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,

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 ≤ 7, PSA ≤ 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
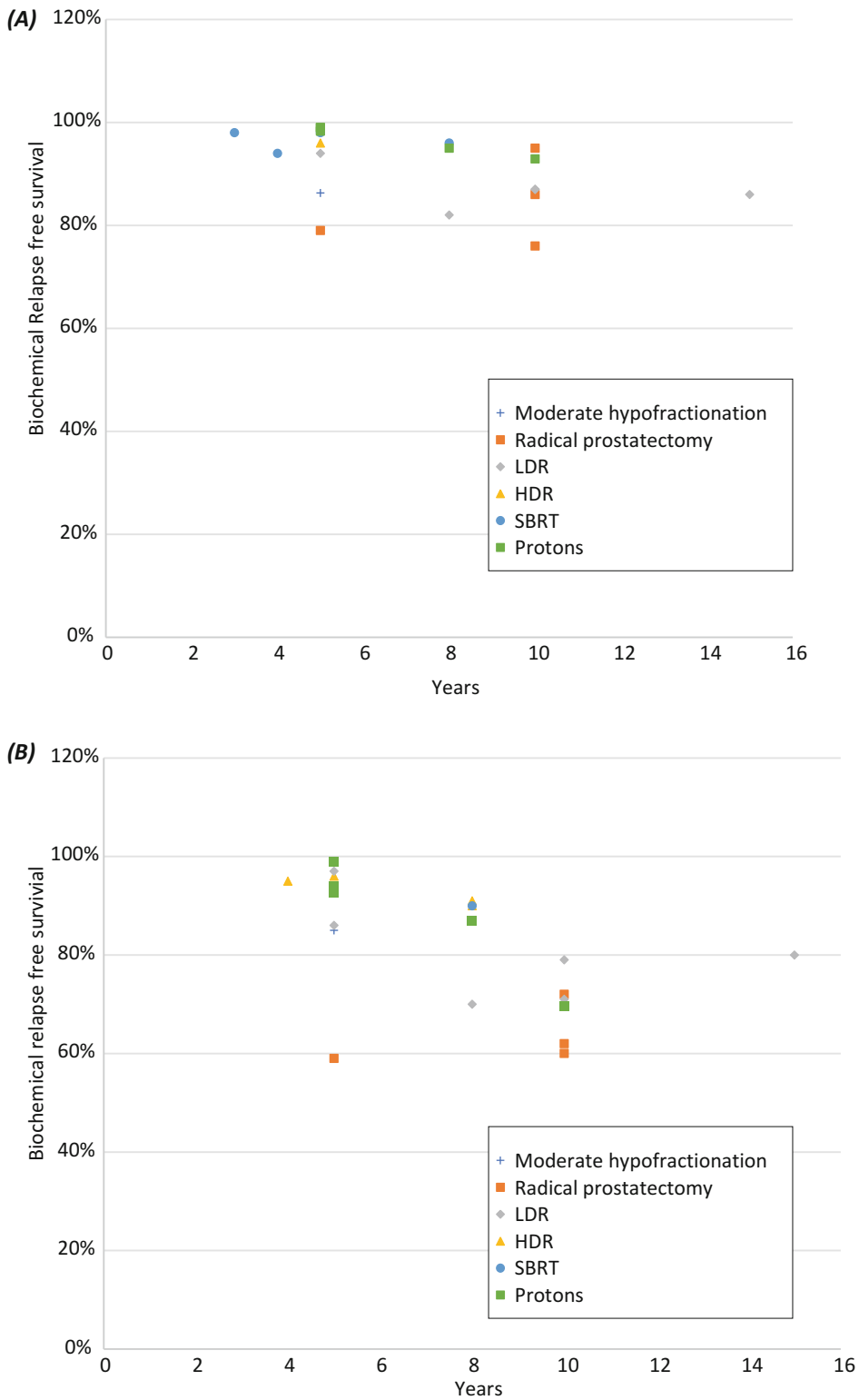
Fig. 7.1 Comparison of reported biochemical relapse free survival with various treatment modalities in series that reported low-risk patients (**a**), intermediate-risk patients (**b**) or both low- and intermediate-risk patients (**c**)
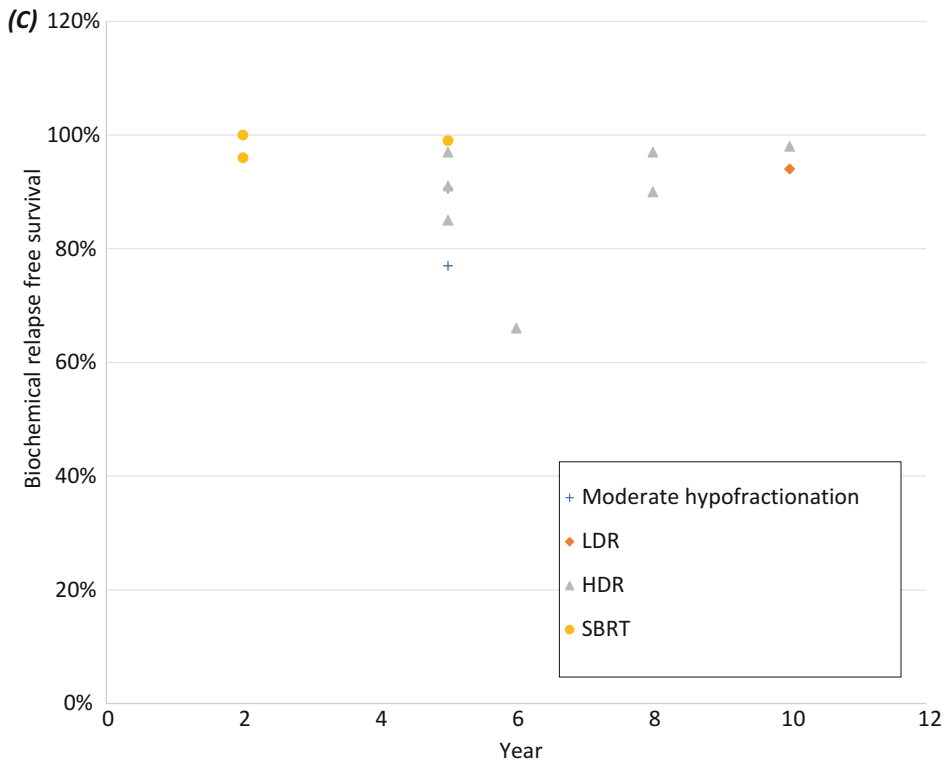
Fig. 7.1 (continued)

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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