniques (e.g. CyberKnife®) if care is not taken to protect the testicles from both entering and exiting beams [76]. Androgen deprivation therapy (ADT) is associated with a far more pronounced sexual symptom profile than any form of radiation therapy alone [77]; a full review of its effects are beyond the scope of this chapter.

In the long term, the biggest risk of SBRT is a decrease in the ability to achieve erections [78]. The effect of radiation is somewhat difficult to quantify in these patients, as most men treated with SBRT are at an age where erectile dysfunction (ED) secondary to other causes is common. Nonetheless, it is clear from studies of conventionally fractionated EBRT that radiation therapy has a detrimental effect on erectile function, and single arm studies and retrospective reviews suggest that similar trends exist in patients treated with SBRT [79]. In one analysis of men who did not receive hormone therapy and were able to achieve erections "firm enough for intercourse"

prior to treatment, there was gradual decline in overall sexual function over time, although the most precipitous drop occurred in the first year [78]. At 2 years post-SBRT, only 54.4% of men were able to achieve erections "firm enough for intercourse," and 26.7% of men felt their sexual function was a moderate to big problem, up from 13.4% prior to radiotherapy. A more recent analysis confirmed these findings with more patients and longer follow-up [80]. At 5 years post-treatment, 47% of men maintained their pre-treatment erectile function.

The etiology of ED following SBRT is not fully understood. The penile bulb is commonly used as an avoidance structure, but given the limited dose delivered with SBRT and the lack of an obvious dose response [78, 81], it may have a minimal role in loss of function over time. Vessel-sparing radiotherapy, which aims to spare the neurovascular bundles immediately posterior to the prostate, is a promising approach with up to 90% of men preserving potency at 5 years following conventionally fractionated therapy [82]. However, given concerns for potential diminished effectiveness and marginal miss, this strategy should be considered strictly investigational.

Very little effect on overall testosterone levels has been observed in patients treated with SBRT without concomitant ADT [78, 83, 84]. This is unsurprising given testicular scatter dose of approximately 2 Gy spread out over five fractions. Nonetheless, a small proportion of patients may experience chronic hypogonadism following treatment, particularly if they receive extended courses of ADT in addition to SBRT.

8.4.2 Management and Prevention

There are limited steps that can be taken currently to mitigate the risk of ED following prostate SBRT. Certainly testicular and penile bulb dose should be taken into account, but with accurate contouring and appropriate treatment planning these doses should be quite low even if unconstrained. Research is ongoing as to whether there is a role for delineation and constraint of the neurovascular bundles which run immediately posterior to the prostate, and have been implicated in erectile dysfunction following radical prostatectomy [82]. MRI is critical for accurate contouring of these structures, and given their close proximity to the target volume it is unclear whether they can be meaningfully spared without compromising PTV coverage and risking oncologic efficacy.

The approach to medical management of ED after SBRT is identical to that taken in treating men without a history of prostate cancer. First-line management involves phosphodiesterase 5 inhibition with prescription medication (e.g. sildenafil, tadalafil, vardenafil), which is frequently successful, particularly in patients with limited symptoms [85]. However, refractory patients who are highly motivated may require more invasive interventions, such as intracavernosal alprostadil, intraurethral alprostadil, or placement of a penile prosthesis.

A small proportion of patients, particularly those who have received ADT, may suffer from diminished testosterone production, leading to a wide variety of clinical symptoms. In men without a previous history of prostate cancer, exogenous testosterone supplementation can produce meaningful improvements in overall QoL and patient well-being. However, given the potential for diminished oncologic efficacy in patients who have been treated for prostate cancer, many practitioners have concerns over the potential for disease recurrence [86, 87]. Careful consideration and discussion of the risks and benefits should be pursued prior to initiation of treatment.

8.4.3 Comparison to Other Treatments

In the ProtecT trial, patients treated with EBRT were more likely to report erections firm enough for intercourse, less likely to report problems with erectile dysfunction, and endorsed a higher sexual quality of life than men who were treated with radical prostatectomy. It is important to note that most patients received nerve-sparing prostatectomies, and although this was associated with a lower rate of erections "not firm enough for intercourse" than non-nerve-sparing procedures

at 3 years (68 vs. 87%), the majority of these patients still suffer from erectile dysfunction. It is also worthwhile to recognize that all patients undergoing EBRT in this study were treated with neoadjuvant and concurrent ADT, even though most patients had low-risk disease by the D'Amico criteria [2, 3].

Analogously, the PROSTQA study demonstrates a similar effect of brachytherapy and IMRT, with approximately 50–60% of patients reporting at least a MCIC in sexual symptoms following treatment [29]. However, an MCIC was observed in only 20–40% of patients over all time points following SBRT, although these patients had higher rates of baseline sexual dysfunction, which might impact the reliability of this finding. Another study evaluated patients treated with SBRT and compared the rate of functional erections to model-derived estimates for EBRT and brachytherapy [80]. Thirty-four percent of all patients and 57% of those with baseline erectile function achieved functional erections at 2 years, rates that were highly similar to those predicted for other treatment modalities. Given that SBRT at a minimum does not appear to be worse than IMRT or brachytherapy, this treatment is likely as good or better than prostatectomy for potency preservation.

8.5 Summary and Suggestions to Minimize SBRT Toxicity

The placement of intraprostatic fiducial markers is mandatory when using the CyberKnife system, and is strongly recommended for other delivery systems, even when cone beam computed tomography (CBCT) is available for set-up. Typically, 1 week is required between fiducial placement and simulation to allow for seed migration. Furthermore, asking the patient to use an enema several hours prior to simulation and each fraction is recommended to minimize stool and gas within the rectum. At Georgetown University Hospital, all patients are asked to consume a low-fiber diet beginning 5 days prior to simulation and ending following the final treatment fraction. Finally, all patients are treated prophylactically with tamsulosin (0.4 mg once daily) if they are not already taking an alpha-adrenergic antagonist medication. Patients who experience bothersome, refractory symptoms are given a short steroid taper (dexamethasone, 2 mg BID for 1 week, followed by 2 mg daily for 1 week).

MRI is extremely useful for treatment planning and appears to minimize target volumes and improve delineation of the rectoprostatic interface [88]. Furthermore, MRI allows delineation of the prostatic urethra, which is not visible on CT. In patients for whom MRI is contraindicated (*e.g.* presence of metal, pacemaker, etc.) CT urethrogram is recommended for delineation of the membranous urethra [89]. While the role of the prostatic urethra in producing urinary toxicity is not clear and true urethral sparing may be associated with diminished biochemical outcomes, avoidance of hot spots in this organ is strongly recommended.

Sample dose constraints, which are in use at Georgetown University Hospital, are provided as a reference in Table 8.3. A sample plan and DVH are represented in Fig. 8.4. Institutional preference is to treat patients ever other day over 2 weeks (Monday, Wednesday, Friday, Tuesday, Thursday), given the apparent toxicity benefit

Table 8.3 Sample dose targets and constraints for treatment planning

36.25 Gy plan constraints	
Global max dose	120% of 36.25 Gy (43.5 Gy)
PTV	V (36.25 Gy) $\geq$ 95%
CTV	V (36.25 Gy) $\geq$ 99%
Prostatic urethra	V (36.25 Gy) $\geq$ 95%
	V (42 Gy) $\leq$ 0.03 cc
Membranous urethra	V (37 Gy) $<$ 50%
Bladder	V (37 Gy) $<$ 5 cc
	V (100%) $<$ 10%
	V (50%) $<$ 40%
Rectum	V (36 Gy) $<$ 1 cc
	V (100%) $<$ 5%
	V (90%) $<$ 10%
	V (80%) $<$ 20%
	V (75%) $<$ 25%
	V (50%) $<$ 40%
Sigmoid colon	V (30 Gy) $<$ 1 cc
Penile bulb	V (29.5 Gy) $<$ 3 cc
Testicles	D (20%) $<$ 2 Gy

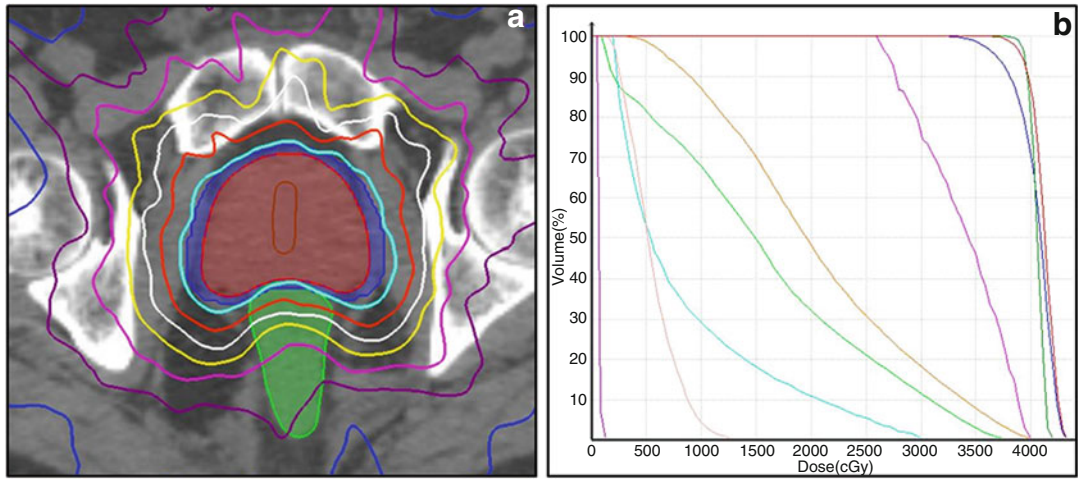


Fig. 8.4 Sample prostate SBRT treatment plan. (**a**) Representative axial slice from simulation CT with following dose distribution: 36.25 Gy (cyan), 30 Gy (orange), 25 Gy (white), 20 Gy (yellow), 15 Gy (pink), 10 Gy (maroon), 5 Gy (blue). (**b**) DVH with following structures: prostate (red), PTV (blue), prostatic urethra (dark green), membranous urethra (pink), bladder (orange), rectum (light green), penile bulb (cyan), femoral head (salmon), testicles (purple)

from treatment prolongation that is described above. However, in the case of patients who must travel great distances and such a schedule is challenging, a mildly extended treatment course over 9 days may be considered as an alternative (Wednesday, Thursday, Friday, Monday, Tuesday).

Although large prostates ($\geq$50 cc) do not appear to be a contraindication to radical radiation therapy with SBRT, the likelihood of acute urinary morbidity appears to be higher in this group of patients. Much like brachytherapy, ADT or finasteride may be considered for several weeks prior to treatment to decrease the prostatic volume, although the effect of this approach on morbidity may be limited. Similarly, while previous prostatic procedures such as TURP or simple prostatectomy may increase the long-term risk of developing hematuria, these procedures are not a contraindication to SBRT as the hematuria is usually self-limiting and reduced with finasteride [90].

Inflammatory bowel disease (IBD), which includes both ulcerative colitis and Crohn's disease, puts patients at significant risk for complications following radiation therapy is typically considered a relative contraindication to radiation therapy. There is limited data regarding prostate SBRT in patients with IBD, although use of a hydrogel rectal spacer is strongly recommended to minimize rectal dose as much as possible. The role of hydrogel rectal spacers for patients treated without IBD remains unclear, although there appears to be a clear clinical benefit in patients treated conventionally fractionated IMRT. While their use does not appear to be necessary in routine practice, they appear promising for dose escalation, where severe rectal toxicity has been observed. All patients should have up-to-date routine screening colonoscopy evaluation prior to SBRT to rule out synchronous colorectal cancer or other pathology.

In summary, a growing wealth of prospective data has demonstrated not only the safety and tolerability of SBRT, but also potential improvements in QoL compared to other treatments. Given the convenience of the short regimen, especially compared to conventionally fractionated radiotherapy, national utilization of SBRT is likely to continue rising for the foreseeable future. Nonetheless, SBRT is a technically demanding technique, and careful attention to treatment preparation, planning, and delivery

should be given to minimize the risk of potential side effects and enhance patient quality of life.

Conflicts of Interest

Sean P. Collins is a Clinical Consultant for Accuray.

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Quality of Life Outcomes After SBRT

9

Thomas Zilli and Raymond Miralbell

9.1 Introduction

In the curative treatment of localized prostate cancer, stereotactic body radiation therapy (SBRT) has gained great popularity as an emerging treatment modality. This results from a combination of technological developments integrating accurate dose delivery, organs at risk (OARs) sparing and target motion control together with a better knowledge of radiobiology of prostate cancer. Hypofractionation is deeply linked to SBRT development, with the technology behind this delivery technique ensuring the implementation in the clinical practice of hypofractionated schedules. Combination of SBRT and extreme hypofractionation results therefore in a potential therapeutic gain derived by a radiobiological dose escalation. Moreover, SBRT treatments, often delivered in five or less fractions, results to be more cost effective than standard normofractionated regimens [1], ensuring an easier access to the healthcare system and a better patient convenience. Last but not least, fewer fractions may reduce the psychological burden and can improve the overall quality of life (QoL) of prostate cancer patients compared to standard treatments of longer duration.

In the last years, single-institution [2–4] or multi-institutional [5] series on prostate SBRT have reported encouraging results in terms of disease control and acute toxicities with extreme hypofractionation, although long-term outcome data remain scarce and different concerns regarding toxicity and treatment schedules have been evoked. Data published so far for prostate SBRT have shown, although with a limited follow-up, late grade 3 toxicity rates for rectal and genitourinary toxicities lying within a $\leq$3% range [4, 6, 7]. However, as in patients with prostate cancer extended life expectancy is often observed, the possible impact on health-related QoL of SBRT treatments represents one of the highest research questions and constitutes a central consideration for treatment decisions [8]. Better understanding of QoL effects of SBRT may help to an individualized patient selection and provide additional elements to the decision-making process of prostate cancer patients. Therefore, comparative analyses between SBRT fractionation schedules and future clinical trial need to merge not only physician-reported toxicity but patient-reported outcome (PRO) on QoL as well.

9.2 Quality of Life Assessment

Due to the close proximity of the prostate gland to the rectum, the bladder, and sexual anatomical structures side effects on those organs represent

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the major concern for prostate SBRT treatments and therefore constitute the most used clinical endpoints for phase I/II SBRT studies. Toxicity grading is traditionally constituted on a clinician-based assessment using the Radiation Therapy Oncology Group (RTOG) scale for acute effects or items from the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) scale from the National cancer Institute (NCI). However, physician assessment of radiation-induced toxicities is often unreliable [9], with the risk to underestimate severity of side effects [10, 11]. On the other hand, low-grade toxicity tends to resolve spontaneously during the follow-up, with the risk to over-estimate its severity in the actuarial estimations of radiation-induced toxicities [12].

Patient-reported outcome assessment has gained importance as a better modality to report longitudinal evolution on the long-term of radiation-induced side-effects compared to physician-reported data by providing at the same time a more accurate and sensitive evaluation of patient satisfaction [13]. An added value in symptom control and communication between patient and physician has been observed with PRO [14]. In new trials PRO instruments are therefore currently implemented in order to evaluate the real impact of prostate cancer treatments and to better compare different toxicity profiles when a similar efficacy is expected [15]. Although, consensus in regard to the appropriate PRO endpoints that should be integrated in the evaluation of SBRT treatment outcome is presently lacking, different validated questionnaires have been used to evaluate the QoL impact of SBRT.

The Expanded Prostate Cancer Index Composite (EPIC)-26 [13, 16], is a validated PRO questionnaire, probably the most widely used in SBRT trials. It is a set of 26 questions evaluating 5 different QoL domains ranging from urinary incontinence and urinary irritative symptoms to bowel, sexual, and vitality domains. The domain scores are translated and averaged into a 0–100 scale, with higher values representing a more favorable outcome satisfaction. Those scores represent probably the "gold standard" instrument to assess health-related QoL of prostate cancer treatments.

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) is one of the most common tools presently used in cancer clinical trials. This instrument is composed of multi-item and single-item scales. These include five functional scales (physical, role, emotional, social, and cognitive), three symptom (fatigue, nausea and vomiting, and pain), and a global health status/QoL scale with six items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The reliability and validity of the questionnaire has been internationally validated and it is highly consistent across different language-cultural groups. In addition, the EORTC PR-25 is a module providing specific QoL information for patients with prostate cancer. The QLQ-PR-25 assesses urinary, bowel, and sexual symptoms and functioning, and the side-effects of hormonal treatment, as well.

The International Prostate Symptom Score (I-PSS) is probably the most widely used tool to assess changes in the urinary status following SBRT treatments [17]. The I-PSS is based on the answers to seven questions concerning urinary symptoms and one question concerning quality of life. Each question concerning the patients' urinary status allows them to choose one out of six possible answers directly related to the severity of a particular symptom. The answers are assigned points from 0 to 5. The questions refer to the following urinary symptoms: (1) Incomplete emptying; (2) Frequency; (3) Intermittency; (4) Urgency; (5) Weak Stream; (6) Straining; (7) Nocturia. Question eight refers to the patient's perceived quality of life. The total score with the seven symptoms can range from 0 to 35 (asymptomatic to very symptomatic); which may be classified as "mild" (symptom score $\leq$ 7); "moderate" (symptom score range 8–19); "severe" (symptom score range 20–35).

The International Index of Erectile Function (IIEF) is a validated, multi-dimensional, self-administered investigation that has been found useful in the clinical assessment of erectile dysfunction (ED) and treatment outcomes in clinical trials [18]. A score of 0–5 is awarded to each of the 15 questions that examine the 4 main domains

of male sexual function: erectile function, orgasmic function, sexual desire and intercourse satisfaction. A simplified five-items version (IIEF-5) provides an easier and more widely used diagnostic tool to study the prevalence of ED [19]. The possible scores for the IIEF-5 range from 5 to 25, and ED was classified into five categories based on the scores: severe (5–7), moderate (8–11), mild to moderate (12–16), mild (17–21), and no ED (22–25).

Other questionnaires commonly used in SBRT trials are: the Fox Chase Bowel/Bladder Toxicity [20], the Spitzer Quality of Life Index (SQLI), the UCLA-PCI (University of California, Los Angeles Prostate Cancer Index), and/or the FACT-G and P (Functional Assessment of Cancer Therapy General and Prostate) [20–22]. Moreover, the subjective symptoms from the CTCAE scale have been adapted for a patient reporting [23]. Table 9.1 summarizes available questionnaires for general health and prostate-specific QoL assessment.

The correct clinical implementation, interpretation, and timing assessment of PRO questionnaires remain a challenging point.

Minimally important difference (MID) thresholds, the smallest differences in a questionnaire domain score perceived by patients as a meaningful change, are used to define levels beyond which changes are considered clinically significant. MID are commonly used for interpretation of questionnaire results and sample size computation for clinical trials assessing QoL as primary endpoints. The definition of MID can be characterized as a statistical function using one-half SD of the baseline domain score specific of the study population [24], although with this approach information on the clinical relevance of the observed changes is unavailable [25]. Other approaches using distribution-based and anchor-based techniques have been developed [26, 27], with MIDs in the range of 5–10% of the instrument range.

Table 9.1 Quality of life questionnaires for localized prostate cancer

	Domains
Generic	
EORTC QLQ-C30 core questionnaire	Physical, role, emotional, social and cognitive; symptoms; global health status/QoL; single items
FACT-G (Functional Assessment of Cancer Therapy-General)	Emotional, functional, physic and social health status
MOS-SF36 (Medical outcome Study Short Form)	Limitations in physical, social, usual role activities for health, physical and/or emotional problems; bodily pain; general mental health; vitality; general health perception
Spitzer Quality of Life Index (SQLI)	Activity, daily living, health, support of family and friends, and outlook
Prostate-specific	
EORTC QLQ-PR25 questionnaire	Urinary, gastrointestinal, sexual, treatment-related symptoms
EPIC-26 (Expanded Prostate Cancer Index Composite)	Urinary, gastrointestinal, sexual, hormonal, vitality
UCLA-PCI (University of California, Los Angeles Prostate Cancer Index)	Urinary, gastrointestinal, sexual
FACT-P (Functional Assessment of Cancer Therapy-Prostate)	Urinary, gastrointestinal, sexual
Fox Chase Bowel/Bladder Toxicity	Urinary, gastrointestinal, sexual
IPSS (International Prostate Symptom Score)	Urinary
ICS (International Continence Society) male questionnaire	Urinary (incontinence)
IIEF (International Index of Erectile Function)	Sexual
CSFQ (Chronic Sexual Function Questionnaire)	Sexual
BMSFI (Brief Male Sexual Function Inventory)	Sexual

A *multidomain decline* assessment has been developed to evaluate treatment effect on patients who experience declines in multiple concurrent domains [28]. Concomitant assessment of MID thresholds in four or five domains has been demonstrated to better depict treatment-related toxicity profiles that may be more burdensome for patients and of more difficult management for clinicians.

The open question remains on what is the best time to assess PRO endpoints. Although, the PRO assessment at baseline and at a later key time point may be used for clinical trial design purposes, longitudinal evaluation of QoL impact of SBRT treatments on the long-term beyond 1 year of follow-up may yield a more accurate profile of treatment tolerance. Indeed, if acute toxicities usually resolve with time and mostly during the first 12 weeks, late toxicities impacting QoL are often observed 2–3 years after SBRT. The inclusion of PRO to evaluate the impact of curative radiation treatments before, during, and after treatment is encouraged to fully capture treatment tolerance based on the patient voices.

Future international consensus processes are welcomed to provide standardization in assessment, documentation and evaluation of PRO.

9.3 Quality of Life and Prostate SBRT

In 2013, King et al. analyzed the QoL impact of SBRT in 864 patients with localized prostate cancer enrolled in different phase II clinical trials (median dose of 36.25 Gy in five fractions for 84% of them and 39 Gy in four fractions for the remaining 16%). A 14% of patients received, in addition, concomitant androgen deprivation, ADT [29]. Using the EPIC questionnaire, the authors observed a transient decline in the urinary and bowel domains within the first 3 months after SBRT, with a complete and durable recovery to baseline or even better within 6 months after SBRT (Table 9.2). No impact of age, use of ADT, and the degree of early toxicity was observed on recovery, while the decline in the sexual activity was mostly observed during the first 9 months from SBRT, not altered by ADT or age.

Other series studied long-term effects of prostate SBRT on QoL [30–38] (Table 9.2). In all these series, the urinary domain was the most affected one during the acute phase and up to 6 months after the SBRT end. Long-term effects on QoL remained mild to moderate with most patients reporting the same QoL scores compared to baseline. Of note, patients with the highest baseline urinary QoL scores presented a greater risk of clinically significant change in QoL after prostate SBRT [37]. On the other hand, in a context of management of QoL issues following SBRT treatment, recovery in urinary, bowel, and sexual function was better than baseline status especially in patients with a poorer baseline function [29]. The sexual domain slowly declines during follow-up in the majority of studies [29, 40]. For patients with functional erections at baseline, 57% and 45% retained erectile function at 24 months and 60 months, respectively [41]. Patients aged $\geq$65 years presented a continuous decline compared with the plateau phase observed in younger patients. Based on validated prediction models, sexual function outcomes after SBRT appear to be comparable to external beam radiotherapy (EBRT) and brachytherapy [41]. However, results should be interpreted in the context of population's age of SBRT studies, considering that ED increases sharply between the ages of 60 and 70 years [42].

Dess et al. evaluated the incidence of multidomain QoL decline in a large prospective, single-center study including 713 consecutive patients treated with SBRT (35–36.25 Gy in five fractions) for localized prostate cancer [39]. Multidomain decline was defined as a concurrent decline in four or five domains equal or exceeding one time or twice the MID threshold (*1× or 2× multi-domain decline*). During the acute phase (up to 3 months from SBRT), 8–15% of patients experienced multi-domain declines. The corresponding rates after 6–60 months follow-up were approximately 10% and 5% for 1× and 2× multi-domain decline, respectively. For patients experiencing a more significant 2× multi-domain decline, the long-term impact

Table 9.2 Mean or median health-related quality of life changes over time relative to baseline for all patients following prostate stereotactic body radiation therapy

Authors	Number of patients	Total delivered dose, Gy	Follow-up (median, months)	QoL scale	Urinary domain	Bowel domain	Sexual domain
King et al. [29]	194	35–40	60	EPIC	B: 89/L: 90.8	B: 95/L: 95.9	B: 53/L: 39.9
Batthasali et al. [30]	197	35–36.25	24	EPIC	B: 89.6/L: 87	B: 95.1/L: 93.7	B: 56.3/L: 44.5
Boike et al. [31]	45	45–47.5–50	30	EPIC	No significant increase from baseline		
Boyer et al. [32]	60	37	28	EPIC	B: 94.4/L: 96.3	No change	B: 67.8/L: 54.2
Elias et al. [33]	84	35	51	EPIC	B: 89.4 MCIC: 18%	B: 92.2 MCIC: 26%	B: 46.6 MCIC: 38%
Evans et al. [34]	381	35–40	24	EPIC	MCIC: −0.2 points (obstructive/ irritative) −3.4 points (incontinence)	MCIC: −1.3 points	MCIC: −14 points
Mantz et al. [35]	102	40	60	EPIC	B: 85.4/L: 81.1 (irritation/ obstruction)	B: 92/L: 91	B: 51.4/L: 47.9
McBride et al. [36]	45	36.25–37.5	44.5	EPIC	B: 92/L: 91	B: 95.5/L: 93	B: 43/L: 21
Quon et al. [37]	114	35 40	56	EPIC	MCIC 35 Gy: 19.5% MCIC 40 Gy: 24%	MCIC 35 Gy: 26.8% MCIC 40 Gy : 41.4%	MCIC 35 Gy: 42.9% MCIC 40 Gy : 38.5%
Woo et al. [38]	174	35–36.25	36	EPIC	B: 89/L: 86.5	B: 95/L: 92.6	
Dess et al. [39]	659	35–36.25	60	EPIC	B: 88/1 × MID: 28%	B: 100/1 × MID: 23%	B: 61/1 × MID: 56%

Negative values indicate a decline and positive values indicate an improvement over baseline scores
Abbreviations: *B* baseline, *L* late follow-up, *EPIC* Expanded Prostate Cancer Index Composite, *MCIC* minimal clinical important change, *1 × MID* 1 × decline exceeding the clinically detectable threshold in ≥4 EPIC-26 domains (multidomaine decline)

on health status was unrelated to the SBRT treatment or cancer progression in more than half of the subjects. These results highlight the importance of comprehensive treatment care using a cross-modality comparison of QoL decline in multiple domains to better understand the real impact of SBRT treatments in prostate cancer patients.

The RTOG 0938 trial is a randomized phase 2 study comparing two fractionation schedules for low-risk prostate cancer: 36.25 Gy in 5 fraction of 7.25 Gy in 2 weeks versus 51.6 Gy in 12 fraction of 4.3 Gy in 2.5 weeks. Patients were treated either with robotic radiosurgery (22%) or with intensity-modulated radiotherapy (IMRT) or volumetric arc therapy (VMAT) (78%). Closed to accrual in 2014, the primary objective of the study was to demonstrate that 1-year QoL for at least one hypofractionated arm was not significantly lower than baseline as measured by the Bowel and Urinary domains of the EPIC instrument. Presented as an abstract during the American Society for Radiation Oncology (ASTRO) 2016 meeting, a 1-year EPIC decline from baseline for bowel and genitourinary symptoms was observed in 23.5% versus 23.1%, and in 35.3% versus 34.7% of patients treated in the 5-fractions and 12-fractions arms, respectively. The frequency of EPIC changes was below the rate considered per-study as unacceptable in both arms.

Preliminary results of the Scandinavian phase III HYPO-RT-PC trial have been also presented

at the 2016 ASTRO annual meeting. Between July 2005 and November 2015 this non-inferiority trial accrued 1200 intermediate risk prostate cancer patients randomizing patients to either receive 78 Gy to the prostate in 39 fractions of 2 Gy over 8 weeks, or 42.7 Gy in 7 fractions of 6.1 Gy over two and a half weeks using image-guided radiotherapy (RT). Most patients (80%) received three-dimensional conformal RT (3-D CRT), and the remaining patients received VMAT, without ADT. In a preliminary analysis of 866 patients who reached a 2-year follow-up, men who were treated with extremely hypofractionated RT in 7 fractions experienced similar side effects 2 years following treatment as those who received conventional RT in 39 fractions. Rates of physician-reported grade $\geq$2 toxicities (RTOG scale) at 2 years following treatment did not differ significantly between RT arms, with similar rates of urinary and bowel side effects (5.4 vs. 4.6% and 2.2 vs. 3.7% for extreme and conventional fractionation, respectively). Similarly, the Prostate Cancer Symptom Scale questionnaire at 2 years following treatment also did not differ significantly between treatment groups for overall bother from urinary ($p = 0.17$), bowel ($p = 0.12$) or sexual function ($p = 0.71$) symptoms. On the other hand, acute bowel toxicity at the end of RT was higher for the extreme-hypofractionated treatment than for conventional fractionated (9.4 vs. 5.3%; $p = 0.023$), though with similar acute urinary toxicity. Patient-reported bowel function at the end of RT was also significantly worse following extreme hypofractionation than following conventional for seven of ten symptoms assessed, even though these differences dissipated after 3 and 6 months follow-up. At 1 year post-treatment, patient-reported urinary function was significantly worse among extreme-hypofractionation patients for 4 of the 14 symptoms measured.

9.4 Quality of Life: Comparison with Other Treatment Modalities

Substantial differences on long-term patient-reported functional outcomes have been observed among curative treatment strategies for prostate cancer [13, 43, 44]. EBRT has been associated with a greater impact on bowel QoL, while declines in urinary incontinence and sexual function are less important compared to radical prostatectomy. Despite significant technological progress in both surgical and RT fields, the same findings on QoL in previous trials using older treatment techniques (mostly 3D conformal RT techniques and non-robotic prostatectomy) were observed in a more recent study including a population-based prospective cohort of 1141 patients mostly treated with robotic prostatectomy and IMRT techniques (86.6 and 94.8% of the patients, respectively) [45]. These findings have been confirmed by Katz et al. comparing radical prostatectomy with SBRT. Using the EPIC questionnaire changes in QoL were observed mostly during the first 6 months, with sexual and genitourinary domains mostly affected by surgery and bowel QoL declines more frequently detected after SBRT [46]. Most important, long-term urinary and sexual QoL declines remained significantly lower for surgery patients but not for the SBRT ones.

In a multi-institutional pooled cohort analysis of 803 patients, using the EPIC questionnaire Evans et al., compared patient reported QoL before and after conventionally fractionated RT with IMRT, brachytherapy, and SBRT for localized prostate cancer [34]. QoL after SBRT (7–8 Gy per fraction for five fractions) was similar for urinary and sexual domains but it was associated with a smaller impact on bowel QoL compared to the other treatment options. As expected, a decline in urinary QoL was observed in the acute phase for all the three techniques, consisting mostly of urinary irritation flares resolving within 6 months after treatment. Comparing altered fractionations, Johnson et al. analyzed changes in PRO QoL following moderate hypofractionation (<5 Gy/fraction) or extreme hypofractionation with SBRT (5–10 Gy/fraction) [47]. Using a pooled analysis of multiple prospective studies including 912 patients, patients treated with SBRT presented similar bowel and sexual symptoms compared to patients treated with moderate hypofractionation, even though the later

experienced a less worsening of urinary symptoms at 2-years.

As far as dose escalation is concerned, a secondary analysis of two prospective clinical trials investigated the impact on QoL of dose escalation from 35 to 40 Gy in five once-weekly fractions [37]. In this study dose-escalated prostate SBRT from 35 to 40 Gy was not associated with a decline in long-term QoL as assessed by the EPIC questionnaire. Nevertheless, a proportion of patients reported significant declines in average urinary, gastrointestinal, and sexual scores of 20.5% versus 24.1%, 26.8% versus 41.4%, and 42.9% versus 38.5% (all p = NS) for the low and the high-dose arm, respectively. In contrast, further dose escalation with SBRT may be linked to an increased risk of toxicity compared to daily doses ranging between 7 and 8 Gy. In a phase I/II dose escalation trial, up to 10% of severe grade 3–4 rectal toxicity were observed at 2-years median follow-up delivering 50 Gy in five fractions, suggesting probably a threshold of approximately 90–95 Gy in equivalent 2-Gy per fractions with a alfa/beta ratio of 1.5 Gy [48]. Dosimetric parameters such as prostate size and greater bladder doses have been linked to an increased risk of worsening urinary QoL [49, 50] and may be easily implemented in the clinical practice to optimize SBRT treatments.

The patient's perspectives on treatment experience between modern RT techniques have been explored by Shaverdian et al. [51]. A survey was performed exploring the decision-making experience, expectations of toxicities versus reality and decision regret among 329 patients treated with IMRT, SBRT or HDR brachytherapy. Patients treated with SBRT experienced less treatment regret and less toxicity than expected. Indeed, only 5% of patients treated with SBRT expressed regret compared to 18 and 19% for the HDR and IMRT groups, respectively.

In addition to the Scandinavian phase III HYPO-RT-PC trial that closed to recruitment in 2015 and the RTOG 0938 trial, two other major studies comparing outcomes and health-related QoL results of SBRT versus other RT fractionation schedules or curative treatments are currently ongoing. The Prostate Advances in Comparative Evidence (PACE, ClinicalTrials.gov Identifier: NCT01584258) is comparing prostate SBRT (36.25 Gy in 5 fractions) versus laparoscopic radical prostatectomy or conventionally fractionated EBRT (78 Gy in 39 fractions or 62 Gy in 20 fractions) in early-stage organ-confined prostate cancer. The Miami HEAT (Hypofractionation via Extended versus Accelerated Therapy) trial (ClinicalTrials.gov Identifier: NCT01794403), is a randomized trial comparing 36.25 Gy delivered in 5 fractions versus 70.2 Gy given in 26 fractions. The primary endpoint of this trial is the 2-year failure rate defined as a positive biopsy 2 years post treatment completion or earlier evidence of biochemical or clinical failure. Final results of these randomized controlled trials are eagerly awaited in the next years to provide an answer to open questions on efficacy, toxicity, and QoL after SBRT.

9.5 Future Perspectives

Impact on QoL of modern SBRT techniques exploring organ-sparing approaches or using schedules with longer overall treatment time (OTT) remain to be determined. The use of recto-prostatic spacers [52] or endorectal balloons [53, 54] to minimize rectal doses or to reduce intra-fractional motion has been tested by some authors. In a dosimetric comparative study, Chapet et al., observed that hyaluronic acid injections between the rectum and the prostate reduced significantly the dose to the rectal wall, allowing a dose escalation from 6.5 to 8.5 Gy without increasing the dose to the rectum [55]. Improvements in QoL previously observed with a spacer in normofractionated IMRT remains still to be confirmed in SBRT series [56].

The impact of OTT and urethra-sparing has been explored by Zilli et al. in a randomized phase II trial comparing a once-a-week versus every-other-day SBRT schedule (ClinicalTrials.gov Identifier: NCT01764646) [57]. From 2008/2012 through 2012/2015, 170 patients from 9 - European institutions with cT1c-3aN0M0 prostate cancer and a low risk of nodal involvement were recruited and randomized according to two

different OTT schedules: either 9 days (arm A), or 28 days, once-a-week, the same week-day (arm B). The prescribed dose was 36.25 Gy in five fractions of 7.25 Gy to the prostate ± seminal vesicles in both arms, with the prostatic urethra, with a surrounding margin of 3 mm, receiving a lesser dose of 5 × 6.5 Gy = 32.5 Gy. All patients were treated either with a VMAT or IMRT technique under stereotactic conditions using Novalis™ linacs and ExacTrac™ image-guided technology, with the majority of patients treated using an endorectal balloon. Acute toxicity was mild for both arms, with IPSS scores returning to the baseline 3 months after SBRT end. During months 6–18, the incidence of grade-2-genitourinary toxicity was 8 and 4% in arms A and B, respectively, while the incidence of grade-2 gastrointestinal toxicity was below 2% in both arms. Concerning IPSS-based QoL rates, the rate of pts satisfied at baseline, 3-months and 18-months were 80, 78, and 89% for arm A and 77, 80 and 88% for arm B, respectively. No changes in EORTC QLQ-PR25 scores for genitourinary, gastrointestinal, and sexual domains were observed in both arms between baseline and 3 months, while an improvement was observed at 18 months for urinary domains. A longer follow-up is obviously required to confirm the potential influence of OTT and urethra-sparing on outcome and long-term tolerance.

As far as sexual domains are concerned, the impact of vessel-sparing techniques in preserving the erectile function as previously tested by some authors with normo-fractionated IMRT is promising and merits further investigation in prospective SBRT trials [58].

The question of how far can the number of fractions with SBRT be reduced is an exciting research matter with an undoubtful goal, face the challenge of assessing the potential for cure of prostate cancer patients with a single and unique fraction of high dose irradiation similar to what is already undertaken with radiosurgery. As already explored by some authors in the context of brachytherapy [59–61], monotherapy treatment seems feasible with acceptable toxicity profile and promising outcome. Two monotherapy studies exploring the role of single fraction SBRT for localized prostate cancer are currently ongoing. The phase II randomized trial PROSINT-IGRT (ClinicalTrials.gov Identifier: NCT02570919) will compare 45 Gy in five consecutive fractions with a single dose of 24 Gy. Comparison between schedules in terms of toxicity, outcome as well as post-treatment biopsies is the major endpoints of this trial. In the ONE-SHOT trial (ClinicalTrials.gov Identifier: NCT03294889), a phase I/II multicenter study exploring the safety and efficacy in terms of biochemical control of a single-fraction of 19 Gy with a urethra-sparing approach, strict QoL assessments using the EPIC-26 questionnaires will provide in the next future a clear evaluation of the clinical impact of a single-dose SBRT for patients with localized prostate cancer.

Last but not least, incorporation in clinical trials of web-based tools for QoL assessment will further help to increase participation and response rates for long-term evaluation of SBRT outcomes [62, 63]. Comparability between electronic and print reporting is well demonstrated [64], with benefits resulting from electronic reporting confirmed by a recent meta-analysis [65]. Not surprisingly, completion rates of the EPIC questionnaire in a prostate cancer trial at 1-year were 82% for electronic reporting, versus 36% only for the printed forms [63].

Conflicts of Interest

The author and co-authors have no conflicts of interest to declare.

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Techniques for Reducing Toxicity After SBRT

10

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10.1 Introduction

Ultra-hypofractionated radiation therapy for prostate cancer must be performed carefully and accurately to minimize the risk of bowel, urinary, and sexual toxicity. With the emergence of advanced technologies, such as image-guided radiation therapy (IGRT), it is now possible to deliver extraordinarily precise radiation treatments for prostate cancer, which has further facilitated the escalation of radiation dose in an increasingly safe manner.

Results from the early phase clinical trials and retrospective studies of prostate SBRT demonstrate that it is generally well tolerated [1–10]. Acute grade 1–2 gastrointestinal (GI) and genitourinary (GU) toxicities do occur in the many patients, however acute grade 3 or higher toxicities are extremely rare. The reported incidence of late grade 1–2 GI and GU toxicities is $<30\%$ with grade 3 or higher late toxicities experienced by $<5\%$ of patients. In patients who are potent prior to SBRT and not treated with androgen deprivation, the incidence of late erectile dysfunction appears to be $<30\%$.

Multiple factors are thought to influence the likelihood of incurring complications after prostate SBRT. These include, but are not limited to, predisposing patient baseline characteristics, such a pre-existing urinary symptoms, prostate volume, and comorbidities, as well as radiation dose to the surrounding normal tissue, including bladder, rectum and erectile tissues. Given that many prostate cancer patients will be cured and/or have long life expectancies following treatment, reducing treatment sequelae and optimizing post-treatment quality of life is a crucial goal of therapy.

10.2 Reducing Gastrointestinal Toxicity

The most common gastrointestinal (GI) side effects of prostate SBRT include radiation proctitis, hemorrhoid flares, change is bowel habits, and tenesmus. These symptoms typically peak within the first month of SBRT and resolve within 3 months. Mechanisms of acute rectal injury are primarily related to inflammation in response to direct mucosal damage from radiation exposure. Subsequent late GI side effects, such as rectal bleeding and reduced compliance, are the result of progressive epithelial atrophy and fibrosis associated with obliterative endarteritis and chronic mucosal ischemia [11]. Endoscopic findings in patients with radiation proctopathy include telangiectasias and rare mucosal ulceration.

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10.2.1 Patient Selection

Prior to offering prostate SBRT, patients should be evaluated for underlying conditions that might increase their sensitivity to radiation-related GI side effects. Inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease, have been shown to increase risk of bowel toxicity with external beam radiation therapy [12]. It must be noted, however, that data regarding the specific risk of IBD in patients undergoing SBRT is lacking. Additional comorbidities that may predispose patients to bowel toxicity include conditions that affect the microvasculature including diabetes, hypertension, and collagen vascular diseases [13]. Patients with a history of hemorrhoids and those on anticoagulation have higher rates of rectal bleeding following radiation therapy and thus may have higher risks with SBRT as well [14, 15]. Prior bowel/rectal surgery and/or pelvic radiation may also factor into decisions regarding treatment. While the presence of these factors are not absolute contraindications to the use of prostate SBRT, patients should be advised of their potential increased risk of toxicity.

10.2.2 Treatment Planning and Delivery

The risk of GI toxicity after prostate radiation therapy is directly related to rectal dose [16–19]. Several SBRT studies have examined the effect of dose on rectal morbidity. A multicenter phase I/II dose-escalation trial of SBRT using 45, 47.5, and 50 Gy in five fractions for low and intermediate risk prostate cancer reported increasing rectal toxicity with increasing dose per fraction [5, 6]. At the highest dose level, 6/61 patients (9.8%) experienced grade 3 and higher rectal toxicity, five of whom required a diverting colostomy; compared to 0% in the lower dose arms. In a separate analysis of these patients, high grade late rectal toxicity was significantly more common when >3 cc of the rectal wall received 50 Gy and when >35% of the rectal circumference received 39 Gy [20]. The authors also demonstrated that acute grade 2 and higher toxicities were associated with >50% of the rectum circumference receiving 24 Gy or higher. More studies like this are needed to determine reliable rectal dose constraints for prostate SBRT.

Currently the rectal dose constraints vary by institution and protocol. RTOG 0938 (NCT01434290), a study evaluating 36.25 Gy in five fractions, suggests limiting the rectum maximum dose to <105% of the prescription dose, 3 cc < 95%, 90% < 80%, and 50% < 50%. Other studies report similar rectal planning goals of V50% < 50% of the prescribed dose, V80% < 20%, V90% < 10%, and V100% < 5% [21].

Consistent dosimetry can be achieved only with careful attention to anatomic reproducibility from simulation through treatment delivery. Rectal volume can be influenced by daily variations in stool and gas content and can distort anatomy significantly. Simple measures to empty the rectum, such as low-residue diet, pretreatment enemas, and/or bulking agents can improve the accuracy of dose delivery [22, 23]. Another technique to achieve consistent rectal volumes includes the use of an endorectal balloon, which can also reduce prostate motion [24, 25]. Rectal balloons do, however, increase patient discomfort and may not be practical for all patients/centers. Regardless of technique used to reproduce rectal volume, careful attention to anatomy on daily pretreatment cone-beam CTs is crucial and radiation therapists should be trained to identify and correct anatomic distortions. If a full rectum is seen on the pretreatment cone-beam CT, a rectal tube can be placed to release air or patients can be instructed to have a bowel movement and/or pass flatus.

The interval between fractions is another important consideration that appears to be associated with risk of GI side effects. In a prospective phase II trial of prostate SBRT (36.25 Gy in five fractions) for low risk patients, King et al. found less rectal toxicity in patients treated every-other-day (QOD) compared to those treated with a five-consecutive day (QD) regimen [26]. Compared to the patients treated QOD, patients treated

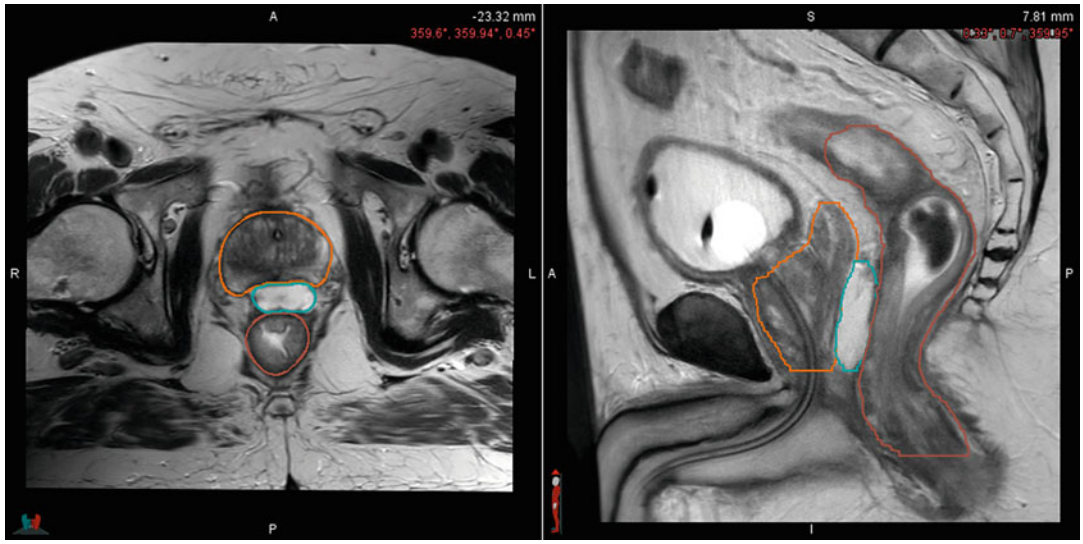

Fig. 10.1 Example of a T2-weighted MRI after injection of a hydrogel rectal spacer (orange = prostate, blue = spacer, brown = rectum)

QD more frequently reported Expanded Prostate Cancer Index (EPIC) bowel quality of life (QOL) scores of 4–5 ("moderate" or "big problem") for any rectal symptom (38% vs. 0%, $p < 0.01$) and overall rectal QOL (24% vs. 0%, $p < 0.05$). Similar results were also seen in a multicenter Canadian randomized phase II trial comparing prostate SBRT in 11 versus 29 days overall treatment time [27]. In this trial 152 low to intermediate risk prostate cancer patients were randomized to receive 40 Gy in five fractions delivered QOD versus once per week. Clinically important worsening of acute ($\leq$3 month) EPIC bowel QOL scores was more common in patients treated QOD versus weekly (90% vs. 70%, $p < 0.01$). Acute grade 1, 2, 3 GI toxicities were also significantly worse in the patients treated QOD compared to those treated weekly (64%, 18% 0% vs. 41%, 11%, 0%, $p < 0.01$).

10.2.3 Rectal Spacers

Given the proximity of the anterior rectal wall to the prostate, it is difficult to deliver tumoricidal doses to the prostate while sparing the rectum. One approach to overcome this limitation is to physically separate the prostate and rectal wall using a rectal spacer (Fig. 10.1). Rectal spacers are either injectable, biodegradable agents (hyaluronic acid, collagen, blood, polyethylene glycol hydrogels) or absorbable balloons. Most studies show spacers can increase the separation between the prostate and the rectum by more than 1 cm, which has been shown to result in meaningful reductions in rectal dose.

Prada et al. were the first to report on the use of a hyaluronic acid injection in the perirectal fat of 27 patients undergoing prostate external beam radiation with an HDR brachytherapy boost [28]. A mean distance achieved between rectum and prostate was 2 cm without migration or volumetric changes in hyaluronic acid for 1 year. The additional space between the prostate and rectum led to a 28% reduction in mean rectal dose. The same group conducted a clinical trial that included 69 patients receiving LDR brachytherapy as monotherapy with or without a hyaluronic acid rectal spacer [29]. At a median follow-up of 18 months, the use of a spacer led to significantly lower rates of proctoscopic evidence of rectal mucosal damage (5% vs. 36%, $p < 0.002$) and less rectal bleeding (0% vs. 12%, $p = 0.047$).

The largest reported experiences have been with the use of synthetic polyethylene glycol-based hydrogels, such as SpaceOAR™

(Augmenix Inc., Waltham, MA), which is an FDA approved commercially available device [30–36]. Pinkawa et al. reported early results using the hydrogel spacer in 18 patients undergoing dose-escalated prostate radiation to 78 Gy (3D-CRT and IMRT) [30]. Comparing treatment plans prior to and following spacer placement, a mean separation of 1 cm was achieved and significant reductions in rectal doses were demonstrated. Mean NTCP for severe GI toxicity was reduced by >50%. A multi-institutional prospective pilot study reported comparative dosimetry for 52 patients undergoing prostate IMRT to 78 Gy before and after hydrogel spacer placement [31]. Although no differences in PTV, rectal, or bladder volumes were noted, significant dose reductions were seen at all rectal dose levels. The rectal V70 decreased by ≥25% in 95.7% of patients, with a mean reduction of 8 Gy (13% vs. 5.1%, $p < 0.001$). Despite inter-institutional variations in plan conformity and target definitions, rectal V70 reductions were noted across these heterogeneous groups.

More recently, a multi-institutional prospective phase III trial including 222 low and intermediate risk patients treated with conventionally fractionated IGRT to 79.2 Gy without androgen deprivation randomized patients to receive or not receive a hydrogel rectal spacer [34, 35]. A mean separation of 1.26 cm and reduction in mean rectal V70 was achieved in spacer patients (10% vs. 2%, $p < 0.0001$). At 3-year follow-up, late grade ≥1 rectal toxicity was 9% in the control arm compared to 2% in the spacer arm ($p < 0.03$) and late grade ≥2 rectal toxicity was 0% in the spacer arm but 6% in the control arm ($p < 0.02$). Additionally, changes from baseline bowel quality of life as measured by the EPIC questionnaire was also less in the spacer arm than the control arm [37]. The percent of men with a >5-point change from baseline was 41% in the control arm versus 14% in the spacer arm ($p = 0.002$) and for a >10-point decline was 21% versus 5% ($p = 0.02$). Similar results were also seen in a German retrospective study of 114 patients with prostate cancer treated with IMRT to 76–78 Gy in 2 Gy fractions, where patients who received a hydrogel spacer reported better EPIC bowel quality of life scores [38]. A bowel bother score change >10 points was found in 6% versus 32% ($p < 0.01$) at 17 months and in 5% versus 14% ($p = 0.2$) at 63 months with versus without a spacer.

The technique of transperineal placement of a rectal spacer is a relatively simple one. Under light sedation and/or local anesthesia, transrectal ultrasound guidance is used to first hydrodissect the rectroprostatic space followed by injection of the polyethylene glycol gel precursors, which polymerize and form a firm gel. The gel may be visualized to some extent on ultrasound; however, is not clearly seen on CT scan and requires an MRI for simulation and treatment planning. The hydrogel remains stable for approximately 90 days, dissolves over 6 months, and is renally excreted [39]. One concern regarding the use of a rectal spacer is the potential for displacement of prostate cancer cells and inadvertent underdosage of disease in patients with posterior extracapsular extension. While this issue remains theoretical, it may be prudent to avoid using a rectal spacer in this population.

Various less commonly used spacers have also been investigated. Noyes et al. injected 20 ml of collagen into the perirectal space of 11 patients undergoing prostate IMRT to 75.6 Gy [40]. The mean separation was 1.27 cm and the mean reduction in dose to the anterior rectal wall was 50%. There were no rectal adverse events reported during the course of radiotherapy or during the follow-up period. The ProSpace™ (BioProtect Ltd., Israel) biodegradable balloon is another type of rectal spacer in use. The balloon is made from poly(L-lactide-co-caprolactone) and inflated with sterile saline. Gez et al. transperineally implanted balloons in 27 patients receiving prostate radiation [41]. The mean prostate-rectum distance increased from 0.22 ± 0.2 to 2.47 ± 0.47 cm after the implant and the spacing did not significantly change during the course of radiation.

10.3 Reducing Genitourinary Toxicity

Genitourinary (GU) toxicity is the most common toxicity seen following prostate radiotherapy and

typically consists of both irritative (i.e. frequency, urgency, dysuria) and obstructive (i.e. weak stream, incomplete emptying) symptoms. Most patients experience some transient urinary bother either toward the completion of or immediately following SBRT. Medical interventions (i.e. alpha blockers, anti-inflammatory medication, anticholinergics) to reduce early toxicity may be helpful and likely improve patient quality of life. Acute urinary symptoms typically resolve by 3–6 months after treatment. Late complications may include persistent urinary bother, urethritis, hemorrhagic cystitis/urethritis, and/or urethral strictures. Although the reported rates of moderate to severe GU toxicity is low, every effort should be made to reduce the risk of such outcomes.

10.3.1 Patient Selection

One important step in evaluating a patient for prostate SBRT is a careful and complete urinary evaluation including history of prior TURP or strictures, prior prostate interventions, and a full assessment of baseline urinary dysfunction ideally with the use of a validated patient-reported questionnaire (i.e. IPSS, EPIC). Measurement of the prostate volume by pretreatment imaging is important and patients with large volume glands or the presence of a prominent median lobe may be at higher risk of urinary obstruction after SBRT. Prior to treatment, efforts can be made to medically optimize urinary function and/or cytoreduce the prostate, however whether these interventions reduce urinary obstruction requiring catheterization is currently unknown. Fortunately, when catheterization is necessary for acute urinary retention, it is typically needed only for a brief period.

Similar to patients undergoing brachytherapy, prostate volume might predict for urinary morbidity in patients undergoing SBRT. Repka et al. reported the acute urinary toxicity in a cohort of 103 men treated with prostate SBRT to 35–36.25 Gy in five fractions using CyberKnife (Accuray Inc., Sunnyvale, CA, USA) [42]. All patients received prophylactic alpha-blockers starting 5 days prior to SBRT. At 7 days following treatment, 22.3% had a >5-point increase from baseline IPSS with prostatic volume >36 cc being a significant independent predictor on multivariate analysis. Similarly, Katz et al. found prostate volume >60 cc to be predictive of late grade 2 or higher GU toxicity compared to patients with prostates <60 cc (14.7% vs. 7.5%, $p = 0.03$) [2].

The relationship between prostate size and late urinary toxicity, however has not been consistently demonstrated. In a study of 216 patients undergoing prostate SBRT, a late urinary symptom flare was noted in 13.4% of patients, which peaked 9–18 months post-treatment [43]. There did not appear to be a correlation between flare and prostate volume or baseline urinary function. Interestingly, young age was the only independent factor associated with risk of late urinary symptom flare in this study. In another series, Janowski et al. reported urinary toxicity outcomes of 57 men with prostate volumes $\geq$50 cm^3 (median 62.9 cm^3, range: 50–138.7 cm^3) treated with 35–36.25 Gy in five fractions using CyberKnife [44]. They found a 23% incidence of late urinary symptom flare in the first 2 years following SBRT. The 2-year actuarial incidence of grade $\geq$2 GU toxicity was 49.1% with a late grade 3 event rate of 3.5%.

A history of prior TURP for benign prostatic hypertrophy is important to note and may predict for worse toxicity in those undergoing SBRT, although reported data is relatively lacking with only small case reports. In an Italian study, three of seven patients with prior TURP experienced late urinary side effects, but only one was grade 3 [45]. Chen et al. also reported a late grade 3 GU toxicity in a patient with a large prostate who underwent 2 TURPs prior to SBRT [46].

Prostate SBRT is also being explored as a potential salvage treatment after failed primary radiotherapy, cryotherapy, and HIFU, however only small case series with limited follow-up are currently reported [47, 48]. While we await more robust data in this patient population, caution is advised, as these patients are likely at elevated risk of side effects.

10.3.2 Treatment Planning and Delivery

GU toxicity after prostate radiation is likely related to radiation dose delivered to critical normal tissue, such as the bladder and/or urethra, however this relationship is poorly understood. Anatomical sub-sites of these organs (i.e. bladder trigone/neck or membranous urethra) might be relatively more important to avoid with high doses of radiation [49, 50]. Although dose constraints are frequently used for the planning of conventionally fractionated external beam radiation and brachytherapy, specific constraints in the setting of prostate SBRT are currently not well defined.

Despite the lack of large-scale, detailed dosimetric studies, radiation dose to the prostate does appear to be important in patients undergoing prostate SBRT. In the multi-institutional phase I/II five fraction dose escalation study reported by Hannan et al., acute grade 1–2 GU toxicity was more frequent in the highest dose (50 Gy) group at 78.7% compared to 60 and 46.6% in the intermediate (47.5 Gy) and low (45 Gy) dose groups respectively [5]. The only late grade 4 GU toxicity (cystitis requiring ureteroileal diversion) occurred in the highest dose group as well.

To date, there have been relatively few defined dose–volume relationships for prostate SBRT that have predicted for more significant GU toxicity. The low rates of moderate to severe urinary morbidity and relatively small patient cohorts make establishing these relationships quite difficult. The volume of bladder receiving high doses might be important. Repka et al. found bladder wall D15.5% $>$ 32.6 Gy to be significantly associated with acute urinary toxicity [42]. An NTCP modeling study of late urinary flare after prostate SBRT (35–36.25 Gy in five fractions) demonstrated a significance of dose to the hottest 12.7% of the bladder volume and suggested a dose constraint of D12.7%$\leq$ 33.5 Gy [51].

Bladder and urethra dose constraints for prostate SBRT vary by institution and protocol. For the five-fraction arm of RTOG 0938 (NCT01434290), the bladder dose limits are D1 cc $<$ 105%, D10% $<$ 90%, and D50% $<$ 50%. The urethra max dose constraint is $<$107%. The treatment protocol by Katz et al. used bladder goals of V50% $<$ 40% (i.e. the volume receiving 50% of the prescribed dose $<$40%) and V100% $<$ 10% [21].

One important consideration for treatment planning is the optimal identification of the urethra, which can be facilitated using a Foley catheter during simulation. Additionally, attention should be given to institutional consistency with bladder filling instructions prior to simulation and treatment. Advantages of treatment with a full bladder include reducing the volume of bladder near high dose region, as well as elevating bowel away from the target area. Bladder filling consistency can be monitored prior to treatment with the use of cone-beam CT. Furthermore, intrafraction motion monitoring using implanted fiducial markers or transponders is also essential to verify stability of prostate positioning during treatment delivery, which ensures the accuracy of each treatment.

10.3.3 Prophylactic Medical Therapies

Baseline lower urinary tract symptoms (LUTS) are frequently encountered in patients being considered for prostate SBRT and are best assessed using validated patient-reported outcome tools, such as the American Urological Association Symptom Index (AUASI) and International Prostate Symptom Score (IPSS). These include a constellation of symptoms, such as urgency, increased frequency, nocturia, hesitancy, and weak stream. Optimization of urinary symptoms prior to treatment, should improve tolerability of radiation-related side effects and patient quality of life during and after SBRT. Depending on the underlying cause, multiple medical therapies might be useful to reduce urinary symptoms before SBRT including alpha-blockers, anticholinergics, or five-alpha-reductase inhibitors. Androgen deprivation therapy for cytoreduction prior to SBRT may be useful in some patients with large volume glands and high IPSS scores, as has been suggested in brachytherapy literature [52].

Prophylactic medications, such as alpha-blockers and/or anti-inflammatories (NSAIDs or steroids), are used by some centers with the goal of preventing acute urinary morbidity thought to be related to radiation induced prostatitis and edema [53–55]. There are limited data, however, that these regimens significantly reduce the risk of symptoms and their theoretical benefits must be balanced against their known risks of side effects.

10.4 Reducing Sexual Dysfunction

Preservation of sexual function is strongly correlated with patient satisfaction after prostate cancer treatment [56]. Sexual dysfunction after prostate radiation is multifaceted and can include changes in ejaculate quantity, loss of libido, and difficulty achieving or maintaining an erection. Most analyses focus on erectile dysfunction, which is best assessed using validated questionnaires, such as the International Index of Erectile Function (IIEF) and the Sexual Health Inventory for Men (SHIM).

10.4.1 Patient Selection

Multiple factors contribute to the post-treatment erectile dysfunction following prostate SBRT including pre-treatment dysfunction, as well as physical and psychosocial comorbidities. The etiology of radiation-related erectile dysfunction is likely multifactorial, including vascular changes, soft tissue/muscle fibrotic changes, and nerve dysfunction [57]. Patients with comorbidities that also affect vascular and nerve tissue, such as hypertension and diabetes are predisposed to post-treatment erectile dysfunction. Advancing age alone has been shown to correlate with deteriorating erectile function in healthy subjects and is particularly relevant in the prostate cancer population [58]. Additionally, the use of androgen deprivation has a significant impact on both early and late erectile dysfunction. In the study by Katz et al., 252 of the 375 patients (67.2%) that were potent prior to prostate SBRT remained potent at last follow-up (median 72 months) and use of androgen deprivation was significantly associated with the development of erectile dysfunction [2].

10.4.2 Treatment Planning and Delivery

Complex physiological interactions are involved in the maintenance of a functional erection. The etiology of impotence after conventionally fractionated prostate radiation is thought to most likely be related to vascular pathology, but also possibly cavernosal dysfunction and less likely nerve injury [59, 60]. The pathophysiology of erectile dysfunction after SBRT is likely similar but not yet fully understood.

Whether dose to the penile bulb, penile proximal crura, specific blood vessels or nerves, and/or the neurovascular bundles affect sexual function is still an open question. Several brachytherapy and external beam radiotherapy studies have attempted to demonstrate correlations between dosimetric variables to these structures and erectile dysfunction.

Accurate delineation of target and normal adjacent tissues is essential to reduce radiation related side effects. MRI-based treatment planning approaches (MR simulation or CT/MRI fusion) are superior to CT-based approaches for this purpose. Prostate volumes contoured on MRI are smaller and less variable than those contoured on CT which may also reduce dose to these proximate tissues [61, 62]. Additionally, erectile tissues are better visualized on MRI than on CT [63]. Studies are ongoing to assess whether MR-based nerve and vessel sparing radiation is safe and beneficial for erectile function preservation.

It is possible that rectal spacers (discussed above), in addition to reducing GI toxicity, can help minimize sexual toxicity after prostate SBRT. Secondary analyses of the phase III trial evaluating the hydrogel rectal spacer during prostate IMRT to 79.2 Gy showed that the spacer decreased dose to the penile bulb and was associated with preserved erectile function [64]. At 36 months follow-up, men with good

baseline function who had a spacer reported better sexual quality of life across multiple items including overall function, erection ability, erection quality, erection frequency, morning erections, and orgasm ability. There was also less sexual bother in the spacer arm. Pinkawa et al. also found that at 5 years there were significantly more patients in with a spacer reporting erections firm enough for intercourse compared to patients without a spacer and patients with good baseline function were significantly more likely to preserve function than those without a spacer [38].

10.4.3 Phosphodiesterase Type 5 Inhibitors

The use of phosphodiesterase type 5 (PDE5) inhibitors during and after prostate SBRT might be effective at preventing and/or treating post-SBRT erectile dysfunction. PDE5 inhibitors block the degradation of cGMP, which increases to smooth muscle relaxation in the blood vessels supplying the corpus cavernosum, resulting in increased blood flow to the penis. Multiple studies in the post-radiation setting have shown that episodic or "on-demand" use of PDE5 inhibitors (i.e. sildenafil citrate and tadalafil) can improve erectile function, however response decreases as time from radiation increases [65–71]. PDE5 inhibitors also can help men treated with radiation combined with androgen deprivation, but to a lesser extent than patients treated without androgen deprivation [72].

Compared with episodic use of PDE5 inhibitors, regularly scheduled administration improves cavernosal vasodilatation and erectile function in men without prostate cancer that have erectile dysfunction [73]. A randomized prospective trial of 6 months of daily sildenafil citrate versus placebo in 279 men undergoing prostate radiotherapy demonstrated a significant improvement in erectile function with PDE5 inhibitors that persisted to 24 months. This study also showed that the benefit diminishes with time and is less pronounced in patients treated with androgen deprivation in conjunction with radiation. It is possible that longer than 6 months of treatment might have produced more durable effects. Another randomized, placebo-controlled trial of daily tadalafil for 6 months failed to show a statistically significant difference in erectile function. It is possible that this lack of benefit was related to the choice of study drug, dosing, or insufficient power to detect a difference.

Based on the current evidence, patients undergoing prostate SBRT should be offered sexual counseling and informed about the availability of effective treatments for sexual dysfunction. It is reasonable to offer daily PDE5 inhibitors of $\geq$6 months starting at the time of SBRT for prevention or to use it early in response to reported erectile dysfunction.

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SBRT for High-Risk Prostate Cancer

11

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11.1 Introduction

High-risk prostate cancer (HRPCa) is an biologically aggressive and distinct form of the disease known to have a greater risk of distant metastasis and mortality than low- and intermediate-risk prostate cancer [1]. Although there is no universally accepted definition of HRPCa most clinicians and investigators accept the criteria put forth by the NCCN (National Comprehensive Cancer Network) [2] including either a high Gleason score (GS) (e.g. 8–10) clear risk for extracapsular extension, seminal vesicle invasion and/or a high risk of lymph node involvement. These three features potentially limit the effectiveness of radical prostatectomy and radiation when treatment is directed exclusively at the prostate.

External beam radiotherapy (EBRT) combined with androgen deprivation (ADT) improves the overall survival in high-risk patients compared to treatment with only androgen deprivation therapy (ADT) [3, 4], while dose escalation has been shown to improve biochemical control [5–12]. Compared with dose-escalated EBRT, low dose rate (LDR) brachytherapy has demonstrated an improvement in biochemical control [13]. High dose rate (HDR) brachytherapy boost appears to provide similar advantages as a LDR brachytherapy boost. Some favor HDR brachytherapy because it may be technically easier to perform and improves dose delivery and provides coverage of extra-prostatic disease [14]. The standard treatment for high-risk prostate cancer patients includes the use of long-term ADT, with studies have showing that 2–3 years of ADT results in an improvement in overall survival (OS) compared to short term ADT [15, 16].

Stereotactic body radiotherapy (SBRT) is a technique that delivers highly conformal, high-dose radiation in usually one to five treatment fractions. In prostate cancer, SBRT is used to provide the radiobiological advantage of a low α/β ratio, as well as the convenience of a short treatment course. Multiple pre-clinical and clinical studies have shown that prostate cancer has a low α/β ratio in the range of 1–1.9 Gy [17–20]. The organs at risk close to the prostate have a higher α/β ratio, typically assumed to be between 3 Gy and 5 Gy. This difference in sensitivity is the theoretical basis for increasing the fraction size; thus, it is possible to achieve dose escalation through hypofractionated SBRT without causing more damage to the organs at risk [21]. Additionally, SBRT has some advantages over other forms of radiation because it is more convenient for the patients, it is non-invasive compared with brachytherapy, and shorter in duration when compared with EBRT.

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Fuller et al. [22] made a dosimetric comparison between HDR brachytherapy and CyberKnife (CK) SBRT, and concluded that the robotic radiosurgery delivers a radiation dose distribution that very closely resembles the distribution delivered using HDR brachytherapy. Many centers have extrapolated their planning goals, doses, and fractionations from HDR brachytherapy to SBRT. SBRT is considered to be a safe and effective treatment for low- and intermediate-risk prostate cancer patients [23], although the role in high-risk patients is still unclear. This review summarizes the rationale for SBRT, what is known about this treatment modality, its potential advantages and limitations and future directions.

11.2 SBRT As Monotherapy

The treatment of HR patients with SBRT as a monotherapy option is not considered "standard of care" although the somewhat limited reports suggest surprisingly favorable outcomes [24], with no randomized studies exist to support its use. However, some patients are neither candidates for brachytherapy boost nor for a course of protracted EBRT, but may be suitable candidates for SBRT. Thirteen published studies [25–37] that included HR patients treated with SBRT monotherapy are summarized in Table 11.1. The definition of HR varied between series. The total dose of radiation used in the monotherapy studies ranged from 32 to 40 Gy in four or five fractions. All studies used ADT in some patients. The 5-year bDFS was 81–91%. The longest bDFS was reported by Katz et al. [30] who reported an 8-year bDFS of 65% in HR patients. The results of SBRT monotherapy studies (see Fig. 11.1) should be interpreted cautiously, because, it could be explained by selection bias. However, it is a promising treatment for HR prostate cancer patients with a short treatment time and leverages the advantage of hypofractionation.

11.3 SBRT As a Boost

The SBRT boost is a promising option with more clinical evidence needed. In a recent review [24], five published studies with HR patients treated with SBRT boost were included [38–42] and two studies combined HR patients who received SBRT as a monotherapy or as a boost [43, 44] (see Table 11.2). In the SBRT boost only studies the median follow-up ranged from 2 to 5 years. Three studies [38, 40, 42] had a follow-up of four or more years. All studies except for one used ADT. The boost dose reported in these studies varied from 10 Gy in two fractions to 21 Gy in two or three fractions. Two SBRT boost studies [38, 39] delivered whole pelvis radiotherapy to lymph nodes if the risk of lymph node involvement predicted with the Roach formula was more than 15%. Two studies [40, 41] treated all patients with whole pelvic field to 45 Gy in 25 fractions before the SBRT boost to cover pelvic lymph nodes. Two studies [38, 39] (with more than 50% HR patients) reported a 5-year bDFS of 90 and 98%. However, no studies report specific 5-year bDFS for HR patients exclusively. In the two combined studies, the first study by Katz et al. reported [43] on HR patients using SBRT monotherapy to a total dose of 35–36.25 Gy in five fractions in 52 patients and an SBRT boost to a dose of 19–21 Gy in three fractions in 45 patients. At a median follow-up of 5 years, the 5-year bDFS was 63 and 69% for unfavorable intermediate- and HR patients. The second study by Freeman et al. [44] reported SBRT monotherapy or SBRT boost on 2000 patients with 172 being HR patients. Eighty-six percent of the patients received SBRT monotherapy to a total dose of 35–40 Gy in five fractions, and 14% received an SBRT boost to a total dose of 19.5–21.75 Gy. At a median follow-up of 2 years, the 2-year bDFS was 87% for HR patients. In this recent literature review [24] the 5-year bDFS in the SBRT boost studies (69–98%) is comparable to the results reported in HDR boost studies (72–93%) and DE-EBRT plus ADT studies (75–90%) [45–47], although more studies and research is needed due to the lack of randomized evidence (see Fig. 11.2). The nPSA has been related with bDFS [48–51], and nPSA levels <0.5 ng/ml have been associated with better biochemical outcomes and improved distant metastases-free survival [50]. In the SBRT boost only studies the nPSA appear to be higher than in

Table 11.1 Series of high-risk prostate cancer patients treated with SBRT as a monotherapy

Author, year, origin	No. patients (HR pts)	HR definition	Dose	Median FU (years)	ADT/ duration	Toxicity (scale used)	Outcomes HR patients[a]
Kang et al. [29], Korea	44 (29)	D'Amico	8 Gy × 4, 8.5 Gy × 4 or 9 Gy × 4	3.3	Yes/ 24 months	Acute: GU & GI Gr. 1/2: 43% & 25%. Late GU & GI Gr. 1/2: 16% & 14%[b]	5-years-bDFS: 90.9%
Bolzicco et al. [25], Italy	100 (17)	NCCN	7 Gy × 5	3	8 HR pts received/NS	Acute: GU & GI Gr. 2: 12% & 18%. Late GU Gr. 3: 1%[c]	3-years-bDFS: 94% (all patients)
Chen et al. [26], USA	100 (8)	D'Amico	7–7.25 Gy × 5	2.3	"Most" received 3–6 months/ 2 HR pts 2–3 years)	2-years-actuarial GU & GI Gr. ≥2 (31%) & (1%). 21% late GU flare[b]	2-years-bDFS: 99% (all patients)
King et al. [31], USA	1100 (125)	D'Amico	7–8 Gy × 5	3	38% of HR pts/4 months	NS[d]	5-years-bDFS: 81%
Lee et al. [34], Korea	45 (13)	NCCN	7.2 Gy × 5	5.3	Yes/NS	Acute: GU & GI Gr. 2: 4% & 4%. Late GU & GI Gr. 2: 4% & 4%[b]	5-years-bDFS: 89.7% (all patients)
Janowski et al. [28], USA	57 (9)	D'Amico	7–7.25 Gy × 5	2.9	Yes/NS	2 years actuarial Gr. >2 GU & GI: 49% & 1.8%[b]	2-years-bDFS: 98% (all patients)
Davis et al. [27], Radiosurg. Society	437 (33)	NCCN 2015	7–9.5 Gy × 4–5	1.6	15 HR pts received ADT/NS	Late Gr. 1 & 2 GU were 25% & 8%. Late Gr. 1/2 proctitis was 3% & 2%[b]	2-years-bDFS: 90% but with PSA >20 ng/ml: 62.5%
Fan et al. [36], Taiwan	31 (16)	NCCN	7.5 Gy × 5	3	82% HR/NS	No Gr. >3. 7 pts acute GU Gr. 2. 2 pts Late GU Gr. 2[b]	3-years-bDFS: 82%
Rana et al. [37], USA	102 (8)	D'Amico	5–8 Gy × 5	4.3	8.9% of pts/4 months	Late Gr. 2 GU & GI: 9.9% & 3%[c]	3-years-bDFS: 100% (all patients)
Ricco et al. [35], USA[e]	270 (A1: 32)	NCCN 2015	7–7.5 Gy × 5	4.1	27% of all SBRT pts/NS	No late GU & GI Gr. 3[c]	6-years-bDFS for SBRT: 92%. 4-years-bDFS for HR & VHR: 95% & 72%

(continued)

Table 11.1 (continued)

Author, year, origin	No. patients (HR pts)	HR definition	Dose	Median FU (years)	ADT/ duration	Toxicity (scale used)	Outcomes HR patients[a]
Katz et al. [30], USA	515 (38)	NCCN 1.2016	7–7.25 Gy × 5	7	Yes/NS	Acute: GU & GI Gr. 2: <5%; Late GU & GI Gr. 2: 9% & 4%. Late GU Gr. 3: 1.7%[c]	8-years-bDFS: 65% for HR. Favorable and unfavorable intermediate 7-years-bDFS ~93% and 68%
Kotecha [33], USA	24 (13)	NCCN	7.25–10 Gy × 5 to LDPTV and HDPTV SIB	2	Yes/NS	Acute GU Gr. 2: 38%. Late GU & GI Gr. 2: 4% & 8%[b]	2-years-bDFS: 95.8% for all pts. 2 HR pts biochemical failures
Koskela [32], Finland	218 (111)	D'Amico	7–7.25 Gy × 5	2	88.3% of HR/48% of HR pts ADT >24 months	No acute GU & GI Gr. 3 Int.-term GU & GI Gr. 3: 1.8 & 0.9%[b]	23-months-bDFS: 92.8%

ADT androgen deprivation therapy, *bDFS* biochemical disease-free survival, *FU* follow-up, *GI* gastrointestinal, *GU* genitourinary, *HDPTV* high-dose planning tumor volume, *HR* high risk, *LDPTV* low-dose planning tumor volume, *NCCN* National Comprehensive Cancer Network, *NS* not specified, *PSA* prostate-specific antigen, *SBRT* stereotactic body radiation therapy, *SIB* simultaneous integrated boost, *VHR* very high risk

[a]At least otherwise specified

[b]Common terminology criteria for adverse events, version 3–4 scale

[c]Radiation Therapy Oncology Group scale

[d]*NS* Not specified

[e]This study has two arms, one of SBRT (A1) and the other of intensity modulated radiation therapy (A2). Table modified from Gonzalez-Motta and Roach [24]

the LDR BT arm in the ASCENDE-RT trial. However, nPSA after SBRT treatment can decay continuously in time [52] and it is possible that with longer follow-up get a lower nPSA. The biologically effective dose (BED) calculated for a $\alpha/\beta = 1.4$ in SBRT boost series ranged from 201 to 281 Gy comparable to the BED reached with HDR boost [53].

A recent report from UCSF suggest that there may be advantages to performing reverse boost (boost prior to fractionated EBRT) [54]. In this report we observed a more rapid, complete and sustained resolution of complete urinary obstructive (UO) requiring an indwelling catheter. In addition to the possible sequence advantage for relieving UO, there are several other additional potential advantages to using a reverse boost: (1) obtaining the Magnetic resonance imaging (MRI) prior to defining the anatomy on the treatment planning CT may improve the accuracy of defining the target definition. For example, on some occasions a greatly enlarged median lobe on sometimes difficult to identify on routine CT; (2) there may be favorable sequence dependent interactions when the boost is given first analogous to the trial reported by Forman et al. using Neutron boost [55]; (3) occasionally composite plans generated combining SBRT following EBRT reveals unexpected "hotspots", which can be avoided if SBRT is performed first. Finally, we have found scheduling logistically easier when the boost is performed first. A randomized trial would be required to confirm the advantages of these sequence dependent interactions but it is doubtful this would be feasible in the near future.

11.4 Toxicity

The nature of late toxicity following SBRT remains challenging to evaluate because it is reported in different manners, and the instruments

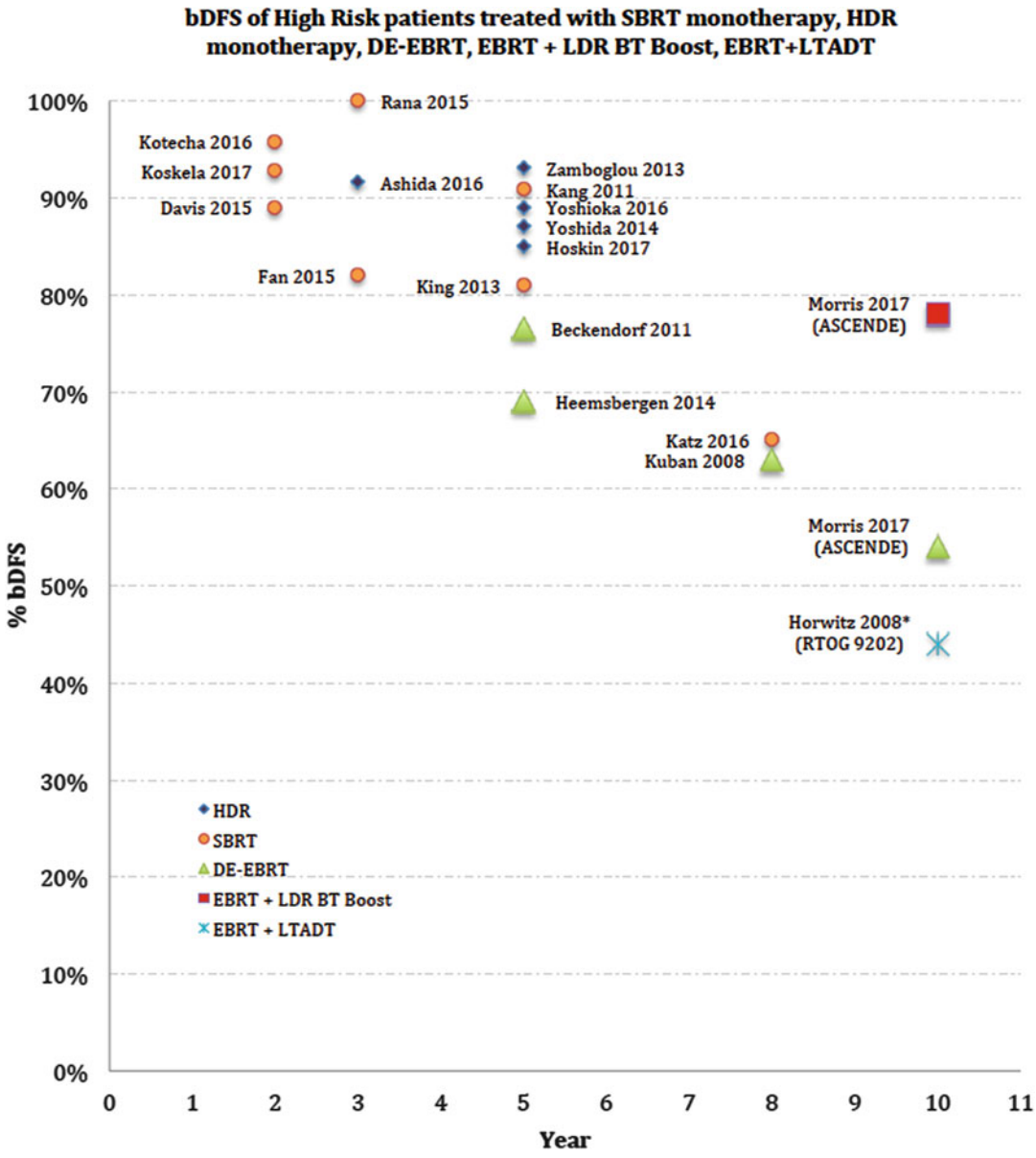

Fig. 11.1 Biochemical disease-free survival (bDFS) (Phoenix) of high-risk (HR) patients treated with stereotactic body radiotherapy (SBRT) monotherapy, high dose rate (HDR) brachytherapy monotherapy studies, a external beam radiotherapy plus long-term androgen deprivation therapy (EBRT + LTADT) study, dose-escalated external beam radiotherapy (DE-EBRT), and low dose rate prostate brachytherapy (LDR BT). Data from the ASCENDE-RT trial was estimated from the Kaplan–Meier curve of bDFS for HR patients. Data for RTOG 9202 (EBRT + LTADT) was estimated from biochemical rate reported. *RTOG 9202 used ASTRO definition for biochemical failure. **DE-EBRT arm of the ASCENDE-RT trial received 8 months of neoadjuvant androgen deprivation therapy. Modified from Gonzalez-Motta and Roach [24]

Table 11.2 Selected series of high risk prostate cancer treated with SBRT ± external beam radiation therapy (EBRT)

Author, year, origin	No. pts (HR pts)	HR definition	Dose	Med. FU (year)	ADT/duration	Toxicity (scale)	Outcome for HR patients[a]
Miralbell et al. [38], Spain	50 (33)	D'Amico	5, 6, 7 or 8 Gy × 2 (boost)	5.25	32 pts/15 pts with GS >8: 24–30 months	Acute GU & GI Gr. 2: 46% & 8%. Late GU Gr. 2: 12.5%. Proportion of pts GI Gr. >2: 16% at year 3 and 8% at year 5[b]	5-years-bDFS: 98% for all pts
Lin et al. [41], Taiwan	41 (41)	NCCN	7 Gy × 3 (boost)	3.5	92.7% of pts/24	Acute: GU & GI Gr. 2: 27% & 12% No grade 3 late GU or GI toxicity[c]	4-years-bDFS: 92%
Katz et al. [43], NY	97 (97)	NCCN	7–7.25 × 5 (mono) 18–21 Gy in 3 (boost)	5	51.5% of pts/Med. 5 months	Late GU & GI Gr. 2: 2.3–7.8% & 0–13.3%. Late GU grade 3: 2.3–3.9%[b]	5-years-bDFS were 69% and 63% for HR & unfavorable intermediate
Freeman et al. [44], registry for prostate cancer radiosurgery	2000 (172)	NCCN	7–8 Gy × 5 (mono) 6.5–7.25 × 3 (boost)	2	NS[d]	No late GU Gr. 3 Late grade GI Gr. 3: 1 patient[c]	2-years-bDFS: 87%
Anwar et al. [39], UCSF	48 (34)	NCCN	9.5–10.5 Gy × 2 (boost)	3.5	88% of pts/NS[d]	No acute Gr. 3. One single patient late Gr. 3 GU toxicity[c]	5-years-bDFS: 90% for all pts
Mercado et al. [42], Georgetown	108 (59)	D'Amico	6.5 Gy × 3 (boost)	4.4	63.6% of pts/NS[d]	Late accumulative rate GU & GI Gr. >2: 40% & 12%[c]	3-years-bDFS: 89%
Kim et al. [40], Korea	42 (11)	2.2014 NCCN	7 Gy × 3 (boost)	4.4	No	Acute: GU & GI Gr. 2: 24% & 19%. Late GU & GI Gr. 2: 12% & 12% (NS)	4-years-bDFS: 71%

eMRI endorectal magnetic resonance imaging, *fx* fractions, *LINAC* linear accelerator, *QOL* quality of life, *SV* seminal vesicles, *WPRT* whole pelvis radiation therapy. All other abbreviations as in Table 11.1

[a]At least otherwise specified

[b]Radiation Therapy Oncology Group scale

[c]Common terminology criteria for adverse events, version 3–4 scale

[d]*NS* Not specified

Table modified from Gonzalez-Motta and Roach [24]

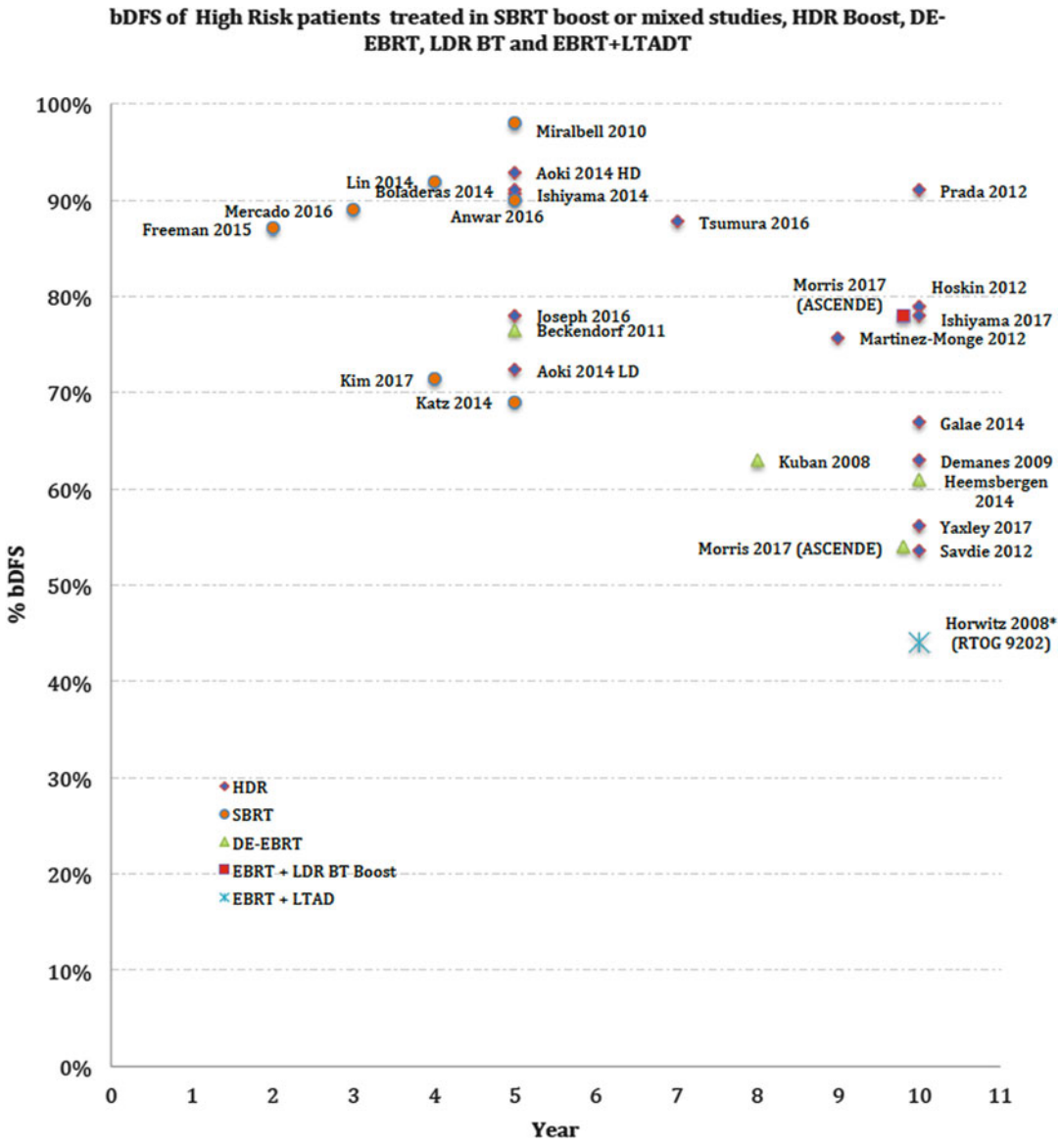

Fig. 11.2 Biochemical disease-free survival (bDFS) (Phoenix) of high-risk (HR) patients treated with stereotactic body radiotherapy (SBRT) boost, high dose rate (HDR) boost, external beam radiotherapy plus long-term androgen deprivation therapy (EBRT + LTADT), dose-escalated external beam radiotherapy (DE-EBRT), dose rate prostate brachytherapy (LDR BT) arm of ASCENDE-RT trial. Data from the ASCENDE-RT trial was estimated from the Kaplan–Meier curve of bDFS for HR patients. Data for RTOG 9202 (EBRT + LTADT) was estimated from biochemical rate reported. *RTOG 9202 used the ASTRO definition for biochemical failure. **DE-EBRT arm of the ASCENDE-RT trial received 8 months of neoadjuvant androgen deprivation therapy. Modified from Gonzalez-Motta and Roach [24]

used varies between series and they are also mostly retrospective. Some use common terminology criteria for adverse events (CTCAE) and others used the Radiation Therapy Oncology Group (RTOG) scale. In SBRT monotherapy series the incidence of acute grade 2 (RTOG or CTCAE) genitourinary (GU) ranged from 4.4 to 38% and the acute grade 2 (RTOG or CTCAE) gastrointestinal (GI) toxicity ranged from 0 to 18% [24]. The incidence of late grade 2 (RTOG or CTCAE) GU ranged from 3 to 16% and the late grade 2 (RTOG or CTCAE) GI toxicity ranged from 0 to 11%. The late grade 3 GU and GI toxicity ranged from 0 to 4.4% [24]. In the SBRT boost and mixed studies, the acute grade 2 (RTOG or CTCAE) GU and GI toxicity ranged from 23.8 to 46% and from 8 to 19%, respectively. The late grade 2 (RTOG or CTCAE) GU ranged from 2.3 to 25% [24]. The late grade 3 (RTOG or CTCAE) GU and GI toxicity ranged from 0 to 2.3% and from 0 to 10% [24].

11.5 Unresolved Questions About SBRT for High Risk Prostate Cancer

11.5.1 Role of Whole Pelvic Radiation Therapy (WPRT)

The inclusion of whole pelvic radiation therapy (WPRT) is still hotly debated in high-risk patients. Some studies argued in favor of inclusion of WPRT for a progression-free survival improvement [56], while others did not find a benefit in terms of event-free survival (EFS) and overall survival (OS) [57]. The GETUG-01 study was far too small a trial, and included relatively favorable patients, it also used an unacceptably small pelvic field, all factors that may explain why this was a "negative study" [58]. Results from the ongoing randomized trials, RTOG 0924 for intermediate-risk and favorable high-risk patients and the GETUG-AFU-23 for unfavorable high-risk patients, will help answer this question. Two SBRT boost studies [38, 39] delivered whole pelvis radiotherapy to lymph nodes if the risk of lymph node involvement predicted with the Roach formula was more than 15%. Two studies [40, 41] treated all patients with whole pelvic field to 45 Gy in 25 fractions before the SBRT boost to cover pelvic lymph nodes. Results from trials using only prostate SBRT as monotherapy for high-risk patients are suggestive with 5-year b-DFS between 81% and 91% [29, 31]. Katz et al. [43] published a study of SBRT with or without WPRT for high-risk patients and did not find a statistical difference between patients who received WPRT and patients who did not. Longer follow-up and additional studies ideally randomized trial are desired to elucidate the required of WPRT when SBRT is used.

11.5.2 Volumes

There is not a consensus on the ideal volumes for prostate SBRT, and this is probably an immediate challenge to developing a new program. The development of an expert consensus on contouring volumes for prostate SBRT is critically needed due to the rising use of SBRT for prostate cancer. Volumes may need to be impacted with the inclusion of the whole pelvis as previously discussed. Most SBRT boost studies [39–43] define the volume of the boost as the prostate, with some including the proximal seminal vesicle(s) if assumed to be at risk, or when there is radiographic evidence of extracapsular extension [40–42]. At UCSF we treat HR patients with two volumes sequentially in the first volume we include lymph nodes, prostate, proximal seminal vesicles with intensity-modulated radiotherapy.

In the second, boost volume, we include the prostate, seminal vesicles depending on seminal vesicles invasion, not infrequently a single the proximal portion of a seminal vesicles is included (see Fig. 11.3 below) using the CK.

11.5.3 ADT Use, Sequence and Duration

There is a debate as to should ADT should be recommended when a high BED used to definitively treat prostate cancer patients. Some studies

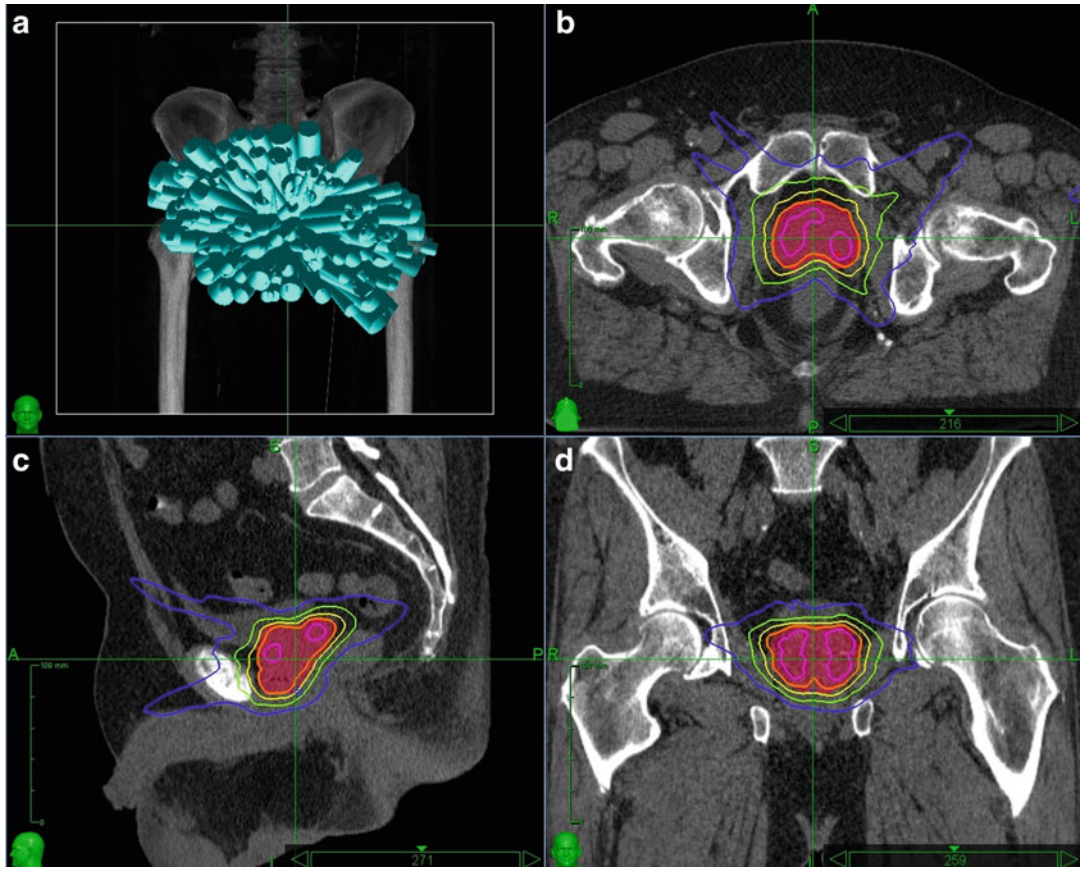

Fig. 11.3 (**a**) A typical CK plan uses over a hundred non-coplanar, non-isocentric beams, as shown in (**a**). Isodose line distribution in the (**b**) axial, (**c**) sagittal and (**d**) coronal views of an example CK prostate SBRT plan with urethral sparing and extension to include the proximal seminal vesicles. The isodose shown in white represents 120% of the prescription dose

in HDR suggest that ADT may be of no benefit when prostate cancer is treated with such large fractions [59]. However, as shown in Tables 11.1 and 11.2 below, the majority of SBRT studies in HR patients used ADT [25–37]. Katz et al. [43] reported a prospective study on 97 patients, 46 of them received ADT. However, ADT use was not found a significant factor for bDFS. Even in patients treated with brachytherapy monotherapy or boost the role of ADT is not fully understood. The American Brachytherapy Society Task Group Report stated that [60] "The inherent selection bias in retrospective studies, unclear risk stratification, inconsistent use and duration of ADT, and inconsistent treatment allocation precludes any definitive conclusions regarding use of ADT in brachytherapy-treated patients." They also consider that [60] "In unfavorable intermediate risk and high-risk disease, ADT is likely to still play a role through spatial co-operation for suppression of micrometastatic disease. The optimal duration, however, remains to be determined". The European Association of Urology [61] recommends that "The optimum duration of androgen deprivation therapy (ADT) with external beam radiation therapy (EBRT) is well established in the literature. There is no evidence that these durations should change when using brachytherapy boost with EBRT." In conclusion, there is more research needed to establish the role of ADT in this group of patients. We recommend using the same ADT regimen as in EBRT at least 2 months of neoadjuvant therapy and then 24–26 months of adjuvant ADT

treatment. However, we recognize that patients unable to receive ADT, SBRT treatment as monotherapy or a boost is a treatment option to overcome the non-use of ADT. In patients treated with SBRT monotherapy however, short term ADT following SBRT may be reasonable based on the findings from RTOG 9413.

11.5.4 Dose

There is not a standardized dose of SBRT for prostate cancer patients. Most SBRT boost studies in HR patients try to use doses similar to HDR boost doses prescription. Doses of SBRT used as a boost ranged from 5–10.5 Gy × 2 fractions to 6–7 Gy × 3 fractions. Kim et al. [62] published a dose-escalation study that showed that 50 Gy in five fractions had an unacceptable level of rectal toxicity. Zaorsky et al. [63] conducted a meta-analysis that suggested that an increase in BED to 200 Gy (at $\alpha/\beta = 1.5$) was associated with better disease control, whereas doses above 200 Gy did not afford additional clinical benefits. Studies that used an HDR boost have also reported the importance of a higher BED. Martinez et al. [53] reported a 10-year bDFS of 81.1 and 56.9% in patients who received a dose to a BED > 268 Gy ($\alpha/\beta = 1.2$) compared patients who received a dose to a BED < 268 Gy ($\alpha/\beta = 1.2$). SBRT boost can obtain similar BED than HDR boost [38, 39]. Doses of SBRT used as a monotherapy ranged from 5–9 Gy × 4–5 fractions. At UCSF we use two fractions of 9.5 Gy for SBRT boost, and we do not favor the use of SBRT monotherapy for high-risk patients.

11.5.5 Dose Constraints

There are very few evidence-based dose constraints for normal tissues in the setting of SBRT for clinically localized prostate cancer [64]. The authors refer the readers to the AAPM TG101 report [65] and the UK consensus on normal tissue dose constraints for stereotactic radiotherapy [66] for a set of constraints for pelvic organs. These constraints are base on extrapolations from constraints from standard fractionation using biological models, and from un-validated estimates by the authors [64]. The dose constraints for prostate SBRT should be considered as an area of continued investigation because the Linear–Quadratic model has not been validated with the high dose per fraction as used in extreme hypofractionation or SBRT [64]. At UCSF we used a method for determining rectal and bladder dose constraints achievable for a given patient's anatomy [67] with this method the proximity of the organs at risk to the target is quantified by means of the expansion-intersection volume (EIV), which is defined [67] as the intersection volume between the target and the organ at risk expanded by 5 mm. After that, we determine a relationship between EIV and the relevant dosimetric parameters (e.g. the volume of bladder and rectum receiving 75% of the prescription dose). There is a linear correlation between EIV and V75% of bladder and rectum confirming that the dose increases with increasing extension and proximity of these organs to the target [64, 67]. In general, we try to limit V75% of the rectum to <2 cc and V75% of the bladder to <3 cc. Although these parameters are specifically developed for CK treatment, we expect that this or a similar custom approach designed for each center might be useful, see Table 11.3 that summarizes dose constraints used in our clinical practice.

11.6 Treatment Decision

At UCSF we have a broad set of different radiation techniques available for patients. In Table 11.4, below, we share some of the considerations we use for selecting the optimal approach, including our primary preferred indications and relative contraindications. We understand that part of the "Art" of radiation therapy is choosing and tailoring the best treatment for each patient based on patient own clinical features. Based on similar bDFS, nPSA outcomes between HDR boost and SBRT boost and an acceptable toxicity profile of SBRT boost (see Fig. 11.4), we consider them to roughly equivalent. We offered this option for high-risk patients who are not candidates for HDR boost

Table 11.3 Recommended dose constraint for SBRT at UCSF with CyberKnife

Parameter	UCSF	UCSF (monotherapy)
Total dose	19 Gy (boost)	38 Gy
Fractions	2	4
Prescription	>60%	>60%
PTV margin	2 mm/0 mm posterior	2 mm/0 mm posterior
PTV	V100% > 95%	V100% > 95%
Rectum	V75% < 2 cc	V75% < 2 cc
Bladder	V75% < 3 cc	V75% < 3 cc 19 Gy < 15 ml
Urethra	Dmax < 120%	Dmax < 120%

Modified from Roach et al. [64]

(e.g., not candidates for anesthesia, unadvisable discontinuation of anticoagulation, excessive pubic arch interference) and if patients have a strong preference for SBRT and want to avoid a surgical procedure. SBRT is technically less complex for practitioners and less invasive for patients than BT. Outside of a clinical trial, we do not recommend SBRT monotherapy for high-risk patients unless other radiation therapies or surgical treatments are contraindicated.

11.7 Treatment Technique

For a detailed technique description, the authors refer the readers to a recent review on SBRT [64]. In summary, before simulation, three gold seed markers (or fiducials) are implanted in the prostate by an experienced urologist via transrectal ultrasound (TRUS) guidance. Usually, two seeds are placed in the base and one in the prostate apex. Ideally, the marker seeds should be non-collinear in the two-dimensional orthogonal imaging directions and the spacing between each pair of markers should be greater than 2 cm. For CyberKnife, two orthogonal images are acquired at 45° oblique angles throughout the treatment. The live camera images are compared to a library of digitally reconstructed radiographs (DRR) to track the position of the prostate in real time. Three well-placed fiducials are needed in order to correct for both rotations and translations of the prostate during treatment. Gold markers should be placed at least 1 week prior to simulation to allow fiducial movement to stabilize. On the day of simulation, prior to arrival patients are instructed to self-administer an enema to void the rectum. Patients are also instructed to have a "full but comfortable bladder" (We recognize that some radiation oncologist prefers an empty bladder). Care should be taken so that patients do not have an uncomfortable full bladder such that they are unable to hold for the long duration of the treatment. We instruct patients to void bladder 1 h prior to simulation, then to drink two glasses of water while awaiting simulation, to reduce the risk of severe urinary urgency [64].

Patients are simulated [64] with supine arms on the chest. Further, a foot block to prevent femoral head rotations and knee support to ensure patient comfort are used. For CyberKnife treatments a thin (1 mm) CT is obtained covering the entire pelvis. The thinner CT slices (1–1.5 mm) generate high quality digitally reconstructed radiographs (DRRs) that improved the tracking accuracy during image-guided treatment. To improve contouring of volumes and get a better accuracy of the target, at UCSF patients receive a prostate MRI without endorectal coil (to avoid anatomic distortion), with both T1 and T2-weighted imaging sequences, with similar rectal and bladder preparations as described above. The simulation CT is co-registered with the MRI image series performing a rigid registration. Bony anatomy registration is not sufficient to ensure correct registration, given that the prostate can shift relative to the bony anatomy between CT and MR images. The gold markers are better visualized on the T1-weighted images. The prostate borders and urethra are better to define in the T2-weighted images. We routinely use an MRI to define the urethra as an avoidance structure to insure a hotshot does not reside in it, and if patients have contraindications to have an MRI, we perform

Table 11.4 Radiation therapy "preferred" options and relative contraindications for prostate cancer at UCSF (2017)

Type of radiation therapy	Year[a]	Primary indications[b]	Relative contraindications
IGRT (intensity modulated image guided external beam radiation)[c]	Pre-1996	1. Combination therapy pre/post boost treatment 2. Post-op adjuvant treatment 3. Post-op salvage treatment 4. Large TURP defects 5. Other options not covered by insurance 6. Patient preference	1. Previous full dose radiation 2. Patient preference (e.g. logistically problematic) 3. Focal recurrence (favor focal treatments) 4. Technical issues (e.g. too large for CT scan but BT suitable 5. Inflammatory bowel disease or connective tissue disorder 6. Non-compliant for many visits
PPI (permanent prostate implant) BT (brachytherapy)	1996	1. Monotherapy for low or favorable int. risk pts 2. Boost in clinically T1–2 with IMRT 3. Focal salvage post recurrence after IMRT 4. Focal salvage post recurrence after PPI 5. Patient preference	1. Not a candidate for anesthesia 2. Discontinuation of anti-coagulation is unadvisable 3. Excessive pubic arch interference (PAI) 4. Excessively large TURP defect 5. Severe baseline urinary symptoms (e.g. urinary retention)
HDR (high dose rate) BT	1999	1. Monotherapy for low or favorable int. risk pts 2. Boost in clinically T1–3 with IMRT 3. Focal salvage post recurrence after IMRT 4. Pubic arch interference prohibiting PPI 5. Median lobe too large for SBRT 6. Insurance prohibits SBRT 7. Patient preference	1. Not a candidate for anesthesia 2. Discontinuation of anti-coagulation is unadvisable 3. Excessive pubic arch interference 4. Excessively large TURP defect 5. Severe baseline urinary symptoms (e.g. urinary retention)
SBRT (stereo tactic body radiation therapy)	2005	1. Monotherapy for low or favorable risk pts 2. Boost for clinically T1–4 with IMRT 3. Focal salvage in selected pts post recurrences after IMRT when not candidate for BT salvage 4. Patients presenting with obstruction due to locally advanced disease (e.g. "reverse" boost) 5. Patient preference (e.g. convenience)	1. Very large median lobe 2. Unable to lie still and flat for 45 min (e.g. tremor) 3. Poor localization due to metal artifacts (e.g. hip replacement, presence of PPI seeds . . .) 4. Poor seed positioning ("too close") 5. Not covered by insurance 6. Protocol requires other treatments 7. Excessively large TURP defect

[a]Approximate year program started at UCSF

[b]"Primary preferred": this term reflects the clinical nuances that go into the decisions concerning the use of various radiation options considered while practicing the "Art" of radiation therapy. There may be exceptions to what physicians decide to recommend to specific patients but these "primary preferred" options as listed in this table reflects our typical considerations and our practice habits. It is recognized that for purposes of continuity of care, and presumed clinical equivalence, patients who could be managed appropriately by more than one boost modality, are more likely to be managed via the modality favor by the "clinical lead" Radiation Oncologist as listed above. Modified from Roach and Chung PPRO [64]

[c]Delivered with either conventional or hypofractionation

an urethrogram at the time of the CT or gold seed placement as an alternative.

At UCSF we commonly use a CyberKnife (Accuray Inc.) boost to deliver 19 Gy to the prostate after a whole pelvic field for high-risk patients. The CTV is defined as the entire prostate with the proximal 1 cm of seminal vesicles, depending on the status of seminal vesicles invasion and the patients anatomy but rarely are the entire seminal vesicles are included. The PTV is generated by an expansion of 2 mm the CTV in all directions except posteriorly. A 2 mm is used

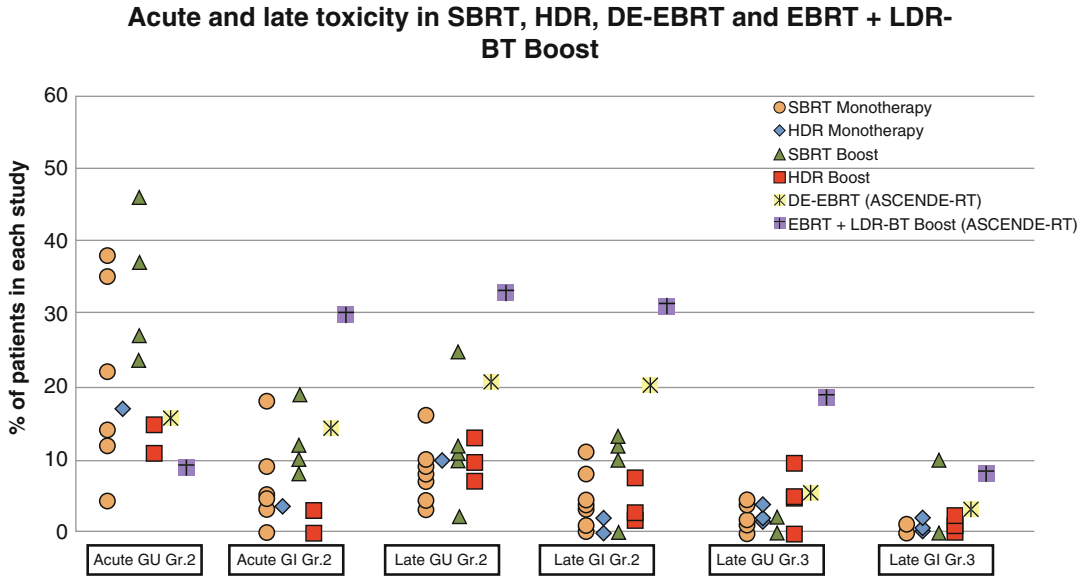

Fig. 11.4 Acute and late toxicity reported in stereotactic body radiotherapy (SBRT), high dose rate (HDR), dose-escalated external beam radiotherapy (DE-EBRT), and dose rate prostate brachytherapy (LDR BT) studies. Not all SBRT and HDR studies reported toxicity data. Three scales were used in the studies: the common terminology criteria for adverse events (CTCAE), the Radiation Therapy Oncology Group (RTOG) scale and the LENT–SOMA (late effects normal tissue task force-subjective, objective, management and analytic) scale. Modified from Gonzalez-Motta and Roach [24]

at UCSF based on data suggesting that is a sufficient margin to account for intra-fraction prostate motion using an imaging interval of 60 s [68, 69], however the margin for seminal vesicles when included should be larger than this. Regarding planning and treatment delivery, a goal would have at least 95% of the PTV being covered by the prescription dose. Limit urethra volume receiving 120% of the prescription dose (V120%) $<$ 0.035 cc and prostate CTV V120% $<$ 50% [69], minimize the volume of the rectum and bladder receiving 75% of the prescription dose (V75%) and avoid hotspots within normal tissue. At UCSF we used a method for determining rectal and bladder dose constraints achievable for a given patient's anatomy [67], the patient is usually imaged every 60 seconds, see Fig. 11.5 for fiducial tracking.

11.8 Conclusions

SBRT promises to potentially replace other forms of dose-escalated radiotherapy including HDR brachytherapy. The theoretical advantages include: (1) a learning curve considerably lower than that required to acquire the technical skills to perform high quality brachytherapy skills; (2) similar radiobiological advantages to those associated with HDR brachytherapy; (3) the absence of a need for anesthesia, particularly important in patients for whom discontinuation of anticoagulation therapy is deemed undesirable. Despite these advantages, there are limited long-term results definitively confirming the apparently acceptable low rate of late toxicity. In addition, there may be subsets of patients for whom SBRT may be contraindicated. For example, men with an extremely prominent median lobe, those with a neurologic movement disorder and some insurance companies do not provide coverage for SBRT in some states. More studies and ideally randomized studies are needed to clear the role of SBRT in HR patients. The evidence for SBRT in HR patients is based on observational studies made up of relatively few patients and represents level III evidence. SBRT, when used as a boost, appears to yield results that are similar to those obtained using HDR and appear to be at least as good as those reported with DE-EBRT, albeit

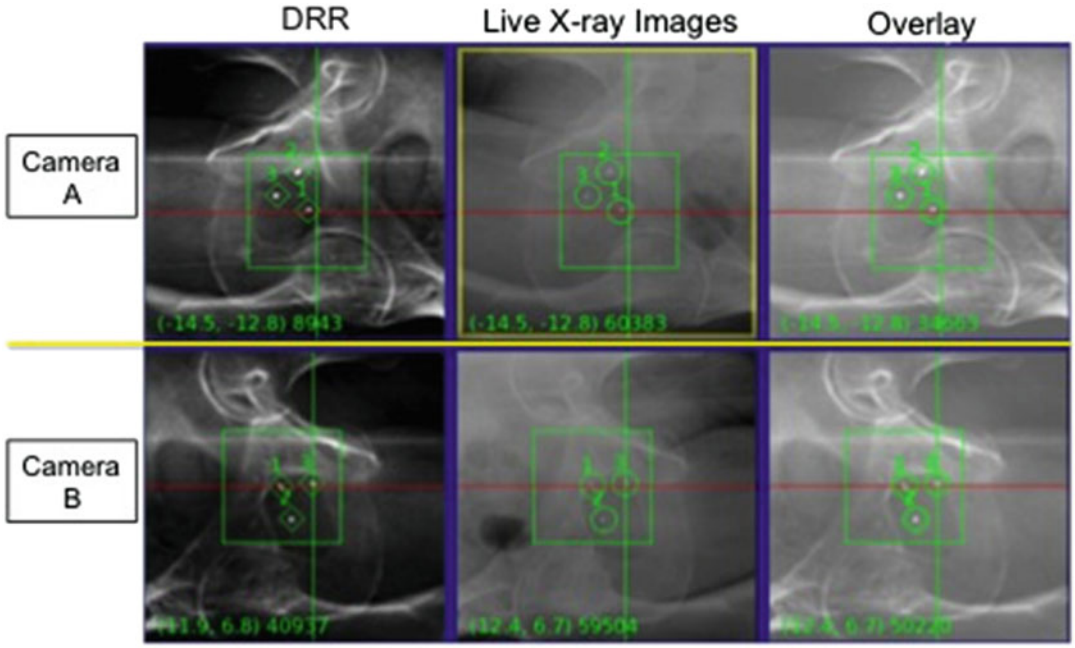

Fig. 11.5 Intrafractional fiducial tracking used for CyberKnife (CK) prostate treatments. The three gold fiducial markers placed in the prostate are visualized on orthogonal DRRs generated from planning CT (left), and on the live kV X-ray images (middle). During treatment delivery, beams are automatically re-targeted based on the registration of fiducials on the two images (right) to account for intrafractional motion (within specific translational and rotational bounds) (Figure from Wahl et al. in Genitourinary sites. In: Sethi RA, Barani IJ, Larson DA, Roach M III, editors. Handbook of evidence-based stereotactic radiosurgery and stereotactic body radiotherapy [70])

with the possibility of higher toxicity. SBRT reduces the treatment time for patients and may be preferred over BT given that it is less invasive. SBRT boost is technically less complex for practitioners, required less infrastructure and may be preferable for some patients. SBRT monotherapy should be used in HR patients only on clinical trials, but as more evidence mature in the future, its use could be more accepted.

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Salvage SBRT for Local Recurrence of Prostate Cancer After Definitive Radiotherapy

12

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Abbreviations

2nd BCR	Second biochemical recurrence
3DRT	3-Dimensionnal Radiation Therapy
AAPM	Association of Physicists in Medicine
ADT	Androgen-deprivation therapy
BCR	Biochemical recurrence
BT	Brachytherapy
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical target volume
EAU-ESTO-SIOG	European Association of Urology (EAU)–European Society for Radiotherapy & Oncology (ESTRO)–International Society of Geriatric Oncology (SIOG)
EBRT	External beam radiation therapy
GI	Gastro-intestinal
GTV	Gross tumor volume
GU	Genito-urinary
HDR	High dose-rate
HIFU	High Intensity Focused Ultrasound
IG-3D-CRT	Image-guided 3D-CRT
IMRT	Intensity Modulated Radiation Therapy
IPSS	International Prostate Symptom Score
OARs	Organ at risks
PCLR	Prostate cancer local recurrence
PSA DT	PSA doubling time
PTV	Planning target volume
PVRV	Post voiding residual volume
SBRT	Stereotactic body radiation therapy
SRP	Salvage radical prostatectomy
TRUS-biopsy	Trans rectal ultrasound biopsy

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12.1 Introduction

Prostate cancer remains the most common cancer among men in developed countries with 1,111,700 new cases in 2012 [1] and radiotherapy plays a key role in its treatment for localized tumors. However, recurrence can occur in up to 25% for high-risk localized prostate cancer after external beam radiation therapy (EBRT) or brachytherapy (BT) and more than half of these recurrences are local [2].

Actually, the most common local relapse treatment administered by physicians is androgen-deprivation therapy (ADT). But according to a literature review [3] and EAU-ESTO-SIOG guidelines [4], a local approach either by surgery

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[5–11], high-intensity focused ultra-sound (HIFU) [12, 13], cryotherapy [14] or BT [15–19] should also be considered.

Regarding BT, this re-irradiation technique appears relevant because it offers a high conformational dose in a small volume and thus, consequently decreases the dose delivered to the surrounding tissues, already irradiated during the first course of EBRT or BT. However, radiotherapy techniques recently evolved notably with high-precision stereotactic body radiation therapy (SBRT) and this technique also achieves this goal. Re-irradiation using SBRT is actually performed in many other anatomical sites with acceptable levels of efficacy and toxicity but its use for prostate cancer is not extensively described in the literature and notably in the recent guidelines.

We therefore performed a comprehensive review of the literature of the role (clinical outcomes and toxicities) of SBRT for re-irradiation of prostate cancer local recurrence (PCLR).

12.2 Material and Methods

We performed a MEDLINE/MeSH research in September 2017, using the key words: SBRT, prostate cancer, local recurrence, salvage, biochemical relapse, re-irradiation. Articles on salvage SBRT for PCLR were reviewed and we excluded unpublished data and non-English-language articles. We did not review articles concerning nodal relapse and other metastatic (bone) irradiation *which are presented in another chapter (need to be confirmed)*.

12.3 Results

From 2010 to 2017, nine articles for re-irradiation using SBRT for PCLR were published. However the case report by Arcangeli et al. [20] was excluded, the authors described a 30 Gy in five fractions regimen with TomoTherapy® with a short 6-month follow-up and no data regarding late toxicity. All the studies were monocentric, retrospective, non-randomized and non-controlled. The total number of patients (pts) was 156, with a global median follow-up of 15.7 months [range: 10–22.6 months].

12.3.1 Patients' Selection and Inclusion Criteria (Table 12.1)

Initial PCLR was defined by the association of biochemical relapse (Phoenix criteria: Nadir PSA after radiotherapy + 2 ng/ml) plus imaging data (choline PET-CT and/or MRI [T1, T2, diffusion, perfusion weighted images]) with positive biopsies when feasible.

The initial treatment was definitive 3-Dimensionnal (3D) or Intensity Modulated Radiation Therapy (IMRT) with or without ADT (101 pts), radical prostatectomy + post-operative EBRT (28 pts) and BT (28 pts). The minimum time interval between primary and PCLR was at least 2 years, except for Vavassori's study (13.5 months) [21]. The median time interval between primary treatment and salvage re-irradiation was 88 months [range: 13.5–126 months]. Seventy-one patients (45.5%) underwent ADT combined with salvage SBRT. Residual toxicities higher than grade 1 related to initial radiotherapy was considered as an exclusion criterion for most re-irradiation studies.

12.3.2 Technical Considerations (Table 12.2)

Among the eight reported studies, 146 patients (94%) were irradiated with a CyberKnife® (Accuray Incorporated, Sunnyvale, CA, USA). The median prescribed dose was 32 Gy [range: 25–36.25 Gy] in five fractions (consecutive or every other day), delivered on the 80% isodose for all studies except one. Indeed, Fuller et al. [22] used "high dose-rate brachytherapy like" SBRT prescription: 95% of the planning target volume (PTV) receiving the prescribed dose; V125 ≈ 50–60%, V150 ≈ 15–25%, V200 ≈ 0–2%.

Table 12.1 Patients' characteristics and Inclusion criteria

Author	No pts	MFU (months)	Age of initial treatment/ recurrence	Initial D'AMICO risk group: L/I/H/ NA	Initial treatment delivered: EBRT/SBRT/ S + E/BT	Median time between relapse (months)	MRI (%)	Choline TEP-CT (%)	Biopsy (%)	ADT (%)	Median PSA Before SBRT (ng/ml)
Leroy T 2017	23	22.6	NA/70	L: 7 (30.4%) I: 8 (34.8%) H: 8 (30.4%) NA: 1 (4.3%)	EBRT (83%) BT (17%)	65	100	91 (11C)	NA	61	2.5
Mbeutcha A 2017	18	14.5	62/69	L: 10 (55.6%) I: 5 (27.8%) H: 2 (1.11%) NA: 1 (5.6%)	BT (83%) EBRT (17%)	49	100	100 (11C)	NA	55	4.5
Janoray G 2016	21	11.7	NA/74	L: 3 (14%) I: 5 (24%) H: 13 (62%)	EBRT (52%) S + E (48%)	98	100	100 (18F)	NA	9	3.2
Detti B 2016	8	10	65/NA	L: 0 (0%) I: 3 (38%) H: 5 (62%)	S + E (100%)	126	100	100 (11C)	NA	0	4.1
Fuller DB 2015	29	24	NA/73	NA	EBRT (93%) BT (3.5%) SBRT (3.5%)	88	100	NA	10	24	3.1
Zerini D 2015	32	21.3	NA/73	L: 5 (16%) I: 7 (22%) H: 9 (28%) NA: (34%)	EBRT (60%) BT (9%) S + E (31%)	115	53	87 (11C)	59	34	3.1
Jereczek-Fossa BA 2012	19	16.9	NA/68	NA	EBRT (79%) S + E (21%)	66	NA	79	94	37	4.97
Vavassori A 2010	6	11.3	NA	NA	EBRT (100%)	13.5	NA	100 (11C)	NA	67	3.65

MFU median follow-up, *NA* non-applicable, D'AMICO risk groups: L = low; I = intermediate; H = high, *EBRT* external beam radiation therapy, *SBRT* stereotactic body radiation therapy, *S + E* surgery + EBRT, *BT* brachytherapy, *ADT* androgen deprivation therapy

Table 12.2 Technical specifications

Author	Dose/ f (Gy)	T. dose (Gy)	Machines used	Prostate (P)/ prostate bed (PB)	Treated volume: GTV/HG/WG	Volume GTV/CTV (cc)	Volume PTV (cc)
Leroy T	6	36	CyberKnife	23 P	GTV/HG/WG	3.7/22.8/ 29.5	34/48
Mbeutcha A	7	35	CyberKnife	18 P	GTV	26	NA
Janoray G	7.25	36.25	CyberKnife	10 P/11 PB	GTV	7.2/5.4	16.3/ 11.1
Detti B	6	30	CyberKnife	10 PB	GTV	NA	NA
Fuller DB	6.8	34	CyberKnife	24 P	GTV	21.7	NA
Zerini D	5	25	Clinac, RapidArc, CyberKnife Vero	22 P/ 10 PB	GTV/WG	NA	NA
Jereczek-Fossa BA	6	30	CyberKnife	15 P/4 PB	GTV	NA	NA
Vavassori A	6	30	CyberKnife	6 P	WG	38	NA

GTV 11 choline-TEP-CT or MRI (T1,T2, diffusion, perfusion) defined tumor, *HG* half-gland of prostate, *WG* whole gland of prostate, *CTV* clinical target volume, *PTV* planning target volume

12.3.2.1 *CyberKnife*® [17, 21, 23–27]

One to three radiopaque fiducial markers were placed into the target lesion. Three fiducial markers were usually recommended in order to take into account not only translations, but also rotations. Distance between markers had to be at least of 2 cm and fiducials had to be placed in three orthogonal plans (forming a "L" on the anterior and lateral X-ray view). Due to the risk of marker migration, a simulation CT-scan was performed 1 week later. All the patients were immobilized during CT-simulation and treatment, by the use of a customized external vacuum-type cast. The gross tumor volume (GTV) was outlined on the CT-scan, with slice thickness of 1 to 1.5 mm; either with [11C] choline PET-CT or MRI-fusion (T1, T2, diffusion, perfusion sequences). The clinical target volume (CTV) was then delineated either as the whole prostate gland, half-gland or as the GTV only depending on the number and location of positive biopsies (if any). Treatment planning software CyberKnife SRT Multiplan® (Accuray Incorporated, Sunnyvale, CA, USA) was used. A 1- to 2-mm margin was added to the CTV for the PTV to compensate the submillimeter detection inaccuracy of the fiducial marker. Fiducial marker detection was used to target the PTV during the treatment (Fiducial® algorithm). In case of the absence of fiducial markers, the Xsight-Spine® (Accuray Incorporated, Sunnyvale, CA, USA) detection system was used [24, 26]. The dose was prescribed to the mean 80% isodose by the use of non-isocentric CyberKnife treatment technique to cover at least 95% of PTV. The different prescribed doses and organs at risks dose constraints are summarized in Tables 12.2 and 12.3. The algorithm calculation used was probably Raytracing even if not mentioned, as Monte-Carlo calculation was not available at that time for CyberKnife treatment.

In order to accurately monitor the position of the target during beam delivery, radiographic images at 45° were acquired every three nodes, which is equivalent to an interval of about 40 s [28].

In order to minimize patient inconvenience and discomfort when immobilized for a long period of time, daily treatment times were kept below 45–60 min by decreasing the number of beams. This short treatment time was also important to decrease the risk of intra-fraction radiation repair, which can occur during excessively long individual sessions [29, 30].

12.3.2.2 Other Techniques

Zerini et al. [26] used different machines for re-irradiation. First, image-guided 3D-CRT (IG-3D-CRT) was used up to December 2010. Afterwards, IG-IMRT with Rapid Arc® (Varian Medical Systems, Palo Alto, CA) was implemented with a treatment schedule of 25 Gy in five fractions, given every other day within an overall treatment time of 10 days. In 2012, IG-IMRT was implemented with Vero® (BrainLab AG, Feldkirchen, Germany) and this was used together with CyberKnife® for treatment.

Arcangeli et al. [20] meanwhile used TomoTherapy® for re-irradiation using 30 Gy in five consecutive fractions daily. These techniques are not thoroughly described here because they constitute a minority of the radiotherapy techniques (<7%) used for the treatment of LRPC.

12.3.3 Organs at Risk (OAR) and Dose Constraints (Table 12.3)

The dose constraints for different OARs are summarized in Table 12.3 and are compared to the actual dose constraints used by American Association of Physicists in Medicine (AAPM) Task group 101 report for SBRT in five fractions. There was a non-homogenous dose prescription and the same applied for OAR constraints where it seemed that a particular attention was given especially for prostate bed (PB) re-irradiation with lower constraints than usual. Initial dose of radiotherapy and summation were not taken into consideration in those studies.

12.3.4 Follow Up

The median follow-up was 15.7 months [range: 10–22.6 months]. Patients were seen at least 6 weeks after re-irradiation and every 3–6 months. PSA levels and toxicity (CTCAE) were also reported at each consultation. No routine imaging re-evaluation was done. Second biochemical recurrence after salvage SBRT (2nd BCR) was defined using the Phoenix criteria. In case of 2nd BCR, imaging using [11C] choline PET-CT and/or MRI and/or biopsies were used to confirm local, nodal or distant recurrence.

12.3.5 Clinical Outcomes: Biochemical Relapse and Site of Failure (Table 12.4)

The efficacy results were heterogeneous and the main end point used was 2nd BCR. Decrease in PSA and Nadir PSA were also noted because, in some cases, PSA continued to rise after salvage SBRT. Disease-free survival was defined as the time between the first session of re-irradiation and 2nd BCR occurrence. Local recurrence after 2nd BCR was defined as increase in SUV on [11C] choline PET-CT or increase in lesion's dimension on MRI, not necessarily requiring biopsies for confirmation.

12.3.6 Toxicity (Table 12.5)

Toxicity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and 3.0 and is reported in Table 12.5. While the rate of acute $\geq$ grade 3 toxicities remains very low, no $\geq$ G3 late toxicities were reported (acute and late genito-urinary (GU) and gastro-intestinal (GI): 2 and 0%, respectively).

12.4 Discussion

In the frame of salvage local treatment in case of PCLR, SBRT shows promising results and can be considered as a potential salvage option alongside surgery, brachytherapy, HIFU or cryotherapy. Salvage SBRT provides good results in terms of side effects leading to consider that it is possible to re-irradiate an area after initial full dose radiotherapy for primary tumor or in a post-operative intent. However, good results in terms of literature review remain cautionary due to the few numbers of patients, short follow-up as well as heterogeneity regarding technical considerations.

Table 12.3 Dose constraints

OAR	AAPM/Mbeutcha	Leroy	Janoray	Detti	Fuller	Zerini/Jereczek-Fossa	Vavassori
Rectum wall	$D_{max} < 38$ Gy $D_{20\ cc} < 25$ Gy	$V_{27} < 2$ cc $V_{12} < 20\%$	$V_{18.1} < 50\%$ $V_{29} < 20\%$ $V_{36} < 1$ cc	$D_{30\%} < 18.8$ Gy $D_{60\%} < 10$ Gy	$D_{max} < 100\%$ D_{max} Mu $< 75\%$	$D_{30\%} < 13.8$ Gy $D_{60\%} < 6.69$ Gy $D_{30\%} < 8.4$ Gy (PB) $D_{60\%} < 4.08$ Gy (PB)	$D_{max} < 75\%$ NA
Bladder wall	$D_{max} < 38$ Gy $D_{15\ cc} < 18.3$ Gy	$V_{27} < 5$ cc $V_{12} < 15\%$	$V_{18.1} < 40\%$ $V_{37} < 10$ cc	$D_{40\%} < 18.1$ Gy $D_{50\%} < 16.6$ Gy	$D_{max} < 100\%$	$D_{30\%} < 10.58$ Gy	NA
Penile bulb	$D_{max} < 50$ Gy $D_{3\ cc} < 30$ Gy	NA	NA	$D_{50\%} < 29.5$ Gy	NA	NA	NA
Urethra	NA	$V_{24} < 30\%$ $V_{36} < 1$ cc	NA	$D_{max} < 33.7$ Gy $D_{med} < 31$ Gy	$D_{max} < 125\%$ $D_{50} < 105\%$	NA	$D_{max} < 125\%$
Femoral heads	$D_{10\ cc} < 30$ Gy	NA	$V_{14.5} < 5\%$	V14.5 $< 5\%$	NA	NA	NA
Small bowel	NA	NA	NA	NA	NA	$D_{1\ cc} < 21$ Gy	NA

American Association of Physicists in Medicine (AAPM) Task group 101 report for SBRT in five fractions
PB prostate bed

Table 12.4 Salvage SBRT efficacy

Author	MFU (months)	No pts	PSA decrease	Nadir PSA (ng/ml)	Months for PSA nadir	Median DFS (months)	Local relapse	1 year BFS (%)	2 year BFS (%)	Last follow up (other criteria)
Leroy T	22.6	23	19 (82%)	0.35	8	27	5 (22%)	100	54	2 year-OS: 100% 1 year-local DFS: 100% 2 year-local DFS: 76%
Mbeutcha A	14.5	18	13 (72%)	1	7.5	5.5	1 (5%)	NA	NA	LR recurrence: 20% M^+ relapse: 6.7% @ 5 months
Janoray G	11.7	21	18 (86%)	NA	NA	NA	1 (4%) @ 15.2 months	83.3	NA	1 year-BCR-free survival: 83.3%
Detti B	10	8	7 (88%)	0.8	NA	9.3	0	NA	NA	M^+ relapse: 5 (62.5%)
Fuller DB	24	29	NA	0.16	24	NA	0	NA	82	NED: 40.6% Active disease: 46.9% Death: 12.5% BCR alone: 9% R-relapse: 3% M^+ relapse: 22%
Zerini D	21.3	32	NA	NA	NA	9.4	4 (13%)			Disease progression: 33% (P), 50% (PB)
Jereczek-Fossa BA	16.9	19	17 (89%)	NA	NA	10	3 (19%)			BFS: 33% BCR alone: 1 (17%) R-relapse: 1 (17%) M^+ relapse: 2 (34%)
Vavassori A	11.3	6	NA	NA	NA	8.4	NA			

BFS biochemical free survival, *NED* no evidence of disease, *LR*, loco-regional, *M+* metastatic, *R-relapse* regional relapse, *PB* prostate bed

Table 12.5 Acute and late toxicities after salvage SBRT

	Complications								
	Acute				Late				
	GU		GI		GU		GI		
Authors	G < 3	G ≥ 3	G < 3	G ≥ 3	G < 3	G ≥ 3	G < 3	G ≥ 3	Remarks
Leroy T	21	2	23	0					1 G3 neuralgia
Mbeutcha A	18	0	18	0	17	1	18	0	
Janoray G	4	0	2	0	1	0	0	0	
Detti B	1	0	1	0	0	0	0	0	
Fuller DB	NA	1	NA	NA	3	2	0	0	Urethral obstruction + hemorrhagic cystitis
Zerini D	8	0	4	0	8	0	5	0	
Jereczek-Fossa BA	5	1	1	0	2	1	0	0	
Vavassori A	NA	0	NA	0	NA	0	NA	0	

GU geniton-urinary, *GI* gastro-intestinal, *G* grade

12.4.1 Comparison with Other Treatments Available

With a small total number of patients (157) and a short median follow-up (14.5 months), the use of salvage SBRT must be discussed both with the patient and the medical team. By pooling the results of 64 publications with a total number of 4564 pts, a median study size of 40 [range: 4–404] and a median follow-up of 54 months [range: 5–121 months], Philippou et al. reported the clinical outcomes of salvage surgery, brachytherapy, HIFU or cryotherapy. All modalities included, the authors noticed an relapse rate close to 50% with 30% of incontinence, 70% of impotence and 17% of urethral strictures (with 2% of fistula) [31]. The authors acknowledged that they are no significant differences in oncologic outcomes among the salvage modalities but suggested that salvage radical prostatectomy (SRP) may have worse functional outcomes, particularly in terms of incontinence.

12.4.2 Volume Definition

Regarding technical considerations, the definition of the target volume as salvage treatment remains debatable. Many studies using SBRT considered GTV (from MRI or PET-CT) or biopsy mapping (+1–2 mm margins) as target volume. However, prostate cancer is often a multi-focal disease, with risk of extra-capsular involvement and a poor diagnosis sensitivity despite assessment using both TRUS-biopsy and MRI [32]. However, even by using focal re-irradiation in many studies, the local recurrence rate remains quite low (14 patients) even though the follow-up is too short to confirm this trend. Meanwhile, re-irradiation of the whole gland does not seem to differ in term of toxicity and therefore, focal re-irradiation should be considered with caution even if it seems to be a safe procedure to limit re-irradiation volume, thus decreasing the risk of toxicity.

12.4.3 Dose of Initial EBRT Treatment

Regarding initial treatment dose, actual outcomes with dose escalation have indicated significant gains compared with the lower doses of EBRT, and men are less likely to present with such advanced disease. These improvements in disease presentation and EBRT delivery would theoretically make the risks of local relapse less likely. On the other hand, since patients are now usually treated with higher radiation doses for their

primary therapy (76–80 Gy), it is still unknown whether morbidity from a salvage local therapy will be more severe and thus overcome the potential benefit of a re-irradiation course.

12.4.4 Dose Constraints and Optimal Dose for Tumor Control

Dose constraints for re-irradiation are non-homogeneous with either the use of HDR-like brachytherapy constraints or, in certain studies, re-irradiation is done without considering the dose of initial treatment as the delay between first treatment and relapse was quite long. However, special care was taken in dose constraints in prostate bed re-irradiation as multi-modality treatment by surgery and radiotherapy at first treatment may increase toxicity rate. Meanwhile, Zelefsky et al. provided evidence in the ASTRO meeting 2017, that SBRT dose inferior to 35 Gy in five fractions may be sub-optimal in terms of 2-year PSA level and 2-year biopsy outcomes. Dose up to 40 Gy in five fractions seemed well tolerated and the conclusion was that randomized trials would be needed to establish the dose and dose per fraction of SBRT that achieve optimal local control [33]. Therefore, the same may be applied for salvage SBRT for local recurrence.

12.4.5 ADT Before Treatment

ADT is known as a palliative treatment with no benefit on survival [34], even administered early [35] and it has deep impacts on quality of life [36]. In these studies, ADT was added together with SBRT in 71 pts and can therefore be confounding factor for efficacy. The main objective of using salvage local treatment is to postpone the use of ADT due to its toxicity and impact on quality of life. On the other hand, the role of ADT + standard fractionation EBRT is very well established mainly for high-risk patients. But is ADT justified with highly hypofractionated SBRT re-irradiation? Especially considering the low PSA rate at PCLR, insufficient or irrelevant information concerning T-stage or Gleason score after primary radiotherapy.

12.4.6 Machine Consideration

CyberKnife® seems to be the main machine used for this re-irradiation scheme as it was one of the first machine that had continuous tracking of lesions using fiducials. The machine has sub-millimeter high-precision dose delivery and it allows the use of GTV to PTV margins of 1–2 mm only, hence decreasing the volume of re-irradiation and the risk of toxicity. Actually, there are many new machines capable of continuous tracking (Vero®, True Beam Novalis STX. . ..) and even the use of more ancient conventional 3D or IMRT machines seem feasible in term of toxicity.

12.4.7 Patients' Selection Criteria

In most studies, BCR with imaging local recurrence (PET-CT or MRI) is the inclusion criteria for patients. Biopsies were not mandatory and MRI was not always performed. Even though there is no clear evidence of which patients should benefit salvage treatment, there is a general consensus that salvage treatment should be reserved for patients who have documented recurrent local disease of limited aggressiveness (low Gleason score, stage and initial PSA), a long time interval between primary external beam radiotherapy (EBRT) and recurrence and a slow PSA evolution [4, 37].

EAU-ESTRO-SIOG guidelines [4] recommend biopsy status as a major predictor of outcome and histologic proof of PCLR should be obtained at least 18–24 months after initial EBRT given the morbidity of local salvage treatment [38, 39]. MRI can be used for biopsy targeting and guidance of local salvage treatment. Choline PET/CT is also feasible but with a poorer spatial resolution than MRI [40, 41]. However, men with PSA doubling time (PSA DT) < 3 months, T3b or higher stage, Gleason 8–10,

time to BCR < 3 years are at high risk of developing metastases and die from prostate cancer.

Meanwhile, in case of PCLR, a Delphi consensus was proposed by the Uro-GEC groupe [37] for salvage brachytherapy after radiotherapy, suggesting other criteria for salvage treatment such as:

- 80 years old as maximum age limit,
- Life expectancy of at least 5 years,
- Eastern Cooperative Oncology Group/World Health Organization = 1,
- T3b at primary diagnosis or time of relapse,
- Any Gleason score or any lesion size or ADT adjuvant or salvage accepted,
- Any PSA level accepted at first diagnosis and at relapse, maximum PSA level: 10 ng/ml,
- PSA doubling time (PSA DT) > 6 months,
- Nadir PSA after primary treatment of minimum 1.1–1.3 ng/ml,
- International Prostate Symptom Score (IPSS) minimum: 8–15,
- Maximum urinary flow (Qmax) at least 8 ml/s,
- Post voiding residual volume (PVRV) maximum at 200 ml,
- Need for combination of ultra-sound and MRI and minimum of 12–24 biopsies if whole gland treatment is proposed,
- Need to search for metastatic disease either with Choline PET or bone scan,
- Time interval between primary and relapse at least 2 years,
- Dose to primary treatment not taken into account,
- ADT not to be given as salvage treatment.

12.5 Conclusion

SBRT seems to be a safe salvage treatment for local recurrence of prostate cancer. Its long-term efficacy and toxicity as well as optimal total dose and dose per fraction remains to be determined by further studies but patients' selection is the mainstay for success of salvage treatment in case of PCLR.

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13 Dose Escalation for Prostate Cancer Using Oligofractionated, Stereotactic Ablative Radiotherapy

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13.1 Oligofractionated, Ablative Radiotherapy

"Conventional fractionation," or daily fraction sizes of 1.8–2 Gy given Monday–Friday over many (6+) weeks, has been the norm for several decades in radiation oncology, but has certainly not always been the case. Early radiation cancer treatments at the beginning of the 1900s were primarily hypofractionated given in days to a few weeks, with the skin being the primary dose-limiting structure. At the time, practitioners did not have a full understanding of tissue tolerance and dosimetry, and necessary quality assurance measures were not in place. Most irradiated fields were very large to increase the likelihood of encompassing all visible and potential cancer deposits. As a result, significant late skin and other organ toxicity was often observed for a given clinically acceptable tumor response. Following the studies by Henri Coutard presented in the 1930s, which demonstrated that extended courses of fractionated external beam radiation therapy could elicit significant tumor response in cancers of the head and neck with decreased toxicity compared to hypofractionation with the same techniques [1], there was a migration of treatment trends away from high-dose-per-fraction hypofractionation courses to low-dose-per-fraction "conventional" courses.

In the 1950s, Lars Leksell investigated the use of high-dose single session radiation delivery for ablating dysfunctional areas in the brain and later for tumor targets [2]. His approach was made possible through the use of a distributed multi-beam approach and rigid immobilization, as well as limiting the irradiated target volume to the tumor itself without typical large margins. This reduced the volume of normal tissue that would be damaged by these large ablative doses of radiation and led to a well-documented positive clinical experience. The first reported use of this approach outside of the brain was reported by Hamilton and colleagues again using rigid fixation to treat spine lesions [3]. SAbR delivery of 8–10 Gy in a single fraction in patients with progressive metastases after conventionally fractionated radiotherapy led to good subsequent control. Later, Lax and Blomgren at the Karolinska Institute in Sweden reported on the use of hypofractionated, high-dose-per-fraction radiation treatment regimens (with minimum doses ranging from 7.7 Gy to 45 Gy in 1–4 fractions) in the 1990s for

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extracranial sites including the lung and liver using improved immobilization techniques and motion management [4]. Also in the 1990s, Uematsu and colleagues in Japan developed and tested techniques to deliver stereotactic radiation to primary and metastatic lung tumors, delivering doses of 30–75 Gy in 5–15 fractions over 1–3 weeks [5].

These high-dose-per-fraction treatments, called ablative because normal tissue function of tissue is disrupted in the higher dose regions, delivered to precisely defined targets using comprehensive immobilization, motion management, and image guidance have been called extracranial stereotactic radioablation (ESR) [6], then stereotactic body radiation therapy (SBRT) [6, 7], and now stereotactic ablative radiotherapy (SAbR) [8]. While the technology is constantly improving, defining characteristics of SAbR include [9]: (1) fixation/immobilization to limit patient movement for the duration of setup and treatment; (2) accurate and reproducible repositioning from initial simulation throughout treatment; (3) minimization of normal tissue exposure attained by using multiple ($\geq$10) and/or non-coplanar or large-angle arcing small aperture fields; (4) assessment and management or limitation of organ motion (respiratory or otherwise); (5) stereotactic registration (via fiducial markers or surrogates) of tumor targets and normal tissue avoidance structures to the treatment delivery system; and (6) ablative dose fractionation delivered to the patient with millimeter accuracy. (Figure 13.1 provides examples of multiple types of SAbR treatment plans)

13.2 Radiobiologic Modeling of Oligofractionated Radiation Therapy with SAbR

The classically understood mechanism of ionizing radiation-induced tumor cell killing is based on damage to DNA via single- and double-strand breaks from direct (damage of DNA molecules directly from interactions with ionizing particles) and indirect (damage of DNA from free radicals and other chemical species produced near the DNA target by ionizing effects of radiation on non-DNA molecules) effects. The linear-quadratic (LQ) model describes cell killing as a single hit versus double hit hypothesis, where the linear cell kill is expressed by the α component, while the quadratic cell kill is expressed by the β component [10, 11]. The α/β ratio is obtained either from curve fitting of a second order polynomial to the in vitro cell survival curve within the shoulder region or clinically from isoeffect curves using the survival fractions of a cell line at different doses per fraction [12]. In general, a high α/β ratio predicts increased response to low dose per fraction radiation appearing soon after initiation of treatment, while a lower α/β ratio predicts response occurring at higher cumulative dose and appearing considerably later in time. Most malignant tumors typically possess a high α/β ratio (approximately 8–10) relative to normal tissues, which demonstrate lower α/β ratios (approximately 1–4) making a strong case for conventionally fractionated radiotherapy [13]. The LQ model seems to predict biological effective dose (BED) accurately for fraction sizes less than 3.25 Gy [14]; above these doses, it is less predictive for tumor response [14–17].

Analysis and review of clinical outcomes has lent support to a low α/β for prostate cancer of approximately 1.5 [18–22]; these generally represent pooled analyses over a range of Gleason scores, but dominated by lower grade disease. This has formed the basis for several multi-center, randomized controlled trials of modestly larger doses per fraction (on the order of 2.5–3.5 Gy per fraction) versus conventional doses per fraction (1.8–2 Gy per fraction) [23–33]. While no moderately hypofractionated regimen has demonstrated clearly superior oncologic outcomes to conventional fractionation in primary endpoint analysis, one has suggested sub-group benefit in those with high PSA [26], and several have demonstrated non-inferiority (i.e. CHHiP [23], NRG/RTOG 0415 [25]) with minimal differences in acute or late GU and/or GI toxicity. Altogether, these trials show that with care treatment can be delivered much more quickly and conveniently using equivalent effective doses with moderate hypofractionation, without compromising PSA control or incurring

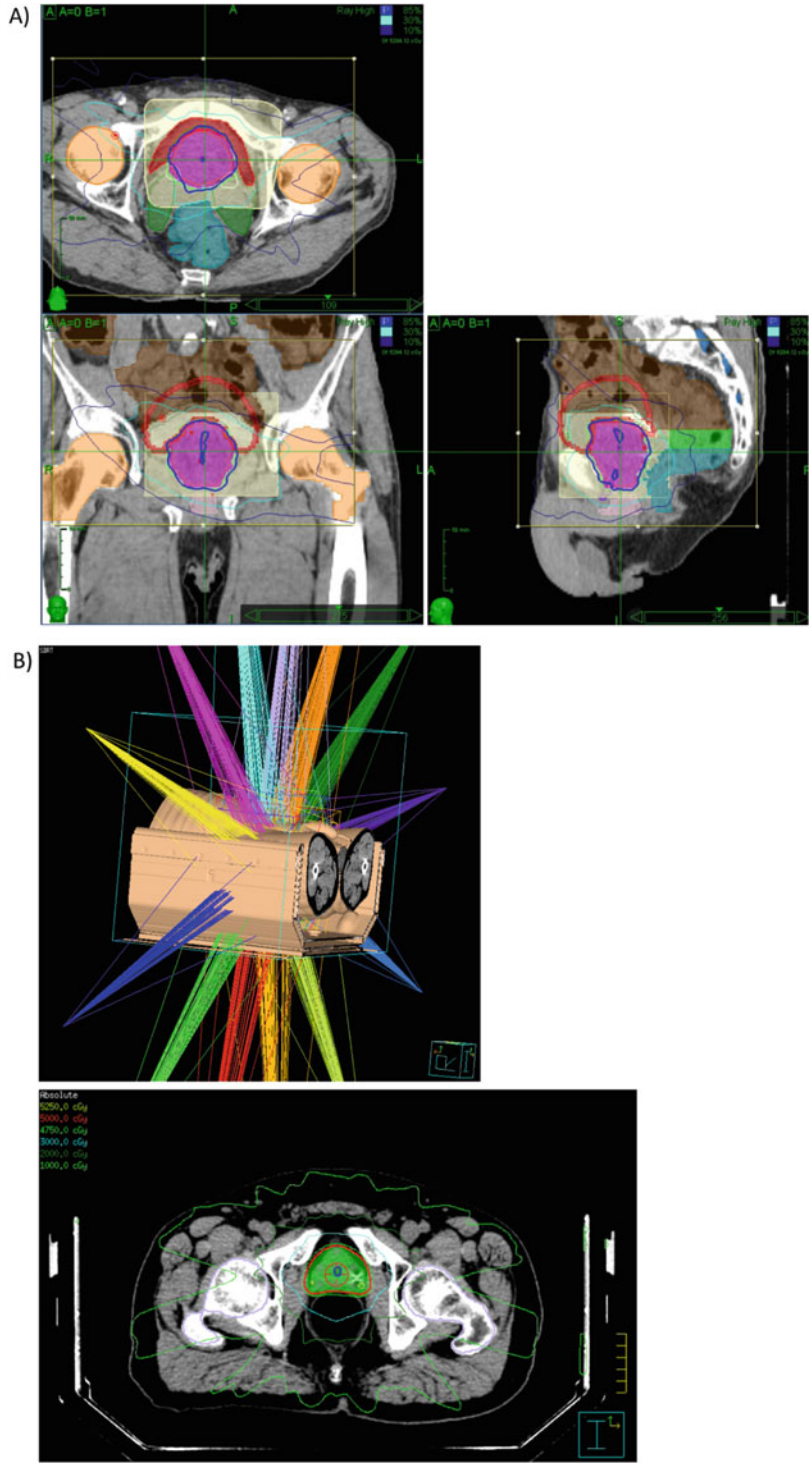

Fig. 13.1 Representative prostate SAbR planning images; (**a**) CyberKnife plan to 45 Gy in 5 fractions, prescribed to 85% isodose line; axial, sagittal, and coronal planes shown. (**b**) 13-field SBRT to 50 Gy in 5 fractions, rectal balloon fixation; top image shows the beam arrangement, lower image an axial dose distribution. (**c**) Volumetric modulated arc (VMAT) plan to 45 Gy in 5 fractions with temporary hydrogel spacer; 4 arcs used; axial, sagittal, and coronal planes shown

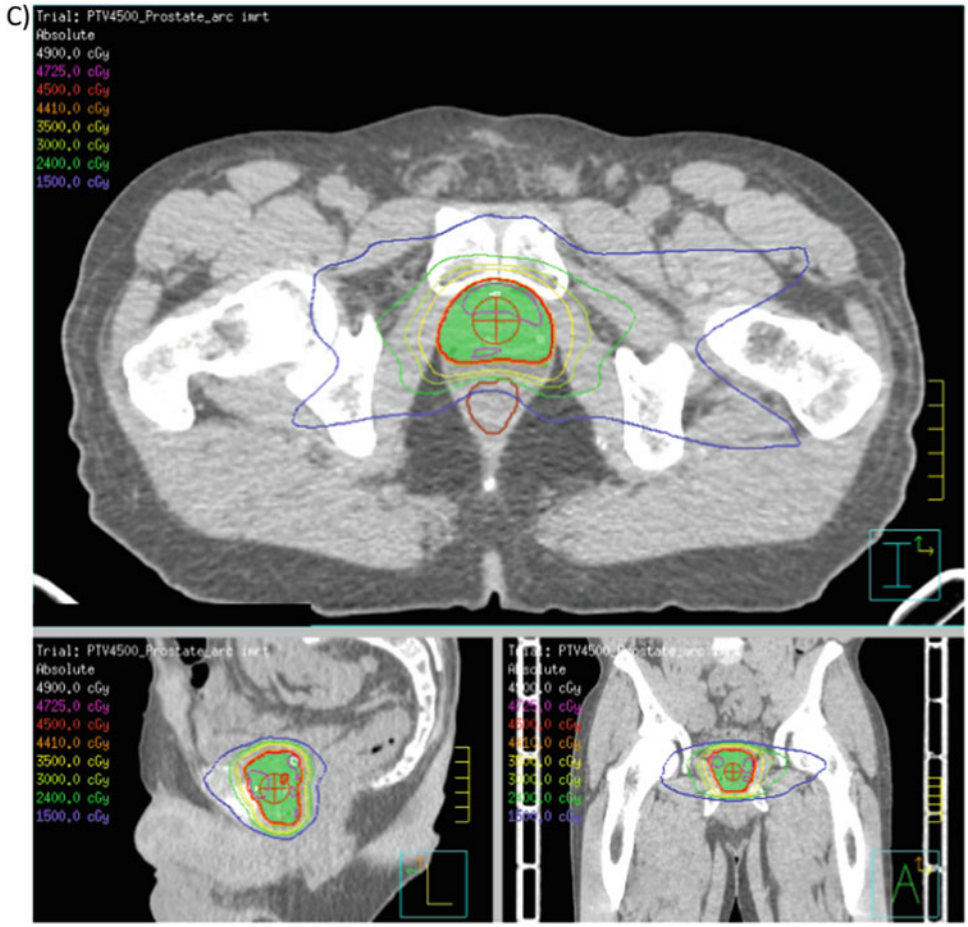

Fig. 13.1 (continued)

significant toxicity, and lend support to the concept of a relatively lower α/β ration for prostate cancer.

At the higher dose-per-fraction regimens used in ablative SAbR regimens with fraction sizes above 6 Gy and commonly called oligofractionation (oligo=few), alternative models have been proposed to more accurately predict the responses of tumors to these higher dose regimens treating past the shoulder of LQ applicability and helped build a theoretical foundation for SAbR, including the universal survival model/curve [34], the modified linear quadratic model (LQL) [16], and the generalized linear quadratic model [14]. Data exists for many cell types in the universal survival model; focusing on prostate cancer, two cell lines are available that assist in modeling of radiation response in low and high grade prostate cancer [35]; these include the DU-145 prostate cancer cell line ($\alpha/\beta = 3$, $Do = 1.91$, $Dq = 1.25$, transition dose = 3.5 Gy, with parameters akin to lower Gleason grade disease) and the PC-3 prostate cancer cell line ($\alpha/\beta = 8.9$, $Do = 1.06$, $Dq = 1.02$, transition dose = 4.2 Gy, with parameters akin to high Gleason grade disease).

For a relatively standard conventional course of radiation therapy to 81 Gy in 45 fractions, the biological equivalent dose (BED) for the DU-145 cell line assuming an α/β of 2.99 in the LQ model would be 130; in 2 Gy equivalents, this would be 77.8 Gy. For a high-dose SAbR treatment of 45 Gy in 5 fractions, the biological equivalent dose (BED) assuming an α/β of 2.99 in the LQ model would be 181; in 2 Gy equivalents, this would be 108.2 Gy. But this is an overprediction based on assumptions inherent to the LQ model.

Application of the universal survival model to this high-dose regimen suggests that for low Gleason grade (DU-145 model), 45 Gy in 5 fractions would have a 2 Gy equivalent of 78.4 Gy or 1.8 Gy equivalent of 81.7 Gy. Thus, prostate cancer treatment with escalated dose per fraction in this range should theoretically allow for at least comparable oncologic outcomes in far fewer treatments than more protracted conventional courses.

13.3 Review of Dose Escalation Studies with SAbR in Prostate Cancer

The majority of prostate cancers diagnosed in the US are organ-confined on initial presentation, and are typically treated with radical prostatectomy or radiotherapy [36]. Increasing the total dose per fraction using conventional fraction sizes has been associated with improved biochemical control in many published series. Long term results from a dose escalation trial reported by Kuban et al. comparing 70–78 Gy in conventional fraction sizes showed that at a median followup of 8.7 years, freedom from biochemical or clinical failure was improved at higher doses, 59% in the 70 Gy arm vs 78% in the 78 Gy arm [37]. Similarly, a randomized trial incorporating proton therapy reported by Zietman et al. comparing patients treated to a total dose of either 70.2 Gray equivalents (GyE) or 79.2 GyE demonstrated 10 year freedom from biochemical failure rates of 67.6% at low dose vs 83.3% at high dose, respectively [38]. At higher doses, biochemical recurrence free survival rates at 8 years of 85% for low risk prostate cancer and 76% for intermediate risk cancer were observed at 81 Gy in 45 fractions [39]; escalation to 86.4 Gy showed biochemical recurrence free survival rates at 7 years of 81.4% in patients with intermediate risk cancer, with the addition of low- or high-dose rate brachytherapy boost increasing biochemical recurrence free survival rates at 7 years to 92% in the same risk group [40]. Registry analysis from the National Cancer Database also suggests a survival advantage for patients with intermediate and high-risk disease treated with conventionally dose-escalated regimens [41]. These results can be achieved with acceptably low toxicity using modern conformal techniques, however at the increased cost and inconvenience of delivering a large number of fractions, 5 days a week over 8–9+ weeks. While biochemical control is clearly improved with conventionally fractionated dose escalation, the similar α/β ratio between tumor and surrounding tissue limits therapeutic gain. In these circumstances, perhaps a more convenient treatment approach using hypofractionation, even oligofractionation, might be a reasonable approach.

These approaches have a well-grounded historical basis; oligofractionation was in fact first established as a treatment technique for localized prostate cancer by Lloyd-Davies et al. at St. Thomas' Hospital in England using a six-fraction regimen of 36 Gy given twice weekly from 1966 to 1984 [42]. These treatments were performed in the pre-PSA era and are difficult to compare to modern outcomes data, but overall patients did reasonably well with manageable toxicity, including moderate acute urinary urgency and tenesmus, and occasional chronic rectal bleeding, as well as two reported rectal strictures. In terms of modern image-guided oligofractionated approaches at 6.5–10 Gy per fraction, summarized in Table 13.1, the first experience reported was the Stereotactic Hypofractionated Accurate Radiotherapy of the Prostate (SHARP) trial by Madsen et al., which described the results from a phase I/II trial at the Virginia Mason Medical Center [43]. In this study, 40 men with low-risk disease (Gleason score $\leq$6, PSA $<$10 ng/mL and clinical stage $\leq$T2a) were treated with 5 fractions of 6.7 Gy per fraction for a total dose of 33.5 Gy using non-coplanar conformal fields. The prostate plus a 4–5 mm margin was treated, with daily image guidance using implanted fiducial markers. At a median follow-up of 41 months, 4-year actuarial freedom from biochemical recurrence (FFBR) was 90%. There was one acute Grade 3 GU toxicity (urinary retention requiring catheterization) and no acute Grade 4–5 toxicities. Late Grade 2 GU and GI toxicity rates were 20 and 7.5% respectively, with no Grade 3 or higher toxicities.

The feasibility of further increasing SAbR dose was then investigated by King et al. at

Table 13.1 Summary of selected prostate SAbR studies

Study	Institution(s)	Trial type	Platform	Patients (N)	Eligibility	Dose regimens	Target/margin	Followup (years)	bRFS	Toxicity
Madsen [43, PMID 17336216]	Virginia Mason Medical Center	Prospective, Phase I/II	LINAC	40	Low-Risk	6.7 Gy × 5 fractions	Prostate + 4–5 mm	3.4	90% at 4 years	Acute G3 GU 2.5% Late G2 GU 20%, G2 GI 7.5%
King [44, PMID 21300474]	Stanford	Prospective, Phase II	CyberKnife	67	Low- and Int-Risk	7.25 Gy × 5 fractions	Prostate + 3–5 mm	2.7	94% at 4 years	Late G2 GU 5%, G3 GU 3.5%, Late G2 GI 2%
Katz [45, PMID 25229051]	Winthrop	Prospective, Phase II	CyberKnife	304	Low-, Int-, and High-Risk	7 Gy × 5 fractions 7.25 Gy × 5 fractions	Prostate + 5 mm (3 mm posterior)	2.5	97% at 5 years, LR 90.7% at 5 years, IR 74.1% at 5 years, HR	Late G2 GU 14%, G2 GI 7%
Katz Update [46, PMID 25229051]	Winthrop	Prospective, Phase II	CyberKnife	477	Low- and Int-Risk	7 Gy × 5 fractions or7.25 Gy × 5 fractions	Prostate + 5 mm (3 mm posterior)	6.0	95.6% at 7 years, LR 89.6% at 7 years, IR	As above, plus Late G3 GU 1.7%
Boyer [47, PMID 28086825]	Duke/Multi-Institutional	Prospective, Phase II	LINAC	60	Low- and Int-Risk	7.4 Gy × 5 fractions	Prostate + 5 mm (3 mm posterior)	2.3	Not reported	Late G2 GU 6.7%, G2 GI 8.3%, G3 GI 1.7%
Jackson [48]	Michigan/ Multi-Institutional	Prospective, Phase II	LINAC	66	Low- and Int-Risk	7.4 Gy × 5 fractions	Prostate + 3 mm	3.0	100% at 3 years	Acute G2 GU 23%. GI 4% Late G2 GU 9%, G2 GI 4%
Meier [49]	21 Community, Regional, and Academic Hospitals	Prospective, Phase II	CyberKnife	309	Low- and Int-Risk	8 Gy × 5 fractions (prostate) 7.25 Gy × 5 fractions (seminal vesicles)	Not reported	12.2	97.3% at 5 years, LR 97.1% at 5 years, IR	G2 GU 35%, G3 GU 1.6%; G2 GI 10%
Mantz [50, PMID 25452933]	Twenty-first century oncology	Prospective, Phase II	LINAC	102	Low- and Int-Risk	8 Gy × 5 fractions	Prostate + 2 mm	5.0	99% at 5 years	Acute G3 GU 2%

Zelefsky [51]	MSKCC	Prospective, Phase I	LINAC	136	Low- and Int-Risk	6.5 Gy × 5 fractions 7 Gy × 5 fractions 7.5 Gy × 5 fractions 8 Gy × 5 fractions	Prostate + 5 mm (3 mm posterior)	5.5 4.5 3 2.5	83% at 3 years 85% at 3 years 90% at 3 years 98% at 3 years	32.5: Acute G2 GU 13.3%, G2 GI 0%; Late G2 GU 13.3%, G2 GI 3.3% 35: Acute G2 GU 8.6%, G2 GI 5.7%; Late G2 GU 14.3%, G2 GI 0% 37.5: Acute G2 GU 13.9%, G2 GI 3.2%; Late G2 GU 8.3%, G2 GI 2.8% 40: Acute G2 GU 6.5%, G3 GU 0.7%, G2 GI 3.2%; Late G2 GU 9.7%, G2 GI 0%
Hannan [54, PMID 27035363]	UTSW/ Multi-Institutional	Prospective, Phase I/II	LINAC/ Tomotherapy	91	Low- and Int-Risk	9 Gy × 5 fractions 9.5 Gy × 5 fractions 10 Gy × 5 fractions	Prostate + 3 mm	4.5	100% at 5 years, LR 98.6% at 5 years, IR	Acute G2 GU 29.7%, G2 GI 20.9% Late G2 GU 20.9%, G3 GU 4.4%, G2 GI 13.2%, G3-4 GI 6.8% (G4 GI 1.6%)
Folkert [56]	UTSW/ MSKCC	Prospective, Phase II	LINAC/ CyberKnife	44	Low- and Int-Risk	9 Gy × 5 fx	Prostate + 3 mm	1.0	100% at 1 years	Acute G2 GU 36.4%, G3 GU 4.5%; G2 GI 22.7%

Stanford University in a phase II trial [44]. 36.25 Gy in 5 fractions of 7.25 Gy was delivered to the prostate plus a 3–5 mm margin, using a robotic linear accelerator technique. In 67 patients with low- to intermediate-risk features (Gleason score 6(3 + 3) or 7(3 + 4), PSA ≤10 ng/mL and clinical stage ≤T2b), at a median followup of 2.7 years, the 4-year biochemical relapse free survival was 94%. There were no Grade 4 or higher toxicities. Late Grade 2 and 3 GU toxicity rates were 5 and 3.5%, respectively. Late Grade 2 GI toxicity was 2%, with no ≥Grade 3 toxicities observed.

The largest reported single-institution study of prostate SAbR using a robotic linear accelerator technique is from Katz et al. at the Winthrop University Hospital [45]. 304 patients (69% low-risk, 27% intermediate-risk, 4% high-risk) were treated. The first 50 patients received 35 Gy in 5 fractions of 7 Gy with the subsequent 254 patients receiving 36.25 Gy in 5 fractions of 7.25 Gy. Fiducials were used, and the prostate was treated as well as a 5 mm PTV expansion, limited to 3 mm posteriorly. Lower-dose patients had a median follow-up of 30 months and the higher-dose patients a median follow-up of 17 months; actuarial 5-year biochemical recurrence-free survival was 97% for low-risk, 90.7% for intermediate-risk, and 74.1% for high-risk patients. There were no Grade ≥3 acute complications. Late Grade 2 GU and GI toxicity was 14 and 7%, respectively. Five patients had late Grade 3 GU toxicity with no late Grade ≥4 toxicities. In a more recent update of their prospective experience with low- and intermediate risk prostate cancer patients, Katz et al. reported on outcomes for 477 patients (67.9% low-risk, Gleason score 6 and PSA <10 ng/mL; 32.1% intermediate risk, Gleason score 7 or PSA 10–20 ng/ml) treated to 35–36.25 Gy in 5 fractions. At a median followup of 72 months, their actuarial biochemical recurrence free survival was consistent with their prior report, 95.6% for low-risk patients and 89.6% for intermediate risk patients. No Grade ≥3 acute GI or GU toxicities were observed, and 1.7% of patients experienced a late Grade 3 GU toxicity, all in the 36.25 Gy in 5 fraction cohort. No Grade ≥3 GI toxicities were observed [46].

Boyer et al. reported on a Phase II study of SAbR using linear-accelerator multi-field or arc-based treatments, in which 60 patients with cT1c-T2c prostate cancer with Gleason score 6 and PSA ≤15 ng/ml or Gleason score 7 with PSA ≤10 ng/ml were enrolled (33% low- and 67% intermediate-risk), and treated to 37 Gy in 5 fractions. The target was the prostate plus a 5 mm PTV expansion, limited to 3 mm posteriorly, and either implanted transponders (Calypso) or ExacTrac system and/or cone beam CT with fiducial markers was used for target registration. While oncologic outcomes data is not yet available, the treatment was very well tolerated with no Grade ≥3 GU toxicity, and only 6.7% late Grade 2 GU toxicity; there was 1.7% Grade 3 GI toxicity, and 8.3% late Grade 2 GI toxicity [47].

In a trial published by Jackson et al., 66 patients with low- (49%) or intermediate-risk (33% favorable, 18% unfavorable) prostate cancer were accrued to a phase II trial at five centers. Treatment consisted of 5 fractions of 7.4 Gy to a total dose of 37 Gy using conventional linear accelerator radiation delivery. Electromagnetic transponders were utilized for motion management, and a 3 mm uniform PTV expansion was used. At a median followup of 36 months, there have been no biochemical recurrences. No Grade ≥3 GU or GI toxicity was observed; acute Grade 2 GU toxicity was seen in 23% of treated patients, and 9% late Grade 2 GU toxicity was observed. Acute or late Grade ≥2 GI toxicity was noted in 4 and 5% of treated patients, respectively [48].

A multi-center phase II trial of low- and intermediate-risk patients performed at 21 community, regional, and academic hospitals was presented at the ASTRO 2016 Annual Meeting by Meier et al. [49]. In this study, 309 patients (55.7% low- and 44.3% intermediate-risk) were treated with robotic linear accelerator techniques to 40 Gy in 5 fractions to the prostate, and 36.25 Gy in 5 fractions to the seminal vesicles. At a median followup of 61 months, they noted actuarial 5-year biochemical recurrence free survival of 97.3% for low- and 97.1% for intermediate risk patients. Five (1.6%) Grade ≥3 GU toxicities were noted, and Grade 2 GU toxicities were experienced by 35% of patients; no Grade

≥3 GI toxicities were noted, with Grade 2 GI toxicities noted in 10% of treated patients.

In a Phase 2 trial reported by Mantz et al. using linear-accelerator multi-field or arc-based treatments and real-time target tracking with implant transponders, 70 patients with Gleason score 6(3 + 3) and 32 patients with Gleason score 7(3 + 4) prostate cancer received a total of 40 Gy in 5 QOD fractions. The target was the prostate alone with a uniform 2 mm PTV expansion. At a minimum followup of 5 years for the cohort, only one patient had experienced biochemical recurrence. Grade 3 acute GU toxicity was observed in 2% of patients, with no late Grade ≥3 GU or ≥2 GI toxicity [50].

Zelefsky et al. recently reported on the largest progressive series of dose escalation for low-and intermediate risk prostate cancer, bridging the dose ranges reported above from 6.5 to 8 Gy per fraction in 5 fractions to a total dose of 32.5–40 Gy [51]. In their Phase 1 study, 136 patients with low- and intermediate- risk prostate cancer received conventional linear-accelerator based SAbR at escalating radiation dose levels. The initial dose level was 32.5 Gy in 5 fractions delivered QOD, and then escalated by 2.5 Gy increments after dose level accrual and the protocol-specified safety observation period was completed. Accordingly, 30 patients received 32.5 Gy in 5 fractions, 35 patients received 35 Gy in 5 fractions, 36 patients received 37.5 Gy in 5 fractions, and 35 patients received 40 Gy in 5 fractions. At a median followup for the increasing dose levels of 66, 54, 36, and 30 months, respectively, the 3-year biochemical recurrence free survival rates were 83, 85, 90, and 98%, respectively. Patients underwent a post-treatment biopsy at 2 years. The incidence of a positive post-treatment biopsy was 45, 12, 17, and 5%, respectively, for the four dose arms ($P < 0.001$), correlating closely with the PSA outcomes. The incidence of acute Grade 2 GI toxicities for dose levels 1–4 were 0, 5.7, 3.2, and 3.2%, respectively. No Grade ≥3 acute GI toxicities were observed. The incidence of acute Grade 2 GU toxicities for dose levels 1–4 were 13.3, 8.6, 13.9, and 6.5%, respectively. Only one patient at the 40 Gy dose level experienced a Grade 3 acute toxicity (urinary retention requiring Foley catheter placement). The incidence of late Grade 2 GI toxicities for dose levels 1–4 were 3.3, 0, 2.8, and 0%, respectively. No Grade 3 or 4 late GI toxicities were observed. The incidence of late Grade 2 GU toxicities for dose levels 1–4 were 13.3, 14.3, 8.3, and 9.7%, respectively. Only one late Grade 3 GU toxicity (urethral stricture) developed in the 32.5 Gy dose arm after treatment which was corrected with transurethral resection. No Grade ≥4 late GU toxicities were observed.

The highest SAbR dose escalation studies to date were reported through studies managed by investigators at UT Southwestern, extrapolated from the HDR brachytherapy experience, where initial dosing was similar to the biologic equivalent margin dose of the HDR brachytherapy experience (ie, 45 Gy in five fractions), and then escalated to 50 Gy in five fractions [52]. In the phase I portion, 45 patients (3 cohorts of 15 at each dose level), were treated with 45, 47.5, and 50 Gy in 5 equal fractions, respectively. In this population, 40% were low-risk (Gleason score ≤6, PSA <10 ng/mL and clinical stage ≤T2a) and 60% were intermediate-risk (Gleason score 7 or PSA 10–15 ng/mL, or clinical stage T2b, with no discrimination between low- and high-intermediate risk subclassification). Treatment was delivered using conventional linear accelerator or tomotherapy system to the prostate only with a 2–3 mm planning margin, with a rectal balloon used for prostate immobilization. No dose-limiting toxicities (Grade 3–5) occurred within the first 90 days post-treatment. GI grade ≥2 and Grade ≥3 toxicity occurred in 18 and 2%, respectively, and GU Grade ≥2 and Grade ≥3 toxicity occurred in 31 and 4%, respectively. Of note, on the initial trial, anoscopies performed on treated patients noted an anterior rectal erosion or ulcer in 100% of assessed patients. Initial PSA control was 100%. These encouraging results led to the further enrollment on a phase II trial at the 50 Gy in 5 fractions dose level to study efficacy and late toxicity. An additional 46 patients were enrolled for a total of 91 (64% intermediate-risk and 36% low-risk). With a median follow-up of 54 months, PSA control remained at 98.6% overall (100% for patients with Gleason 6(3 + 3) or

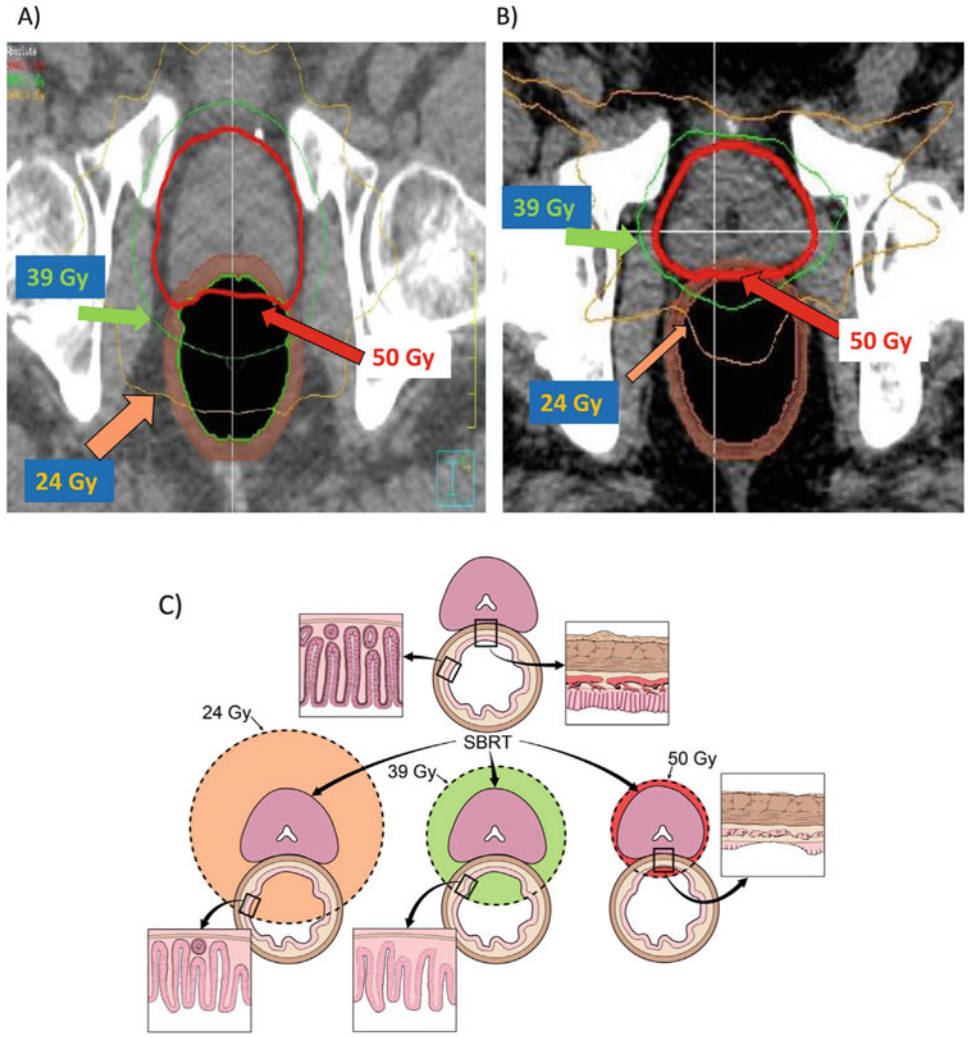

Fig. 13.2 Representative treatment plans of patients treated to 50 Gy in 5 fractions, with (**a**) grade 2 acute and grade 3 delayed rectal toxicity, and (**b**) grade 1 acute/delayed rectal toxicity only. (**c**) Representation of biologic consequence of rectal wall irradiated to 24 Gy, 39 Gy, and 50 Gy. Reprinted from "Predictors of Rectal Tolerance Observed in a Dose-Escalated Phase 1–2 Trial of Stereotactic Body Radiation Therapy for Prostate Cancer" Int J Radiation Oncol Biol Phys 89(3):509–517 (2014) Copyright (2014), with permission from Elsevier

Gleason 7(3 + 4) disease, 93.3% for patients with Gleason 7(4 + 3) unfavorable intermediate-risk disease) [53, 54]. One patient with unfavorable intermediate-risk disease, who was treated on the 45 Gy arm, demonstrated failure to therapy. Overall, 6 (6.8%) patients experienced late Grade $\geq$3 GI toxicity, with 5 requiring a temporary diverting colostomy, all in the 50 Gy dose cohort. There was 1 (1.6%) late Grade 4 GU toxicity, also in the 50 Gy dose cohort; there were no acute Grade $\geq$3 GU toxicities, and late Grade 3 GU toxicity was noted in 4.4% of patients. A dosimetric analysis of GI toxicity demonstrated a significant correlation with the volume of rectal wall receiving 50 Gy >3 cm^3, and treatment of >35% of the rectal wall circumference to doses exceeding 39 Gy [55]. In Fig. 13.2, examples of SAbR plans in which 50 Gy was delivered in 5 fractions are provided with either significant (Fig. 13.2a) or minimal (Fig. 13.2b) rectal overlap with the

Table 13.2 5-Fraction prostate SAbR normal tissue constraints used at UT Southwestern

Organ	Volume/Parameters	Total dose (cGy)
Spinal cord	Maximum point dose	22 Gy (4.4 Gy per fraction)
	Less than 8 cc	20 Gy (4 Gy per fraction)
Cauda Equina	Maximum point dose	27.5 Gy (5.5 Gy per fraction)
	Less than 10 cc	25 Gy (5 Gy per fraction)
Sacral Plexus	Maximum point dose	30 Gy (6 Gy per fraction)
	Less than 10 cc	27.5 Gy (5.5 Gy per fraction)
Rectal wall	Less than 3 cc	50 Gy
Percent rectal circumference	<33% of circumference	39 Gy
	<50% of circumference	24 Gy
Rectum superior to prostate	Maximum point dose	30 Gy (6 Gy per fraction)
	Less than 10 cc	25 Gy (5 Gy per fraction)
Small intestine	Maximum point dose	29 Gy (5.8 Gy per fraction)
	Less than 10 cc	19.5 Gy (3.9 Gy per fraction)
Prostatic urethra	Maximum point dose	No more than 105% of prescription dose
Bladder	Maximum point dose	No more than 105% of prescription dose
	Less than 18 cc	18.3 Gy (3.65 Gy per fraction)
Penile bulb	Maximum point dose	No more than 100% of prescription dose
	Less than 3 cc	30 Gy (6 Gy per fraction)
Femoral heads	Less than 10 cc cumulative (both sides)	30 Gy (6 Gy per fraction)
Skin within fold (e.g., the gluteal fold)	Maximum point dose	20 Gy (4 Gy per fraction)
Skin not within fold	Maximum point dose	27.3 Gy (5.45 Gy per fraction)
Seminal vesicles	No dose constraint	Collect dose statistics for documentation only
Neurovascular bundle (right and left)	Maximum point dose	No more than 105% of prescription dose

50 Gy isodose line; Fig. 13.2c illustrates the increasing rectal mucosal injury resulting with incidental high dose radiation delivery to the rectal wall. Based on these experiences, normal tissue constraints were developed for standard use in patients treated for prostate cancer at UT Southwestern with SAbR (Table 13.2).

To further address these issues of rectal toxicity, a Phase II trial was conducted by Folkert et al., and reported at the 2017 ASTRO Annual Meeting [56]. In this study, patients were treated with SAbR following placement of a temporary hydrogel spacer (SpaceOAR, Augmenix, Inc, Bedford, MA) that had previously been shown in randomized trials to reduce rectal toxicity in the setting of conventional courses of radiation therapy for prostate cancer [57, 58]. Eligible patients included men with localized prostate cancer with Gleason score 6–7, PSA ≤15 ng/ml, and clinical/radiographic stage ≤T2c. Patients underwent hydrogel spacer placement followed by 45 Gy in five fractions to the prostate volume with a 3 mm planning margin; the seminal vesicles were not treated (Fig. 13.1c provides an example of a SAbR treatment with rectal hydrogel spacer in place). A total of 44 patients treated at 2 institutions were included; 7 patients (15.9%) had Gleason 6(3 + 3) disease, 25(56.8%) had Gleason 7(3+4) disease, and 12(27.3%) had Gleason 7(4+3) disease. At a median follow up of 12 months, freedom from biochemical failure was 100%. There were no ≥Grade 3 acute or chronic GI toxicities. Acute and late Grade 3 GU toxicity occurred in 2(4.5%) of patients; one spacer site infection and one urinary tract pain, both resolved. No Grade >3 toxicities occurred. The primary endpoint of the study was a reduction of the mucosal injury rate from the previously observed rate of 90% on the original Phase 1/2 study at UT Southwestern to <70%; a total of 6 rectal erosions/ulcers (five grade 1, one grade 2) were observed (13.6%), meeting the

trial's primary objective. All were minimally symptomatic and resolved on repeat anoscopy within 6 months.

13.4 Conclusions

There is ample evidence that oligofractionated regimens may be at least and possibly more clinically effective in the management of prostate cancer than conventionally dosed therapies, bolstered by advances in imaging and radiation delivery systems. Extensive prospective data has been generated in multiple series to demonstrate that this treatment can be delivered safely and effectively when administered with appropriate expertise and understanding of dosimetric constraints. New techniques such as temporary hydrogel spacer placement facilitate escalation to higher dose levels that have been shown to correlate with improved biochemical outcomes and decreased likelihood of residual viable prostate cancer on post-treatment biopsy. In addition to an increased likelihood of durable biochemical control, this form of treatment is far more convenient for patients, and potentially reduces the overall cost of therapy.

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Summary of Ongoing Prospective Trials Using SBRT for Prostate Cancer

14

Kirsty Morrison and Nicholas van As

Evidence is building to support the use of stereotactic radiotherapy in the management of localised prostate cancer. However, a large number of uncertainties remain, highlighting the need for further prospective trials. This chapter will consider ongoing prospective trials which may influence the future of SBRT in localised prostate cancer. Eighty two trials have been identified following a search of http://clinicaltrials.gov and www.isrctn.com most recently performed in December 2017, using search terms: prostate SBRT; prostate stereotactic; prostate hypofractionation; prostate CyberKnife; prostate focal radiotherapy; and prostate dominant lesion. Trials investigating SBRT for reirradiation or in the preoperative or salvage radiotherapy setting have been excluded, and are not discussed within the scope of this chapter. The larger/most relevant remaining trials are summarised in Tables 14.1, 14.2 and 14.3.

14.1 SBRT in Low- and Intermediate-Risk Prostate Cancer

There is now a wealth of published data from non-randomised studies demonstrating the efficacy and safety of SBRT in low- and intermediate-risk prostate cancer, to be consistent with standard treatment modalities. However, many of these studies are retrospective in nature, and often with short follow up at the time of publication, making it difficult to draw accurate conclusions. Ongoing prospective trials therefore remain vital in this setting. There are a large number of ongoing non-randomised trials evaluating SBRT as monotherapy for low- and intermediate-risk patients. The majority of these are single-arm studies, delivering SBRT in five fractions most commonly at a prescribed uniform dose of 36.25 Gy (range 35–40 Gy) to the PTV. The larger of these studies with an expected accrual of at least 50 patients, are summarised in Table 14.1. Other trials evaluating the use of dose escalation and more extreme hypofractionation will be discussed later in this chapter.

In terms of multicentre trials, the phase II trial by Meier et al. [21] has completed accrual and has recently published 5 year outcomes in abstract form [22]. Over 300 low- and intermediate-risk patients were treated using CyberKnife with a prescription dose of 36.25 Gy in five fractions, aiming to deliver 40 Gy to the prostate. Results were encouraging demonstrating biochemical progression-free survival (bPFS) of 97.1% and low toxicity rates with no grade 3 gastrointestinal (GI) and 2% late genitourinary (GU) toxicity. Within the SMART trial [24] linac-based techniques were used, delivering a dose of 37 Gy in five fractions prescribed to the PTV. Results

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Table 14.1 Randomised SBRT trials

Centre/PI	Year open	Study design	Target accrual	Risk group	Arm 1/Experimental arm	Arm 2/Control arm	Primary objective	Status
PACE, van As (UK) [1]	2012	Multicentre Phase III	1092	L/I	SBRT 36.25 Gy/5 # to PTV CK/Linac	PACE A: Radical prostatectomy PACE B: EBRT 62 Gy/20 # or 78 Gy/39 #	PACE A: QOL 2 years PACE B: bPFS 5 years	PACE B: Active PACE A: Recruiting
RTOG0938, Lukka (CA) [2]	2011	Multicentre Phase II	255	L	SBRT 36.25 Gy/5 # twice weekly	EBRT 51.6 Gy/12 # consecutive days	QOL 1 year	Active Results [3]
HEAT, Abramowitz (US) [4]	2013	Multicentre	456	L/I	SBRT 36.25 Gy/5 #	EBRT 70.2 Gy/26 #	bPFS 2 years	Recruiting
Ellis (US) [5]	2018	Phase III	606	L/I	SBRT 5 # (alt days). Dose NS	EBRT 28 # 5 days/week. Dose NS	Toxicity/QOL 2 years	Not yet recruiting
Poon (HK) [6]	2015	Single centre Phase II	68	L/I	SBRT 36.25 Gy in 5 # twice weekly	EBRT 78 Gy in 39 #	QOL at 1 year	Recruiting
HYPO, Widmark (SE) [7]	2005	Multicentre Phase III	1200	I	EBRT 42.7 Gy in 7 #	EBRT 78 Gy in 29 #	FFBF 5 years	Active
Vuolukka (FI) [8]	2013	Single centre	44	L/I	SBRT 36.25 Gy in 5 # (alt days)	LDR brachytherapy (I125 seeds)	Toxicity 6 months	Active
Lukka (CA) [9]	2015	Single centre	40	L/I	SBRT with CyberKnife 36.25 Gy in 5 #	SBRT with VMAT 36.25 Gy in 5#	Patient acceptability	Unknown
PATRIOT, Ong, Loblaw (CA) [10]	2012	Multicentre Phase II	152	L/I	SBRT (Linac) 40 Gy in 5 # over 11 days	SBRT (Linac) 40 Gy in 5 # over 29 days	Bowel related QOL at 3 months	Active Results [11]
PROSINT, Greco (Portugal) [12]	2015	Single centre Phase II	30	L/I	SBRT 24 Gy in a single # VMAT/urethral sparing	SBRT 45 Gy in 5 # over 5 days VMAT/urethral sparing	Toxicity 5 years	Recruiting
Zelefsky (US) [13]	2017	Multicentre Phase III	200	I	SBRT 40 Gy in 5 # with Degarelix	SBRT 40 Gy in 5 # without hormones	Positive biopsy rate 2 years	Recruiting
Kang (US) [14]	2016	Single centre	40	L/I/H	SBRT 36.25 Gy in 5 # 2–3 times/week with endorectal balloon immobilisation	SBRT 36.25 Gy in 5 # 2–3 times/ week with injectable rectal spacer	Toxicity 4 years	Recruiting

ASSERT Alexander/Kwan (CA) [15]	2016	Multicentre Phase II	80	I/H	SBRT 36.25 Gy/5 # weekly Linac/CBCT and fiducials 6–18 months ADT	EBRT 73.68 Gy/28 # 6–18 months ADT	Toxicity 5 years	Recruiting
Miralbell (CH) [16]	2012	Multicentre Phase II	170	L/I/H	SBRT 36.25 Gy in 5# over 9 days VMAT/urethral sparing (32.5 Gy) ADT in higher risk	36.25 Gy weekly over 28 days VMAT/urethral sparing (32.5 Gy) ADT in higher risk	Toxicity 5 years	Active
SPORT, Jain (UK) [17]	2016	Single centre	30	H	SBRT 36.25 Gy/5 # prostate and 25 Gy/5 # pelvis SBRT	SBRT 36.25 Gy in 5 # prostate alone	Feasibility Acute toxicity/ QOL	Recruiting
Suwinski (PL) [18]	2013	Phase III	350	I/H	SBRT or brachytherapy boost 10 Gy/ 2# following EBRT 76–78 Gy/38–39 #	EBRT 76–78 Gy/38–39 # alone	FFBF 3 years	Not yet open
HYPOPROST, Milecki (PL) [19]	2011	Multicentre	465	H	IMRT 46 Gy in 23 # prostate/pelvis and 30 Gy in 15 # prostate boost ADT up to 24 months	IMRT 46 Gy in 23 # prostate/pelvis and SBRT 15 Gy in 2 # prostate boost ADT up to 24 months	bPFS at 5 years	Recruiting
BLaStM Pollack (US) [20]	2015	Single centre Phase II	164	L/I/H	12–14 Gy in 1 # MRI guided SBRT boost then EBRT 76 Gy in 38 # ADT discretion of clinician	EBRT 76 Gy in 38 # and 91.2 Gy in 38 # SIB ADT discretion of clinician	Pathologic complete response 2–2.5 years	Recruiting

L low-risk, *I* intermediate-risk, *H* high-risk, *SBRT* stereotactic body radiotherapy, *Linac* Linear accelerator, *EBRT* external beam radiotherapy, *LDR* low-dose rate, *#* fractions, *VMAT* volumetric arc therapy, *CBCT* cone beam computerised tomography, *ADT* androgen deprivation therapy, *IMRT* intensity-modulated radiotherapy, *SIB* simultaneous integrated boost, *QOL* quality of life, *bPFS* biochemical progression-free survival, *FFBF* freedom from biochemical failure

Table 14.2 Non-randomised trials in low and intermediate risk prostate cancer

Centre/PI	Year open	Study design	Target accrual	Technique	Schedule	Primary objective	Status
Meier (US) [21]	2007	Multicentre Phase II	298	CK Fiducials	40 Gy/5 # to prostate 36.25 Gy/5 # to proximal SV	Toxicity bDFS 10 years	Active Results [22, 23]
SMART, Lee (US) [24]	2009	Multicentre Phase II	60	Linac Calypso or Exactrac and/or CBCT and fiducials	37 Gy/5 # to PTV (alt days)	Toxicity 3 years	Active Results [25]
Spratt (US) [26]	2011	Multicentre Phase II	66	Linac Calypso	37 Gy/5 # (alt days)	Quality of life 2 years	Completed Results [27]
Florida Robotic Radiosurgery Association, Perman (US) [28]	2010	Multicentre Observational	3000	NS	NS	Overall Survival 5 years	Recruiting
Tran (US) [29]	2013	Multicentre Phase I/II	105	NS	36.25 Gy/5 # (alt days)	Biochemical failure free rate 5 years	Active
HYPOSTAT, Dunst (DE) [30, 31]	2015	Multicentre Phase II	85	CK Fiducials	35 Gy/5 #to PTV (alt days)	Late toxicity 12–15 months	Recruiting
CYBERPROST, Milecki (PL) [32]	2013	Single centre	600	CK Fiducials	NS	bPFS 5 years	Recruiting
PR-PROS, Collins (US) [33]	2012	Single centre Observational	200	CK Fiducials	35–36.25 Gy/5#	QOL 2 years	Active
Rashtian (US) [34]	2013	Single centre	167	CK Fiducials	36.25 Gy/5 # to PTV	Toxicity bPFS 5 years	Recruiting
Woodhouse (US) [35]	2008	Single centre Phase II	100	CK Fiducials	36.25 Gy/5 #	Toxicity/bPFS 5 and 10 years	Unknown
Chua (SG) [36]	2013	Single centre Phase II	80	Linac	36.25 Gy/5 # over 10–11 days	Late toxicity 2 years	Recruiting
Heron (US) [37]	2010	Single centre Phase II	111	CK Fiducials	36.25 Gy/5 # over 2 weeks	Toxicity/bDFS 2 years	Recruiting
Potters (US) [38]	2010	Single centre Phase I	36		Dose level 1: 40 Gy/5 # (alt days) Dose level 2: 45 Gy/5 # Dose level 3: 50 Gy/5 #	Maximum tolerated dose	Active Results [39, 40]

RAD1203, Fiveash (US) [41]	2013	Single centre Pilot	25	Linac	36.25 Gy/5 # over 1–2 weeks SIB to area containing tumour 40 Gy/5 #	Acute toxicity	Active
Orecchia/Jereczek (IT) [42, 43]	2014	Single centre	65	CK/Linac	36.25 Gy in 5 # over 10 days SIB to dominant lesions 37.5 Gy in 5 #	Acute toxicity	Active
Zelefsky (US) [44]	2017	Single centre Phase I	30	Linac	40 Gy in 5 # SIB to MRI defined lesions 45 Gy in 5 #	Toxicity	Recruiting
Ritter (US) [45]	2015	Single centre Phase I/II	160		40 Gy in 5 # (36.25 Gy urethral sparing) SIB to MRI defined lesions 8.5–9 GY per # 37.5 Gy uniform dose (patients not having MRI)	Toxicity bPFS at 5 years	Recruiting Results [46]
Fuller (US) [47]	2007	Multicentre Phase II	253 (259)	CK Fiducials	38 Gy/4 # Virtual HDR technique (DMax 57 Gy)	bDFS/toxicity 10 years	Active Results [48, 49]
Fuller (US) [50]	2006	Single centre Phase II	258	CK Fiducials	38 Gy in 4 # Virtual HDR technique	Toxicity/QOL bDFS at 5 years	Recruiting Results [51]
2STAR, Loblaw (CA) [52, 53]	2014	Single centre Phase I/II	30	Linac Fiducials/CBCT/ endorectal immobilisation device	26 Gy/2 # weekly	QOL 5 years	Active
eHYPO, Sanguineti (IT) [54]	2015	Single centre Phase I/II	59	Linac Fiducials/CBCT/urethral catheter/rectal gel spacer	40 Gy/3 # (alt days)	GU toxicity 1 year	Recruiting
ONE-SHOT, Zilli (CH) [55]	Due 2017	Single centre Phase I/II	45	Linac Calypso	19 Gy in one # 17 Gy to urethra PRV	Acute toxicity bPFS 3 years	Not yet recruiting
Mantz (US) [56]	2006	Multicentre Phase II	350	SBRT NS	Low risk: SBRT 40 Gy in 5 # Int-risk: IMRT 45 Gy in 25 # and SBRT 22 Gy in 4 #	Toxicity up to 10 years	Recruiting
CKNO-PRO, Lartigau (FR) [57]	2010	Multicentre Phase II	76	CK/Linac	SBRT boost 18 Gy in 3 # over 5–9 days following conventional EBRT 46 Gy in 23 #	Toxicity 2 years	Active Results [58]

CK CyberKnife, *NS* not specified, *HDR* high-dose rate, *PRV* planning organ at risk volume, *GU* genitourinary

Table 14.3 Non-randomised trials involving high risk prostate cancer patients

Trial/PI	Year open	Study design	Target accrual	Risk group	Technique	ADT/ Duration	Schedule	Primary objective	Status
Stephans (US) [59]	2012	Single centre	35	L/I/H	NS	Yes As CI	50 Gy in 5 # to high dose PTV 36.25 Gy in 5 # to low dose PTV	Toxicity 1 year	Active Results [60, 61]
Meier (US) [62]	2014	Single centre	146	L/I/H	CK	NS	5 # over 1 week, dose NS	QOL/ toxicity 8 years.	Recruiting
Prorate, Nickers (LU) [63]	2014	Single centre Phase II	60	Elderly L/I/H	CK	NS	36.25 Gy/5 # over 10 days, low/intermediate risk 37.5 Gy/5 # high risk	Toxicity 3 years	Recruiting
FASTR-2 Bauman (CA) [64]	2014	Single centre Phase II	60	H	Linac CBCT	18 months	35 Gy in 5 # prostate over 5 weeks	Toxicity 1 year	Recruiting
pHART8, Loblaw/ Jain(CA/UK) [65]	2011	Multicentre Phase II	30	H	Linac	NS	40 Gy/5 # prostate weekly 30 Gy in 5 # SV	Acute rectal toxicity	Active
Ong (CA) [66]	2013	Single centre Phase I	77	H	NS	NS	36.25 Gy in 5 # to PTV SIB to MRI defined lesions 40 Gy in 5 #	QOL (EPIC)	Not yet recruiting
SPARC, Van As (UK) [67]	2013	Single centre Phase II	20	I/H	CK	Yes	36.25 Gy/5 # to PTV SIB 47.5 Gy/5 # SIB to MRI defined nodules	Acute GU toxicity	Recruiting
Herrara (CH) [68]	2014	Single centre Phase I/II Dose escalation	27	L/I/H	Rectal spacer	NS	36.25 Gy/5 # Phase I: SIB 45 Gy/5 # escalating to 50 Gy/5 # Phase II: SIB MTD from phase I	Phase I: MTD Phase II: Acute toxicity	Recruiting
King (US) [69]	2014	Multicentre Phase II	220	H	NS	≥9 months	40 Gy in 5 # over 2 weeks 25 Gy to pelvic nodes (as indicated)	bPFS 3 and 5 years Toxicity/ QOL 5 years	Recruiting Results [70, 71]
FASTR, Bauman/ Rodrigues (CA) [72]	2011	Single centre Phase II	19	H	Linac CBCT	12 months	40 Gy/5 # weekly to prostate 25 Gy in 5 # pelvis (PTV = CTV + 5 mm)	Toxicity 3 years	Terminated results [73]
SATURN Loblaw (CA) [74]	2013	Single centre Phase II	30	H	Linac	12–18 months	40 Gy/5 # prostate 25 Gy /5 # pelvis over 4 weeks	Acute toxicity 3 months	Active Results [75]

Hanna (US) [76]	2015	Single centre Phase I Dose escalation	50	H	Linac CBCT	24 months	47.5 Gy in 5 # prostate Dose level 1: 22.5 Gy pelvis/50 Gy SIB Dose level 2: 27.5 Gy pelvis/55 Gy SIB	Maximum tolerated dose	Recruiting
AASUR McBride (US) [77]	2016	Multicentre Phase II	58	H	NS	Yes	SBRT with 6 months Leuprolode, Abiraterone and ARN-509 (Apalutamide)	Biochemical failure 3 years.	Recruiting
Hirsch (US) [78]	2014	Single centre	72	I/H	CK boost	Yes As CI	Int risk: 36.35 Gy/5 # prostate monotherapy High risk: EBRT 45–50.4 Gy/25–28 # prostate +/−pelvis and 21 Gy/3 # SBRT prostate boost	bDFS at 5 years.	Recruiting
Harsolia (US) [79]	2012	Single centre	167	L/I/H	CK boost	Yes	Low/int risk: 36.25 Gy/5 # prostate monotherapy High risk: EBRT 50.4 Gy/28 # and 25.5 Gy/5 # SBRT prostate boost	Toxicity/ bPFS 5 years	Recruiting
Eade (AU) [80]	2014	Single centre Phase I Dose escalation	60	NS	Linac Calypso	NS	SBRT prostate boost then 46 Gy in 23 # prostate/ pelvis Dose level 1: 20 Gy/2 # PTV and 22 Gy GTV Dose level 2: 22 Gy PTV, 27.5 Gy GTV Dose level 3: 24 Gy PTV, 30 Gy to GTV	Acute toxicity	Recruiting

CI clinically indictaed, *PTV* planning target volume, *CTV* clinical target volume

published this year at 27.6 months median follow up, demonstrated grade 3 late GI toxicity in one patient, and no grade 3 acute or late GU toxicity [25]. The Florida Robotic Radiosurgery Association are conducting a prospective observational trial involved a multi-institutional registry for prostate cancer SBRT, expecting to recruit 3000 patients [28]. The primary aim of this large study is to determine overall survival at 5 years follow up.

The number of current trials delivering SBRT using CyberKnife or linear accelerator are relatively equal. Linac-based techniques offer advantages in terms of treatment time and patient accessibility, however, it is unclear whether the choice of platform contributes to beneficial treatment outcomes. Lukka et al. were due to open a randomised trial in 2015 to compare SBRT in low/intermediate prostate cancer delivered with CyberKnife or with volumetric modulated arc therapy (VMAT) [9]. The primary objective is to assess patient acceptability of the trial, aiming to recruit 40 patients, although according to the clinicaltrials.gov listing, the recruitment status is currently unknown.

There are a variety of image guidance techniques employed within the trials (Table 14.1). Some of the linac-based trials include intra-fraction tracking of prostate motion using Calypso electromagnetic beacons [24, 26, 55]. Lagerwaard et al. are using stereotactic MR-guided adaptive radiation therapy (SMART) within a phase II trial, involving daily plan re-optimisation. In an interim analysis of 16 patients, they demonstrated that plan reoptimisation improved sparing of the rectum and bladder from high doses in around 20% of fractions [81]. A few trials have included the use of injectable rectal spacers or endorectal immobilisation devices in an attempt to reduce prostatic motion and improve rectal dosimetry. Kang et al. are comparing these techniques in a randomised trial, aiming to evaluate differences in toxicity rates [14].

14.2 Comparing SBRT with Standard Treatment

Ultimately, large randomised trials are required to directly compare prostate SBRT outcomes with conventional treatment modalities and fractionation. The Prostate Advances in Comparative Evidence (PACE) trial is an international, multicentre, phase III trial, sponsored by the Royal Marsden Hospital, consisting of two randomisation groups [1]. Within PACE A, low- and intermediate-risk patients are randomised between surgery with radical prostatectomy, and SBRT; or in PACE B randomised between SBRT and conventionally fractionated radiotherapy (Fig. 14.1). All patients are treated without androgen deprivation therapy (ADT). In keeping with the majority of published trials, SBRT patients are treated with 36.25 Gy in five fractions prescribed to the PTV, ensuring 40 Gy to the CTV, delivered with either CyberKnife or Linac based techniques. In the conventional radiotherapy arm, patients are treated with 78 Gy in 39 fractions or 62 Gy in 20 fractions, following publication of the CHHIP trial data in 2016 demonstrating moderate hypofractionation to be non-inferior to conventional fractionation [82]. Patients will be followed up over 10 years and be assessed with PSA, clinician reported measures of acute and late toxicity (CTCAE, RTOG) and patient reported quality of life scores (IIEF, Vaisey, IPSS, EPIC).

Given the difficulties of a surgery versus radiotherapy randomisation, PACE A recruitment has been lower than anticipated. As a result, the primary endpoint of this group has been changed from biochemical disease-free survival (bDFS) to a quality of life endpoint, in order to reduce the recruitment target to 234. In contrast PACE B has recruited exceptionally well, having opened in 40 centres in UK, Ireland and Canada. It has now closed to accrual, having reached the recruitment target of 858 patients by the end of 2017.

Four other randomised trials have been identified, comparing five fraction SBRT with conventionally fractionated or moderately hypofractionated EBRT. A small Hong Kong based phase II trial led by Poon, et al., is currently recruiting low- and intermediate-risk patients within the Asian population [6]. Randomisation is between IMRT 78 Gy in 38 fractions and SBRT 36.25 Gy in five fractions, with a primary outcome measure of health-related quality of lie (QOL) at 1 year. HEAT [4] is a multicentre

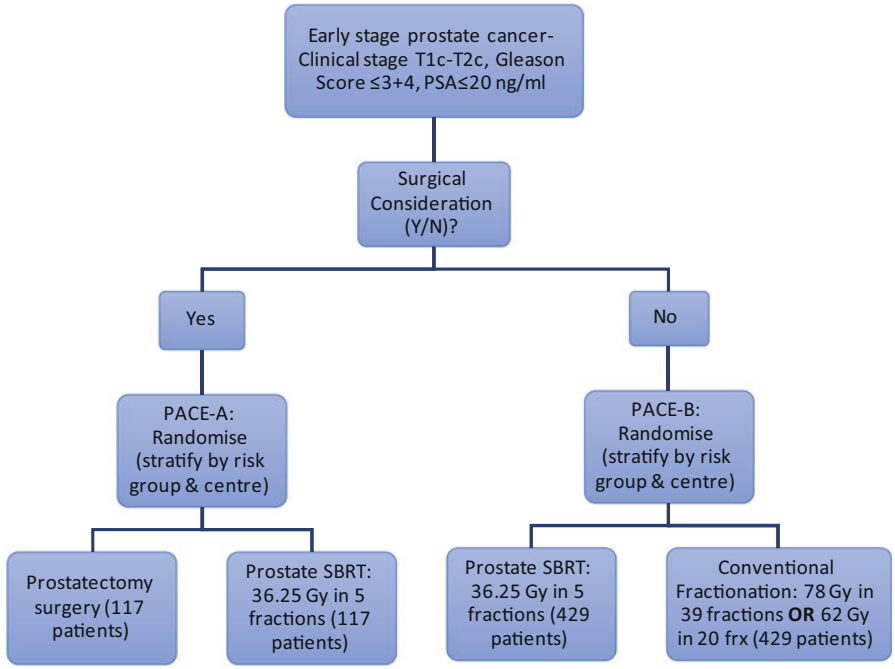

Fig. 14.1 PACE trial schema (taken from the PACE trial protocol, version 9.0, June 2017)

randomised trial from the US which opened in 2013, hoping to recruit 456 patients to determine whether SBRT 36.25 Gy in five fractions is non-inferior to 70.2 Gy in 26 fractions in terms of biochemical or clinical failure rate at 2 years. A further US trial led by Ellis et al. which has yet to recruit will compare SBRT in five fractions and IMRT in 28 fractions with the aim of demonstrating superiority of SBRT in terms of GU/GI toxicity [5]. Early results from The RTOG 0938 trial by Lukka et al., have been published in abstract form in 2016 [2, 3]. 255 patients with low risk prostate cancer were randomised between SBRT, 36.25 Gy in five fractions or a hypofractionated dose of 51.6 Gy in 12 fractions. Both fractionations were well tolerated in terms acute and late toxicity, and patient-reported bowel and urinary outcomes at 1 year.

Although not strictly SBRT, HYPO is Scandinavian-based phase II randomised multicentre trial, comparing a highly hypofractionated schedule of 42.7 Gy in seven fractions on alternate days, with conventional fractionation (78 Gy in 39 fractions) [7]. Recruitment is now closed having accrued 1200 patients with intermediate-risk prostate cancer (stage T3a disease also permitted). Treatment delivery was with either 3D conformal radiotherapy or VMAT, without the use of concomitant ADT. Two-year acute and late toxicity data has been published with a median patient follow up of 4.2 years [83]. No significant difference in toxicity was found between the two arms at 2 years follow up, which included 866 patients. RTOG $\geq$ grade 2 urinary toxicity was 5.4 and 4.6% for the hypofractionated and conventional arms respectively, and bowel toxicity 2.2 versus 3.7%. In results presented at ESTRO (2018) ultra hypofractioanted schedule was shown to be non-inferior to conventional fractionation at 5 years, in terms of freedom from biochemical or clinical failure, with no significant difference in toxicity rate at 4 and 6 years.

LDR brachytherapy is a standard treatment option for suitable patients with low- and intermediate-risk prostate cancer. This is being compared to SBRT within a small randomised trial based in Finland (BRAVEROBO), now

closed to recruitment [8]. Patients are randomised between LDR brachytherapy using I125 seeds, and SBRT 36.25 Gy in five fractions. The primary aim of this study is to detect any differences in acute and late toxicity between the two groups.

14.3 High-Risk Patients

Currently, there is limited data regarding the use of SBRT in high-risk prostate cancer, defined within the National Cancer Care Guidelines (NCCN) as patients with at least one high-risk feature: Gleason 8–10; clinical stage ≥T3a; or PSA >20 ng/ml [84]. Concerns about achieving adequate coverage or potential increased toxicity may have deterred the development of SBRT in this group given the higher risk of disease outside the prostate. Only a few published SBRT studies involve a mixed population which include a small percentage of high risk patients. The pooled multi-institutional analysis of 1100 patients by King et al. was encouraging, demonstrating 81% 5 year bPFS in the high-risk group which made up 11% of the population [85].

Four randomised trials have been identified, which include the delivery of prostate SBRT as monotherapy in high risk patients, all using a dose of 36.25 Gy in five fractions to the PTV (see Table 14.1). The ASSERT trial, which is a Canadian multi-centre trial, aims to compare toxicity from SBRT with a more conventionally fractionated schedule of 73.68 Gy in 28 fractions, in intermediate- and high-risk patients [15]. Table 14.3 summarises ongoing non-randomised trials involving high-risk patients. Of the 20 trials listed, eight have been identified delivering SBRT in five fractions to the prostate alone, where specified at a dose of 35–50 Gy. In some studies, this includes the delivery of a simultaneous integrated boost (SIB) to intraprostatic lesions. Four studies include a mixed group of low-, intermediate- and high-risk patients [59, 62, 63]. Nickers et al., are aiming to determine toxicity in the elderly population. In this trial, low- and intermediate-risk patients are treated at a dose of 36.25 Gy in five fractions which is increased to 37.5 Gy for high risk patients [63].

The largest trial specifically evaluating efficacy and safety of SBRT in the high-risk group, is a multicentre trial phase II trial led by King et al. [69]. They expect to recruit 220 patients, delivering SBRT to the prostate at a dose of 40 Gy in five fractions over 2 weeks. Concomitant androgen deprivation therapy (ADT) and SBRT to the pelvis using a dose of 25 Gy in five fractions, are given at the discretion of the treating clinician. Preliminary results have been published in abstract form in 2017 [70, 71]. Seventy three patients had been treated with a median follow up of 13.8 months. 32% received nodal irradiation and 63% received androgen deprivation therapy (ADT). Overall treatment was well tolerated with no grade 3 GU or GI toxicity seen. 2.7% had evidence of biochemical failure however longer follow up is required to evaluate the efficacy of treatment. The use of ADT or nodal irradiation did not appear to have a significant effect on toxicity, although numbers are too small to draw any conclusions about this. Trials investigating the use of ADT and pelvic SBRT will be discussed later in the chapter.

14.4 Dose Escalation

Dose escalation has been shown to improve biochemical disease-free survival and delay the need for systemic therapy following conventionally fractionated radiotherapy [86–88]. Pollack et al. demonstrated higher rates of freedom from biochemical failure and distant metastases in intermediate- and high-risk patients receiving 78 Gy compared to 70 Gy in 2 Gy fractions [87, 89]. Retrospectively collected data by Zelefsky et al., suggest that doses as high as 86.4 Gy are associated with improved outcomes in high-risk patients, even in combination with hormones [88]. However, any benefit from dose escalation does is likely to come with the disadvantage of increased toxicity [86, 87].

Potters et al., have completed accrual to a phase I study evaluating the tolerability of SBRT dose escalation in low- and intermediate-risk prostate cancer [38]. The study has been designed to recruit 7–15 patients to each of three dose levels: 40 Gy in five fractions, 45 Gy in five

fractions, and 50 Gy in five fractions, escalating to the next dose level if no dose limiting toxicity (DLT) after 90 days in the first seven patients enrolled to a specific dose level. Acute toxicity results from the first two dose levels have been published in abstract form [39, 40]. Twelve patients received 40 Gy in five fractions and ten patients 45 Gy in five fractions. Acute grade 2 (CTCAE v3) GU toxicity was seen in 42 and 50% of patients in each dose level respectively, with no grade 3 toxicity and no ≥ grade 2 GI toxicity. Based on these results the dose was escalated to 50 Gy, the results of which are awaited.

There is not a clear argument for escalating to this dose level, particularly in low risk patients. Studies suggest prostate cancer to have an α/β ratio of <2, lower than that of the surrounding normal tissues and hence sensitive to hypofractionation [90–92]. Even assuming an α/β of 2, an SBRT dose of 36.25 Gy in five fractions has a biologically effective dose (BED) of 168, which is higher than 78 Gy in 39 fractions (BED 156), but has a slightly lower BED (124 vs. 130) in terms of late rectal toxicity, assuming an α/β of 3. Escalating the SBRT dose to 50 Gy in five fractions markedly increases the tumour BED to 305 but at the cost of increasing normal tissue BED to 216, hence increasing the risk of significant rectal toxicity. Dose escalation to 50 Gy has previously been evaluated by the Timmerman group who demonstrated significant toxicity in patients receiving higher dose [93, 94]. Over 6% of patients developed high-grade GI toxicity (≥ grade 3), including five patients who required a colostomy.

Heterogeneous planning techniques could enable dose to be escalated in areas not adjacent to sensitive structures. The PACE trial aims to cover at least 95% PTV with the 36.25 Gy prescription dose while delivering 40 Gy to at least 95% CTV [1]. The technique used by Stephans et al., involves the creation of a high dose PTV (HDPTV) which includes PTV > 3 mm from either urethra, bladder or rectum, and a low dose PTV (LDPTV) which includes PTV within 3 mm of these structures. 36.25 Gy in five fractions is prescribed to the LDPTV, and 50 Gy in five fractions to the HDPTV [59–61]. At 15 months follow up, treatment was well tolerated with low rates of acute and late toxicity in a cohort of 54 patients, of which 30 were high-risk [61]. One patient suffered grade 4 GU and GI toxicity due to prostatic infection, but did have particular risk factors of uncontrolled diabetes and very large prostate (>200 cc). Biochemical failure was seen in four patients (7.4%), all of which were in high-risk group.

Limiting dose escalation to the area of probable disease within the prostate could minimise toxicity and potentially improve efficacy, particularly since there is evidence from retrospective studies that local recurrence following radiotherapy occurs at the site of the primary tumour [95, 96]. In a study of 124 patients with MR imaging pre- and post-radiotherapy, Arrayeh et al. demonstrated the site of the dominant recurrent tumour to be in the same location as the original dominant tumour in eight of the nine patients with disease recurrence [96]. Recently reported results from the FLAME phase III demonstrate no significant increase in toxicity up to 2 years from combining an integrated boost up to 95 Gy to MRI-defined tumour with fractionated radiotherapy 77 Gy in 35 fractions to the entire prostate [97]. Aluwini et al., have previously reported their experience of using SBRT to apply a focal boost to MRI visible tumour [98]. Fifty patients were treated using CyberKnife at a dose of 38 Gy in four fractions, delivering an integrated boost to 14 patients with a dominant tumour nodule visible on MRI, to a mean dose of 47.8 Gy. 6% grade 3 late GU and no grade 3 GI toxicity overall, was reported at 23 months median follow up. Although the number of patients receiving the tumour boost was very small, no increase in toxicity was reported in this group.

Ongoing trials are evaluating the delivery of a simultaneous integrated boost (SIB) in five fractions. Fiveash et al. (RAD 1203) [41] have recruited 25 low/intermediate risk patients to a pilot trial primarily evaluating early toxicity from SBRT with integrated boost to the area in the prostate most likely to be harbouring disease. 36.25 Gy is prescribed to the whole prostate with

an integrated boost of 40 Gy in five fractions. Six trials have been identified which aim to deliver a SIB to dominant lesions within the prostate, as defined by magnetic resonance imaging (MRI) [42, 44, 45, 66–68]. Four of these are currently recruiting. In the intermediate risk setting, Zelefsky et al. are conducting a phase I feasibility study, treating the whole prostate with 40 Gy in five fractions and applying a SIB of 45 Gy [44]. The SPARC trial which includes intermediate and high risk patients, aims to boost dominant tumour nodules up to 47.5 Gy in five fractions, while delivering 36.25 Gy to the prostate and proximal SV [67]. The primary outcome measure is acute GU toxicity up to 12 weeks post SBRT. In the phase I part of a study led by Herrara et al. in Switzerland, 36.25 Gy is given to the prostate, and the SIB dose is escalated from 45 Gy up to 50 Gy in five fractions, to determine the maximum tolerated dose [66]. Within phase II, patients are treated at the highest tolerated dose in order to determine rate of $\geq$ grade 2 acute toxicity (CTCAE v 4.0).

Ritter et al. use IMRT to combine urethral-sparing, and SIB techniques in a non-randomised phase I/II study, expecting to recruit 160 intermediate/low risk patients [45]. Patients that undergo a pre-treatment MRI are treated with 40 Gy in five fractions on alternate days to the prostate, with the dose to urethra, anterior rectal wall and bladder base limited to 36.25 Gy. A SIB of 42.5 Gy–45 Gy is delivered to MRI defined prostatic lesions. Patients unable to have a MRI are treated with a uniform dose of 36.25 Gy in five fractions. In an analysis of the first 16 patients, the SIB approach was found to be feasible in the ten patients able to undergo MRI [46]. At 8 months median follow up, there was no reported grade 3 or 4 toxicity, and only two patients with grade 2 acute urinary symptoms, although it is not reported which technique these patients were treated with.

14.5 Overall Treatment Time and Fractionation

The effect of overall treatment time in prostate SBRT is not yet known. Published and ongoing trials differ, with many using at least alternate day fractionation schedules. There is however no clear evidence that treating on consecutive days is detrimental, and either consecutive or alternate day fractionation is permitted with the PACE trial. Two multicentre randomised trials are evaluating the influence of weekly fractionation in comparison to alternate day fractionation. The Canadian-based PATRIOT trial has recruited 152 low- and intermediate-risk patients to receive prostate SBRT 40 Gy in five fractions, randomising between treatment over 11 or 29 days [10]. Toxicity (RTOG) and QOL (EPIC) results have been reported at median follow up of 13.1 months [11]. The 29-day arm was found to be superior in terms of patient-reported acute bowel and urinary toxicity, although no significant difference in late toxicity was found between the two schedules. A similar European trial by Mirabell et al. has also completed recruitment, randomising patients from all risk groups to receive 36.25 Gy in five fractions in either 9 days or 28 days [16].

Since prostate cancer is thought to have a low alpha/beta ratio, and therefore particularly sensitive to larger fraction size, the logical next step is to investigate the use of more extreme hypofractionation.

SBRT delivery using a dose of 38 Gy in four fractions has previously been reported [98, 99]. In two large trials led by Fuller et al., SBRT with CyberKnife is delivered at a dose of 38 Gy in four fractions, using a heterogeneous planning technique to emulate HDR brachytherapy [47, 50]. Five year outcomes from the multicentre trial have recently been published in abstract form, having completed accrual of 259 patients [48]. 100% bPFS was demonstrated in low risk patients and 88.5% in intermediate risk. 3% grade 3 GU toxicity and one case of grade 4 GU toxicity were demonstrated and although obstructive GU and GI QOL was similar to baseline, 10% urinary incontinence was detected compared to 2% at baseline. The second study continues to recruit, aiming for an accrual of 258 patients. Five year outcomes have been reported after treating 79 patients, demonstrating bPFS of 98% and 92% in low and intermediate risk patients respectively. Toxicity was acceptable although 6% late grade 3 GU toxicity was reported [51].

High-dose-rate brachytherapy (HDR-BT) delivered in either three fractions of 10.5 Gy or two fractions of 13 Gy, has been shown by Hoskin et al. to have acceptable rates of biochemical control and toxicity at 3 years post treatment [100]. Within the SBRT setting, recruitment is ongoing to an Italian-based phase I/II trial (eHYPO) investigating the tolerability and efficacy of three fraction SBRT, at a total dose of 40 Gy delivered on alternate days [54]. SBRT delivery is with VMAT using cone-beam CT (CBCT) with fiducial markers for image guidance, and includes insertion of rectal gel spacer and urinary catheter to aid accurate urethra delineation. In the 2STAR trial led by Loblaw et al., 26 Gy in 2 weekly fractions is given, aiming to determine QOL at 5 years [52].

At the most extreme, Hoskin et al. have also demonstrated acceptable levels of toxicity after single dose HDR-BT, although did note higher rates of urinary toxicity compared to a two fraction schedule, and in those patients treated with 20 Gy compared to a 19 Gy single-fraction [101]. Single fraction SBRT is currently being assessed in a phase II randomised control trial (PROSINT) led by Greco et al. in Portugal [12]. Using a urethral-sparing planning technique, intermediate-risk patients are randomised to receive SBRT with either 45 Gy in five fractions, or a 24 Gy single fraction. SBRT delivery is with VMAT, using rectal balloon immobilisation and urethral catheter loaded with beacon transponders for tracking. The accrual target is 30 patients, primarily to determine toxicity up to 5 years post treatment. In addition, a diffusion-weighted MRI is performed 15 min after the first treatment to determine early physiologic changes, and biopsy performed 2 years post treatment to evaluate pathologic response. A further single–arm trial (ONE-SHOT) by Zilli et al., was due to open in 2017 [55]. Using similar image guidance and planning techniques, they aim to deliver 19 Gy in one fraction to the prostate and proximal SV, and 17 Gy to the urethral planning risk volume (PRV).

14.6 Combining SBRT Boost with Conventional Radiotherapy

There is randomised trial evidence that an HDR-brachytherapy boost combined with EBRT can improve relapse-free survival compared with EBRT alone in intermediate- and high-risk prostate cancer [102]. Based on this data a number of trials are evaluating dose escalation using SBRT as a boost to the prostate in addition to conventionally fractionated EBRT. There is substantial variation in study design and SBRT dose used within these trials. In three trials treatment is allocated based on risk group. In a multicentre trial by Mantz et al. aiming for 350 patients, treatment low risk patients are treated with SBRT monotherapy, 40 Gy in five fractions, and intermediate risk patients with IMRT 45 Gy in 25 fractions over 5 weeks, followed by an SBRT boost of 22 Gy in four fractions [56]. Harsolia et al., aim to deliver 36.25 Gy in five fractions SBRT monotherapy to low/intermediate-risk patients, and 50.4 Gy in 28 fractions followed by an SBRT boost of 27.5 Gy in five fractions to high risk patients, with hormone therapy as indicated [79]. Hirsch et al., are using a three fraction SBRT boost of 21 Gy delivered following pelvic irradiation in high risk patients, combined with ADT [78]. In the BOOSTER trial the SBRT boost is given prior to EBRT and is escalated from an initial dose level of 20 Gy in two fractions to the PTV and 25 Gy to the GTV if identified [80]. Once acceptable toxicity has been established, the dose is escalated to a maximum of 24 Gy in two fractions to the PTV and 30 Gy to the GTV, with a primary outcome measure of $\geq$grade 3 RTOG acute toxicity rate.

Two randomised trials based in Poland aim to determine efficacy from delivery of a prostate boost using SBRT in comparison to standard fractionation. HYPOPROST is a large, multicentre trial aiming to randomise 465 patients to receive either a hypofractionated boost of 15 Gy in two fractions, or a conventionally fractionated boost of 30 Gy in 15 fractions, following IMRT to the

whole pelvis using 46 Gy in 23 fractions in combination with ADT [19]. A further trial by Suwinski et al., which has not yet opened to recruitment, is due to compare conventional EBRT alone at 76–78 Gy in 38–39 fractions, with conventional EBRT 76–78 Gy in 38–39 fractions in addition to a boost of 20 Gy in two fractions given with brachytherapy or SBRT [18].

Within the BLaStM randomised trial, Pollack et al. are treating patients either with EBRT 76 Gy in 38 fractions and a SIB of 91.2 Gy in 38 fractions to the MRI defined GTV, or EBRT 76 Gy in 38 fractions preceded by a single stereotactic boost of 12–14 Gy to MRI defined GTV [20]. The primary aim of the trial is to compare the rate of pathologic complete response between the two treatment arms.

14.7 Pelvic SBRT

The role of prophylactic pelvic node irradiation remains controversial. Conventionally fractionated pelvic radiotherapy is sometimes considered in those patients at higher risk of harbouring micrometastatic disease within the pelvis, however, there is currently no conclusive evidence with regard to efficacy, and there is an associated increased risk of bowel toxicity. Ongoing trials are investigating the use of pelvic SBRT in high-risk patients. As previously mentioned, the trial for high risk patients by King et al. includes pelvic SBRT 25 Gy in five fractions to the pelvis, as directed by the treating clinician [69–71]. Treatment was well tolerated by the initial 23 patients who received pelvic SBRT, although median follow was short at 13.8 months [71].

In the FASTR trial, 16 high risk patients were treated with linac-based SBRT to the prostate and pelvic nodes, in combination with 12 months ADT [72, 73]. 40 Gy in 5 weekly fractions was delivered to the prostate and SV, and 25 Gy in 5 weekly fractions to the pelvic nodes. Unfortunately, the trial was terminated due to higher than expected toxicity at 6 months. There was no $\geq$ grade 3 acute toxicity but one patient suffered grade 3 late GU toxicity, and four patients experienced $\geq$ grade 3 late GI toxicity. As a result, the currently recruiting phase II trial (FASTR2) does not include pelvic SBRT and the prostate dose has been reduced to 35 Gy [64]. Possible factors contributing to the excessive toxicity include a large CTV-PTV margin of 5 mm, the use of CBCT without fiducial markers, and the inclusion of relatively frail patients within the study. Loblaw et al. have employed the same dose fractionation within the SATURN trial, delivering 40 Gy to the prostate/SV and 25 Gy to the pelvis in 5 weekly fractions, with 12–18 months of ADT [74]. In this trial, a 3 mm PTV margin has been applied to the prostate and 6 mm to the lymph nodes. Both CBCT and fiducial markers have been used for image guidance. Early results from 30 patients suggest that this schedule was reasonably well tolerated, demonstrating no $\geq$ CTCAE (version 3.0) grade 3 toxicity at 3 or 6 months [75]. At 6 months G2 late GI toxicity was reasonable at 6.9%, although G2 GU toxicity was 34.5% which seems high in comparison with conventionally fractioned or moderately hypofractionated pelvic IMRT as reported by Ferreira et al. [103].

Recently open to recruitment is the SPORT trial, which is a randomised trial evaluating the feasibility of SBRT in high risk prostate cancer, with or without elective nodal irradiation [17]. Thirty high-risk patients are expected to be randomised between SBRT 36.25 Gy in five fractions to the prostate and SV alone, and SBRT 36.25 Gy in five fractions to the prostate/SV in addition to SBRT 25 Gy in five fractions to the pelvic nodes. All patients are treated in combination with ADT. The primary outcomes of the study are to evaluate adequacy of recruitment rate over 2 years, acute toxicity, QOL, and the number of SBRT plans delivered as planned and on schedule. As part of the study blood, urine and prostate tissue will be taken for analysis to investigate potential predictive markers for patients at greater risk of toxicity.

14.8 Combining SBRT with Systemic Therapy

The role of androgen deprivation therapy (ADT) in combination with SBRT for localised prostate cancer is unclear. Evidence for using ADT with standard radiotherapy in low- and intermediate-risk patients is unconvincing, particularly now in the context of dose escalated radiotherapy [104, 105]. In view if this, many of the current prospective SBRT trials in this group, such as the PACE trial, do not include ADT. One exception is the multicentre trial by Tran et al., where 4 months ADT is given in combination with SBRT (36.25 Gy in five fractions) to intermediate-risk patients. Zelefsky et al., have recently commenced recruitment to a multicentre phase III randomised trial to compare SBRT alone or in combination with hormones, in intermediate-risk patients (those with only radiographic evidence of T3 disease are not excluded) [13]. SBRT is given to all patients at a dose of 40 Gy in five fractions, and patients randomised to the SBRT and hormones arm are additionally given 6 months treatment with Degaralix. The primary endpoint of the trial is to determine the number of patients with a positive biopsy at 2 years in intermediate-risk patients.

In high risk prostate cancer, there is greater evidence for the use of ADT in combination with high-dose radiotherapy, as demonstrated by results from the DART trial which supports the use of long-term ADT in these patients [106]. Where specified in currrently ongoing SBRT trials for high-risk patients, ADT is generally administered, either as mandated or at the discretion of the treating clinician (Tables 14.1 and 14.3). There is however variation in the duration of ADT given. In the ASSERT randomised trial, 6 months and 18 months ADT is given alongside SBRT for intermediate- and high-risk patients respectively [15]. In FASTR-2 the duration of leuprolide has been extended to 18 months from 12 months, as used in the initial FASTR protocol, following the reduction in SBRT dose and exclusion of pelvic node treatment as previously discussed [64, 72].

The development of novel androgen-directed therapies given in combination with LHRH analogues, have improved outcomes in castrate resistant metastatic prostate cancer [107, 108]. The next step is to evaluate any potential benefit in the adjuvant setting. The STAMPEDE trial has demonstrated a survival advantage from giving up-front Abiraterone in combination with LHRH analogues in patients presenting with advanced prostate cancer [109]. Notably, this benefit was also seen in those patients receiving radiotherapy for non- metastatic disease. The currently recruiting AASUR trial is combining Abiraterone and Apalutamide (ARN-509), with Leuprolide and SBRT to determine efficacy in very high risk localised prostate cancer [77]. Abiraterone works by inhibiting CYP17 which is an important enzyme involved in androgen production, and Apalutamide is a competitive androgen receptor antagonist. Patients begin the drug combination 3 months before SBRT, continuing for a total of 6 months.

14.9 Conclusion

SBRT research in localised prostate cancer is rapidly evolving. There is substantial evidence demonstrating SBRT to be a safe and effective treatment in low- and intermediate-risk patients, although questions remain regarding optimal technique, dose and fractionation. However, before SBRT can be internationally classified as a standard treatment option, it is vital to confirm at least equivalence with surgery and conventionally fractionated radiotherapy. Results of randomised trials such as the PACE trial are therefore eagerly anticipated.

Evidence for SBRT in high risk patients is much less developed, although the number of ongoing prospective trials in this setting is encouraging. Larger randomised trials are required to compare SBRT with conventional fractionation, and many questions remain with regard to dose, target coverage including the need for pelvic SBRT, and the potential benefit of combining SBRT with systemic therapy.

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15 Conclusions: Perspectives on the Role of SBRT in the Management of Localized Prostate Cancer

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SBRT is emerging as a promising treatment intervention in the management of patients with clinically localized prostate cancer. The various prospective single institution and retrospective series which have been published in the literature demonstrate what appears to be comparable PSA relapse free survival outcomes for SBRT patients compared to those treated with high-dose conventionally fractionated IMRT [1–6]. While for most published SBRT series the median follow-up has been 4–5 years, these reports so far seem to dispel the notion and concern that such treatment regimens are associated with significant complications and difficult-to-manage toxicities. As well documented in the previous chapters, the incidence of relapsing disease to date as well as acute and long-term toxicities associated with SBRT has been low, and there is no evidence that the prevalence of severe grade 3 and 4 urinary and rectal related toxicities is any higher than what is observed after conventionally fractionated external beam radiotherapy. Of course, longer follow-up will be necessary to confirm these observations.

The utilization of SBRT in the treatment of localized disease has significantly increased over recent years and this is likely attributed to the incorporation of several innovations associated with SBRT delivery. These features include the use of sophisticated treatment planning methods, tighter planning target volume margins thereby including less volume of normal tissue exposed to the higher doses of radiation and the use of image-guidance to achieve the high degree of accuracy needed for high dose-per fraction SBRT. In addition we have adopted MRI-based contouring and treatment planning for routine SBRT [7]. Contours derived from MRI images can better delineate the anatomy, provide more reliable anatomic information regarding the location of the prostate apex, bladder neck and the neurovascular bundles- all anatomic sub-units that may be related to treatment toxicities. The use of a hydrogel spacer injected into the space between the anterior rectal wall and the posterior aspect of the prostate especially for high dose SBRT could possibly be valuable especially for this cohort of patients which effectively spares more of the rectal volume from the high doses of irradiation. A randomized control study has already demonstrated reduced rectal toxicity among patients treated with conventionally fractionated radiation when using the hydrogel spacer compared to radiation alone without the hydrogel spacer [8].

Currently several randomized control trial (RCT) are underway testing the value of SBRT for localized disease compared to the efficacy and tolerance of conventionally fractionated radiation and moderately fractionated radiotherapy

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Table 15.1 Ongoing randomized trials evaluating ultra-hypofractionated SBRT regimens

Trial	To be accrued	Population	Endpoint	Dose arms
HEAT NCT 01794403	456	Low and intermediate risk	PSA-RFS	36.25 Gy/5 f. vs 70.2 Gy/26 fx
HYPO-RT-PC ISRCTN45905321	1200	Intermediate risk	PSA-RFS	42.7 Gy/7 f. vs 78 Gy/39 fx
NRG-GU005	606	Intermediate risk	Quality of life	36.25 Gy/5 f. vs 70 Gy/28fx
PACE B NCT01584258	858	Low and intermediate risk	PSA RFS	36.25 Gy/5 f. vs 78 Gy/39 fx

regimens (Table 15.1). The PACE trial which successfully accrued 1200 patients between July 2005 and November 2015 randomized patients to be treated to 78 Gy delivered in 39 fractions versus an ultra-hypofractionated regimen of 7 fractions of 6.1 Gy delivered every other day for approximately 2.5 weeks. This important study was one of the first of these trials to be initiated and recently the preliminary results were reported at the ESTRO 2018 meeting where the PSA relapse-free survival outcomes were noted to be similar (83% in both arms at 5 years) and the incidence of toxicity was not significantly higher using the SBRT regimen. However, it will require a number more years for the results of these RCT to mature and shed further light on the long-term efficacy and safety of this treatment approach.

The concept of utilizing high doses per fraction in the treatment of prostate cancer as monotherapy has been tested in the form of high dose rate (HDR) brachytherapy and ten year results have been published [9]. We and others have previously noted that the dose distributions of an HDR brachytherapy plan may be associated with less integral dose delivered to normal tissue structures outside of the target region and the potential to more easily deliver greater intensification of dose within the prostate and especially to dominant intra-prostatic lesions as can be seen on MRI through the inherent characteristics associated with brachytherapy [10, 11]. While there are no randomized control trials comparing HDR monotherapy with conventionally fractionated external beam therapy regimens for the treatment of localized disease, the clinical outcomes observed from HDR monotherapy experience serves as further proof of concept that high dose per fraction radiation programs are feasible and can be delivered with respectable tumor control rates without significant late toxicity if normal tissue constraints are adhered to in the planning process. The published reports of HDR monotherapy have demonstrated a low incidence of grade 3 and 4 toxicity rates. Notwithstanding the absence of any prospective comparisons of HDR monotherapy regiments versus SBRT, it would appear that tumor control outcomes are comparable to what is achieved with more standard external beam radiotherapy.

There is still a great deal to learn with the continued maturation of ongoing studies and clinical experiences related to SBRT. What are the tolerance outcomes beyond 5 and 10 years? What is the optimal dose per fraction for SBRT? What is the role of ADT for intermediate risk patients when using SBRT and what is the efficacy of SBRT when using this approach as a boost in the setting of high risk disease such as what is currently routinely employed with brachytherapy in conjunction with conventionally fractionated IMRT? Is there a role using SBRT in the setting of proton therapy and are the outcomes better than SBRT photon therapy?

Compiling to date the significant number of patients with clinically localized prostate cancer treated with SBRT as well as the ongoing randomized control trials, it is difficult to characterize at this time SBRT as experimental. The published single institution reports demonstrate clearly its feasibility and efficacy with follow-up observations extending to 10 years. RCTs will answer the question in the near future whether such treatment regimens will be comparable or superior to conventionally fractionated or moderate-fractionated regimens. In the meantime it will be incumbent upon radiation oncologists introducing SBRT into their clinical practice to

meticulously select patients appropriate for treatment, use state of the art planning approaches such as MRI imaging to help delineate the prostate target and surrounding normal tissue structures, carefully adhere to target and normal tissue dose constraints to insure the safe and accurate delivery of therapy, and apply methods to track and correct for inter- and intra-fraction motion.

We will only learn more about SBRT and address unanswered questions through the enrollment of our patients on prospective clinical trials. At our institution we completed a Phase I–II dose escalation trial where the total SBRT was escalated in a serial fashion from 32.5 to 35 Gy and then 37.5 Gy and 40 Gy in a 5-fraction SBRT regimen. To date there has been only one grade 3 urinary toxicity consisting of a urethral stricture at the high dose 40 Gy dose level and 2-year biopsy outcomes demonstrate excellent tumor control outcomes especially noted for the 40 Gy dose level. We are currently accruing intermediate risk patients on a Phase III randomized trial where eligible patients are randomized to receive SBRT of 40 Gy in 5 fractions with 6 months of androgen deprivation therapy versus SBRT alone. The outcomes of trials such as these and of course the ongoing Phase III studies will ultimately inform clinicians of appropriate clinical practice and how to best incorporate SBRT into the management of clinically localized prostate cancer.

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