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Critical Review

Stereotactic body radiation therapy (SBRT) for high-risk prostate cancer: Where are we now?

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Abstract

Purpose: Stereotactic body radiation therapy (SBRT) is increasingly being used for the management of localized prostate cancer. This trend combined with declining use of brachytherapy (BT) has pushed issues and questions regarding the use of SBRT to the forefront. A systematic literature review was conducted to review the current evidence of biochemical disease-free survival (bDFS) and toxicity of SBRT in high-risk (HR) prostate cancer.

Methods and materials: A search was carried out on the PubMed and Embase databases. Studies were included if HR patients were treated using SBRT monotherapy or as a boost and bDFS was reported. Selected high-dose-rate (HDR) BT studies including HR patients from published reviews were selected to compare with SBRT results. Data from recent published phase 3 trials involving HR patients were also compared.

Results: Our search yielded 8862 articles. Of these, 20 studies with a median follow-up from 1.6 to 7 years were included in this review. The 5-year bDFS was 81% to 91% in monotherapy studies and 90% to 98% in boost studies. For reference, 19 studies that reported treating HR patients with HDR monotherapy or boost were selected. The 5-year bDFS in HDR monotherapy studies and boost studies was 85% to 93% and 72% to 93%, respectively. The incidence of late grade 3 genitourinary toxicity was 0% to 4.4% and 0% to 2.3% in SBRT monotherapy and SBRT boost studies, respectively.

Conclusion: The evidence for SBRT in HR patients in this review is based on observational studies with relatively few patients and short follow-up (level III evidence). Based on these data and the principles surrounding treatment, SBRT boost should ideally be validated in clinical trials. SBRT monotherapy should be used cautiously in highly selected HR patients outside of a clinical trial.

Summary: Stereotactic body radiation therapy (SBRT) is increasingly being used for the management of clinically localized prostate cancer. This trend, combined with the decline in the use of brachytherapy, has pushed issues and questions regarding the use of SBRT to the forefront. A systematic literature review was conducted to establish the current evidence of biochemical and toxicity outcomes of SBRT in high-risk prostate cancer.

Conflicts of interest: M.R. has served as an advisor and lecturer for Accuray Inc. A.G.M. declares no conflict of interest.

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Introduction

In the United States, it is expected that there will be 161,360 new cases of prostate cancer in 2017 and that 26,730 patients will die of prostate cancer in the same year.[1] The addition of radiation to androgen deprivation therapy (ADT) has been shown to improve the overall survival in high-risk (HR) patients compared to ADT alone.[2,3] Dose escalation with external beam radiation therapy (EBRT) has been shown to improve biochemical control compared with EBRT with a conventional dose.[4-11] Compared with dose-escalated EBRT (DE-EBRT), low-dose-rate (LDR) brachytherapy (BT) boost combined with EBRT has demonstrated an improvement in biochemical control.[12] High-dose-rate (HDR) BT boost appears to provide similar advantages as LDR BT boost.[13]

Stereotactic body radiation therapy (SBRT) is a technique that delivers highly conformal, high-dose radiation, typically in 1 to 5 fractions. In prostate cancer, SBRT is increasingly being used to leverage the radiobiological advantage thought to be associated with a low α/β ratio as well as the convenience of a short and noninvasive treatment. SBRT can deliver a radiation dose distribution that closely resembles the distribution associated with HDR BT.[14] As a result, many centers have extrapolated their planning goals, doses, and fractionations from HDR BT to SBRT. SBRT is currently considered to be a safe and effective treatment for low- and selected intermediate-risk prostate cancer patients[15]; however, the role in HR patients is still somewhat controversial. For example, in 1 recent review based on men treated from 2004 to 2012, SBRT was rarely used as a boost compared with EBRT, EBRT+BT, BT, or SBRT alone, suggesting that its use in HR patients was quite low.[16] This review uses a literature-based search to summarize the published clinical evidence documenting the efficacy and complication rates associated with the use of SBRT in the management of patients with HR prostate cancer. For purposes of reference and correlation, we selected several retrospective studies reporting outcomes among HR patients treated with HDR BT. We also selected 5 high-level studies including patients with HR prostate cancer[8,10,12,17,18] treated with EBRT ± ADT, DE-EBRT, and ADT combined with either DE-EBRT or ± LDR BT.

Methods and materials

Search strategy

A literature review was carried out on the PubMed and Embase databases (July 2017). In PubMed, we searched for the following terms: prostatic neoplasms [mh] or prostate cancer [tw] AND radiosurgery [mh] or SBRT [tw] or stereotactic body radiotherapy [tw] or stereotactic ablative radiotherapy [tw]. In the Embase database, we searched for the following EMTREE terms: "prostate tumor"/exp AND "radiosurgery"/exp OR "stereotactic body radiation therapy"/exp OR "stereotactic ablative radiotherapy"/exp. No limits were placed on the dates of publication. After the initial selection of studies was completed, the references of the studies were manually cross-referenced to find additional studies of interest. Abstracts were reviewed, and the full texts of suitable manuscripts were obtained and reviewed.

Study selection

Studies were included if HR prostate cancer patients were treated using SBRT as a monotherapy or a boost treatment and if the study reported the number of HR patients treated with SBRT and stated the definition used for HR patients. All types of studies were included. Only studies written in English were included. When more than 5% of patients were treated with a specific technique that was different from the majority used in that study, then it was required to be classified as a "mixed" study. Studies were excluded for the following reasons: the study did not report the biochemical disease-free survival (bDFS); it used an SBRT technique delivered in more than 5 fractions; the patients in the study had a previous prostatectomy; fewer than 5 HR patients were included in the study; or the study was published only as an abstract at a scientific meeting. When more than 1 study represented information from the same series, we included the latest updated publication.

Data extraction

The following items were extracted from each included study: author, year, country, number of patients treated, number of HR patients, HR definition, dose of SBRT radiation course, median follow-up, use of ADT and duration, toxicity, and the bDFS for HR patients or all patients included in the study. Data from all included studies were extracted by the first author (A.G.M.) and verified by the second author (M.R.). Tables summarizing information were created. Commentary and opinion were formulated through discussions between the authors.

Correlation

To correlate the results of SBRT with HDR BT, we selected studies with HR prostate cancer patients from the HDR BT reviews.[19-22] Only studies published after 2005 that reported bDFS were included to ensure relevance to the current practice of radiation techniques. Data from

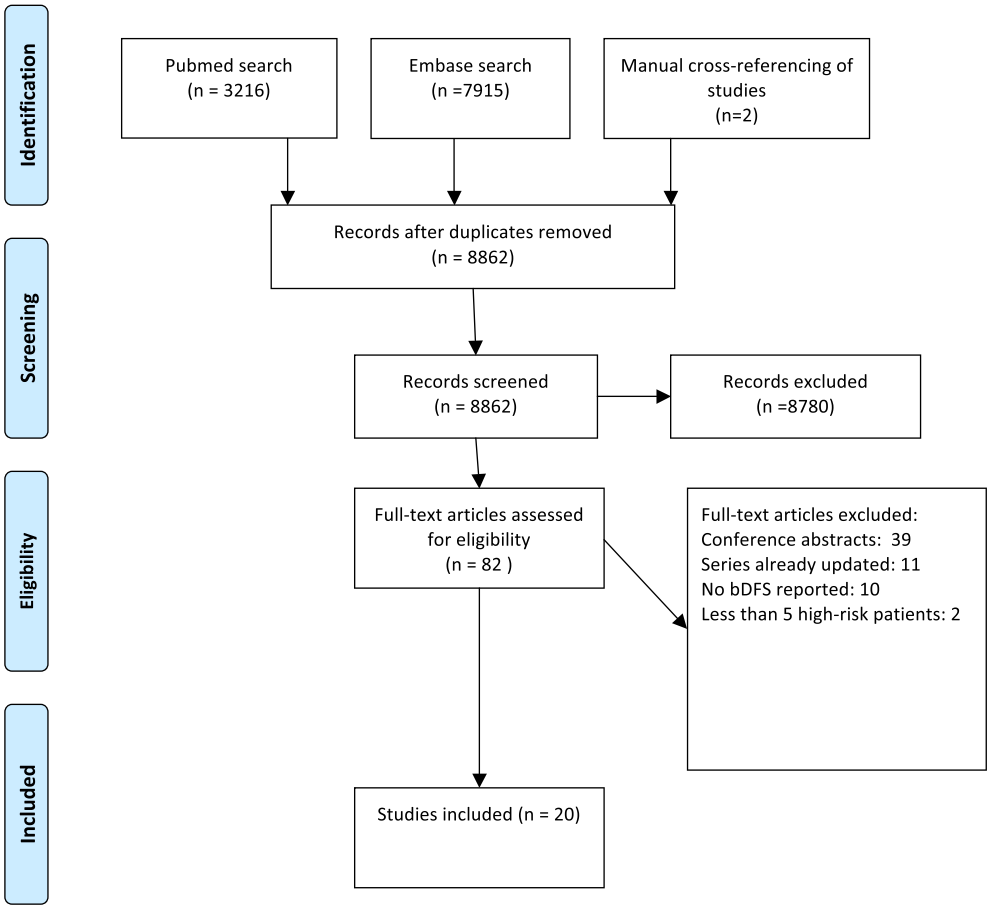

Figure 1 Preferred reporting items for systematic reviews diagram depicting the study selection procedure. bDFS, biochemical disease-free survival.

high-level trials incorporating dose escalated EBRT,[8,10,12,17] EBRT plus long-term ADT,[18] and EBRT plus LDR prostate BT[12,23] were included to place SBRT results in context. Additional information regarding prostate-specific antigen nadir (nPSA) from HDR studies in low- and intermediate-risk patients[24,25] was incorporated to contrast nPSA in the absence of this information in the HDR studies included.

Results

The initial search yielded 3216 references from the PubMed database, 7915 references from the Embase database, and 2 references from cross-referencing. After internal and external duplicates between the 2 groups were discarded, we had 8862 articles. After screening the titles and abstracts of these articles with the inclusion criteria, 82 candidate studies were identified for full text evaluation. Of these, 62 were excluded after the full text was reviewed. A total of 20 studies were included in this review. Figure 1 summarizes the selection process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[26]

SBRT monotherapy in HR patients

No randomized studies were found. Our search identified 13 published studies that included HR patients in SBRT monotherapy regimens.[27-39] Table 1 summarizes the data from the series identified. The median follow-ups ranged from 1.6 years to 7 years with, only 2 studies[32,36] reporting follow-up beyond 5 years. The studies included 7 to 125 HR patients. A total of 459 HR patients were treated with SBRT monotherapy in the studies found. The largest number of studies were reported from the United States (n = 8), followed by Korea (n = 2), with single reports from Italy, Taiwan, and Finland. The 2 largest series were from Finland and the United States and included 111 and 125 HR patients, respectively. None of the studies included exclusively HR patients.

The definition of HR prostate cancer varied somewhat between the series. The D'Amico and/or the National Comprehensive Cancer Network (NCCN) definitions of

Table 1 Series of HR prostate cancer patients treated with SBRT as a monotherapy

Author, y, origin	No. patients (HR patients)	HR definition	Dose	Median FU (y)	ADT/duration	Toxicity (scale used)
Kang 2011, Korea[31]	44 (29)	D'Amico	8 Gy ×4, 8.5 Gy ×4 or 9 Gy ×4	3.3	Yes/24 mo	Acute: GU and GI grade 2: 25%. Late GU and GI 2: 14% [b]
Bolzicco 2013, Italy[27]	100 (17)	NCCN	7 Gy ×5	3	8 HR patients received/NS	Acute: GU and GI grade 2: 12% and 18%. Late GU grade 3: 1% [c]
Chen 2013, USA[28]	100 (8)	D'Amico	7-7.25 Gy ×5	2.3	"Most" received 3-6 mo/2 HR patients 2-3 y	2-y actuarial GU and GI grade ≥2 (31%) and (1%). 21% late GU flare [b]
King 2013, USA[33]	1100 (125)	D'Amico	7-8 Gy ×5	3	38% of HR patients/ 4 mo	NS
Lee 2014, Korea[36]	45 (13)	NCCN	7.2 Gy ×5	5.3	Yes/NS	Acute: GU and GI grade 2: 4% and 4%. Late GU and GI grade 2: 4% and 4% [b]
Janowski 2014, USA[30]	57 (9)	D'Amico	7-7.25 Gy ×5	2.9	Yes/NS	2-y actuarial grade ≥2 GU and GI: 49% and 1.8% [b]
Davis 2015, Radiosurgery Society[29]	437 (33)	NCCN 2015	7-9.5 Gy ×4-5	1.6	15 HR patients received ADT/NS	Late grade 2 GU: 8%. Late grade 2 proctitis: 2% [b]
Fan 2015, Taiwan[38]	31 (16)	NCCN	7.5 Gy ×5	3	82% HR/NS	No grade ≥3. 7 patients acute GU grade 2. 2 patients late GU grade 2 [b]
Rana 2015, USA[39]	102 (8)	D'Amico	5-8 Gy ×5	4.3	8.9% of patients/4 mo	Late grade 2 GU and GI: 9.9% and 3% [c]
Ricco 2016, USA[37, d]	270 (A1: 32)	NCCN 2015	7-7.5 Gy ×5	4.1	27% of all SBRT patients/NS	No late GU and GI grade 3 [c]
Katz 2016, USA[32]	515 (38)	NCCN 1.2016	7-7.25 Gy ×5	7	Yes/NS	Acute: GU and GI grade 2: <5%; Late GU and GI grade 2: 9% and 4%. Late GU grade 3: 1.7% [c]
Kotecha 2016, USA[35]	24 (13)	NCCN	7.25 and 10 Gy ×5 to LDPTV and HDPTV SIB	2	Yes/NS	Acute GU grade 2: 38%. Late GU and GI grade 2: 4% and 8% [b]
Koskela 2017, Finland[34]	218 (111)	D'Amico	7-7.25 Gy ×5	2	88.3% of HR/48% of HR patients ADT ≥24 mo	No acute GU and GI grade 3 Intermediate-term GU and GI grade 3: 1.8 and 0.9% [b]

(*Continued*)

HR prostate cancer were used in all the studies. The total dose of radiation used in the monotherapy studies ranged from 32 to 40 Gy in 4 or 5 fractions. One study[34] used a simultaneous integrated boost with 10 Gy in 5 fractions to high dose planning tumor volume. All studies used ADT in some patients. Six studies reported the percentage of HR patients who received ADT. The duration of ADT treatment was variable among included studies. Five studies reported the bDFS for all patients and 9 studies reported the bDFS specifically for HR patients. From these studies with specific bDFS for HR patients, 2 reported a 5-year bDFS[31,33] of 81% and 91% involving 125 and 29 HR patients, respectively. The longest bDFS was reported by Katz et al,[32] who reported an 8-year bDFS of 65% in

Table 1 (*continued*)

Outcomes HR patients [a]	Comments and conclusions
5-y bDFS: 90.9%	Short FU, small number of patients. EQD2: 87-108 Gy, Urethral avoidance used. T3: 22% patients
3-y bDFS: 94% (all patients)	Short FU. Duration of ADT not reported. Urethral catheter for planning and treatment. 12% of bounce. Favorable HR patients
2-y-bDFS: 99% (all patients)	Short FU. 79% of patients with a pretreatment SHIM score ≥10 conserved potency beyond 2 y. Late urinary flare could be related to urethral dose; urethral sparing not used
5-y bDFS: 81%	No difference in patients with ADT vs no ADT. Median nPSA 0.2 at 3 y. Better bDFS with dose ≥36.25. Short FU. No T stage specified
5-y bDFS: 89.7% (all patients)	GS ≥8: 17.8%, cT3 ≥13.3%, 68%: 70-79 y of age. No specific bDFS for HR patients
2-y bDFS: 98% (all patients)	Only 15.7% HR. Short FU. Prostate volume ≥50 mL. At 2-y median PSA: 0.4
2-y bDFS: 90% but with PSA >20 ng/mL: 62.5%	95% monotherapy. Short FU. No information about use of ADT. Community-based practices. Variable equipment used, different fractionations, planning heterogeneity. Median nPSA 0.3 ng/mL 3 y
3-y bDFS: 82%	Median PSA 0.12 at 12 mo. 45% HR patients. 6% VHR patients
3-y bDFS: 100% (all patients)	24% bounce. Urinary flare after 1 y. T stage and PSA not reported
6-y bDFS for SBRT: 92%. 4-y bDFS for HR and VHR: 95% and 72%	Duration of ADT not reported. Acute toxicity grades 1 and 2 not reported. Authors conclude SBRT "alternative" to IMRT. Monotherapy. Few HR and VHR patients
8-y bDFS: 65% for HR. Favorable unfavorable intermediate 7-y bDFS ~93% and 68%	Author concluded ADT could be of less benefit with SBRT. Only T1-T2a, 32 patients GS ≥8. Author concluded SBRT "equivalent" conventional EBRT. Longest FU but few HR patients
2-y bDFS: 95.8% for all patients. 2 HR patients biochemical failures	SIB. Only 13 HR patients. Patients T ≥3:1. GS ≥8: 12 patients. Short FU. High acute toxicity grade 2 (38%)
23-mo bDFS: 92.8%	Short FU. Long ADT for HR patients. All grade 3 toxicity was in ≥36.25 Gy patients. 51% patients HR. 32% locally advanced (T3-4). GS ≥8: 13%, PSA >20: 15%. Median nPSA: 0.2 at 9-12 mo

ADT, androgen deprivation therapy; bDFS, biochemical disease-free survival; EBRT, external beam radiation therapy; EQD2, equivalent total dose in 2-Gy fractions; FU, follow-up; GI, gastrointestinal; GS, Gleason score; GU, genitourinary; HD, high dose; HDPTV, high-dose planning tumor volume; HR, high risk; LD, low dose; LDPTV, low-dose planning tumor volume; NCCN, National Comprehensive Cancer Network; nPSA, nadir PSA; NS, not specified; PSA, prostate-specific antigen; SBRT, stereotactic body radiation therapy; SHIM, Sexual Health Inventory for Men; 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] This study has 2 arms, 1 of SBRT (A1) and the other of intensity modulated radiation therapy (A2).

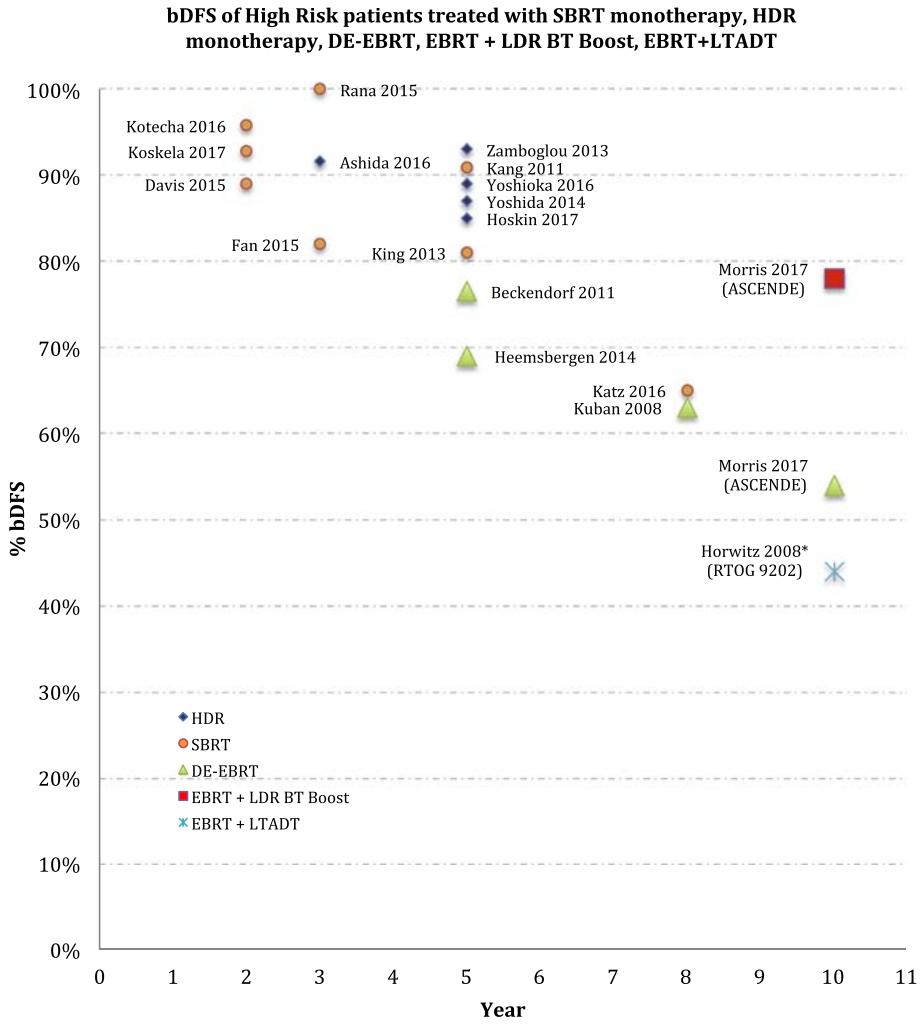

Figure 2 Biochemical disease-free survival (bDFS) (Phoenix) of high-risk (HR) patients treated with stereotactic body radiation therapy (SBRT) monotherapy studies, high-dose-rate (HDR) brachytherapy monotherapy studies, external beam radiation therapy plus long-term androgen deprivation therapy (EBRT + LTADT) study, dose-escalated external beam radiation therapy (DE-EBRT), and low-dose-rate prostate brachytherapy (LDR BT). Data from the Androgen Suppression Combined With Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) trial were estimated from the Kaplan-Meier curve of bDFS for HR patients. Data for Radiation Therapy Oncology Group (RTOG) 9202 (EBRT + LTADT) were estimated from biochemical rate reported. *RTOG 9202 used the American Society for Therapeutic Radiology and Oncology definition for biochemical failure. **DE-EBRT arm of the ASCENDE-RT trial received 8 months of neoadjuvant ADT.

HR patients. See Fig 2 for more details of bDFS and correlation with other radiation therapy techniques (discussed in the following section).

SBRT as a boost in HR patients

Five published studies with HR patients treated with SBRT boost were included.[40-44] Table 2 summarizes the characteristics of series using SBRT as a boost. No randomized studies were found that reported using SBRT as a boost in HR patients. The median follow-up ranged from 2 to 5 years. Three studies[40,42,44] had a follow-up of 4 or more years. The percentage of HR patients in these studies ranged from 26% to 100%. A total of 178 HR patients were treated with SBRT boost in the studies found. The first published study dated back to 2010. The definition of HR prostate cancer varied between the series. The D'Amico and/or the NCCN HR definitions were used in all the studies. All studies except for 1 used ADT. The percentage of HR patients who received ADT and the duration of ADT were not reported in all studies. The highest percentage use of ADT was reported by Lin et al,[43] in which 92.7% of the patients received ADT. The boost dose reported in these studies varied from 10 Gy in 2 fractions to 21 Gy in 2 or 3 fractions. The biologically effective dose (BED) calculated for an $\alpha/\beta = 1.4$ ranged from 201 to 281 Gy. Two SBRT boost studies[40,41] delivered whole pelvis radiation therapy to lymph nodes if the risk of lymph node involvement predicted with the Roach formula was more than 15%. Two studies[42,43]

Table 2 Series of HR prostate cancer patients treated with SBRT as a boost or mixed series of patients treated with SBRT ± EBRT

Author, year, origin	No. patients (HR patients)	HR definition	Dose	Median FU (y)	ADT/duration
Miralbell 2010, Spain[40]	50 (33)	D'Amico	EBRT: 64-64.4 Gy/32-35 fx + boost: 5, 6, 7, or 8 Gy ×2	5.25	32 patients/15 patients with GS ≥8: 24-30 mo
Lin 2014, Taiwan[43]	41 (41)	NCCN	EBRT: 45 Gy/25 fx + boost: 7 Gy ×3	3.5	92.7% of patients/24
Katz 2014, USA[45]	97 (97)	NCCN	7-7.25 ×5 (monotherapy) EBRT: 45 Gy/25 fx +boost: 6-7 Gy ×3	5	51.5% of patients/ median 5 mo
Freeman 2015, Registry for prostate cancer radiosurgery[46]	2000 (172)	NCCN	7-8 Gy ×5 (monotherapy) EBRT: 40-50 Gy + boost: 6.5-7.25 ×3	2	NS
Anwar 2016, USA[41]	48 (34)	NCCN	EBRT: 45 Gy/25 fx + boost: 9.5-10.5 Gy ×2	3.5	88% of patients/NS
Mercado 2016, USA[44]	108 (59)	D'Amico	EBRT: 45-50.4 Gy/25-28 fx + boost: 6.5 Gy ×3	4.4	63.6% of patients/NS
Kim 2017, Korea[42]	42 (11)	2.2014 NCCN	EBRT: 45 Gy/25 fx + boost: 7 Gy ×3	4.4	No

(*continued on next page*)

treated all patients with whole pelvis field to 45 Gy in 25 fractions before the SBRT boost to cover pelvic lymph nodes. In 1 study, patients received treatment to prostate and seminal vesicles in SBRT boost and EBRT without lymph node irradiation.[44] Two SBRT boost studies used intensity modulated radiation therapy (IMRT) for the whole pelvis treatment.[41,43] One study used IMRT or 3-dimensional conformal radiation therapy for the whole pelvis treatment.[40] One study did not report the technique used for whole pelvis treatment.[42] One study[43] reported a 4-year bDFS of 92% in HR patients. Two studies[40,41] (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. See Fig 3 for more details of bDFS and correlation with other radiation therapy techniques.

SBRT monotherapy or as a boost: Mixed studies

Two studies combined HR patients who received SBRT as a monotherapy or as a boost[45,46] (Table 2). Katz et al[45] reported on HR patients using SBRT monotherapy to a total dose of 35 to 36.25 Gy in 5 fractions in 52 patients and an SBRT boost to a dose of 19 to 21 Gy in 3 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, respectively. The other study by Freeman et al[46] reported SBRT monotherapy or SBRT boost on 2000 patients, with 172 being HR patients. According to the recorded data, 86% of the patients received SBRT monotherapy to a total dose of 35 to 40 Gy in 5 fractions, and 14% received an SBRT boost to a total dose of 19.5 to 21.75 Gy. At a median follow-up of 2 years, the 2-year bDFS was 87% for HR patients. The SBRT mixed studies were grouped with SBRT boost studies in Table 2 and Fig 3.

Correlation with selected HDR series

To correlate the studies of SBRT in HR patients, we selected 5 studies that reported treating HR patients with HDR monotherapy[47-51] and 14 studies that reported treating HR patients with an HDR BT boost[52-65]; for this analysis, SBRT mixed and SBRT boost studies were grouped. Tables 3 and 4 summarize the characteristics of the HDR studies included. Figures 2 and 3 graphically summarize outcome between using HDR and SBRT for HR prostate cancer patients. Additional information is also included in Figs 2 and 3 from high-level trials incorporating dose escalated EBRT,[8,10,12,17] EBRT plus

Table 2 (*continued*)

Toxicity (scale)	Outcome for HR patients [a]	Comments and conclusions
Acute GU and GI grade 2: 46% and 8%. Late GU grade 2: 12.5%. Proportion of patients GI grade ≥2: 16% at y 3 and 8% at y 5 [b]	5-y-bDFS: 98% for all patients	Boost to the region of the dominant lesion guided by eMRI. 38 patients: T3-4 X eMRI. Only 1 HR relapse. Used LINAC
Acute: GU and GI grade 2: 27% and 12% No grade 3 late GU or GI toxicity [b]	4-y-bDFS: 92%	Small series but all HR. 40% have T3 and 61% have PSA >20. Mean nPSA 0.05 at 24 mo. Because of long-term ADT, a longer FU needed. Authors concluded that "WPRT + SBRT boost in HR is a feasible option with acceptable toxicity."
Late GU and GI grade 2: 2.3%-7.8% and 0%-13.3%. Late GU grade 3: 2.3-3.9% [c]	5-y bDFS were 69% and 63% for HR and unfavorable intermediate	Majority patients T1c. No T3-4 patients. GS ≥8: 63.9%. Faster declining in PSA with SBRT boost + EBRT compared with SBRT monotherapy but equal after 3 mo. Longer FU still needed. Good tolerance. Pelvic RT could have more value with more advanced disease
No late GU grade 3 Late grade GI grade 3: 1 patient [b]	2-y-bDFS: 87%	80% of men <70 y maintained erections sufficient for intercourse following radiosurgery. Observational registry. No data of T stage
No acute grade 3. One patient late grade 3 GU toxicity [b]	5-y-bDFS: 90% for all patients	44% of patients GS ≥8. 42% of patients with T3. Median nPSA: 0.05 ng/mL at 26.2 mo. Long FU needed to see outcomes long term. 7
Late accumulative rate GU and GI grade ≥2: 40% and 12% [b]	3-y-bDFS: 89%	Patients ≥T3: 1. GS ≥8: 43 patients. Authors concerned about the required margin to cover extracapsular extension and SV invasion. Patients recovered to their baseline urinary/bowel QOL by 2 y. Longer FU needed.
Acute: GU and GI grade 2: 24%/19%. Late GU and GI, grade 2: 12%/12% (NS)	4-y-bDFS: 71%	Lower bDFS for HR compared with other series. Low number of HR patients. 9.5% patients T3. 33% patients: GS >8. nPSA 0.34 ng/mL at 36 mo

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 1.

[a] At least otherwise specified.

[b] Common Terminology Criteria for Adverse Events, version 3-4 scale.

[c] Radiation Therapy Oncology Group scale.

long-term ADT,[66] and EBRT plus LDR prostate BT[12] to place these findings in context. The Phoenix definition[67] (nadir + 2 ng/mL) was used in all studies unless otherwise specified for biochemical failure.

In the HDR monotherapy and boost studies, the percentage of HR patients ranged from 20% to 100% and from 27% to 100%, respectively. When the SBRT studies were correlated with the HDR studies, the SBRT studies had fewer HR patients, and a lower number of studies reported biochemical control at 5 years and shorter follow-up compared with the HDR series. The 5-year bDFS SBRT monotherapy studies ranged from 81% to 91% compared with the 5-year bDFS in HDR monotherapy studies that ranged from 85% to 93%. Seven BT boost HDR studies reported biochemical control beyond 10 years, whereas SBRT boost studies only had biochemical control reported results out to 5 years. Katz et al[45] reported a 5-year bDFS of 69% for HR patients and 2 more studies[40,41] (with more than 50% HR patients) reported a 5-year bDFS of 90% and 98%. The 5-year bDFS for HR managed with a HDR boost ranged from 72% to 93%.

nPSA

Ten SBRT monotherapy studies reported nPSA. The median nPSA in SBRT monotherapy studies at 3 years was reported to be 0.2 to 0.45 ng/mL.[27,29,33,39] Three SBRT boost or combined studies reported the median nPSA; 1 reported the mean nPSA. The median nPSA in SBRT boost studies at 3 years was reported to be 0.1 to 0.32 ng/mL.[42,45] Figure 4 provides more details on nPSA among studies and correlation with HDR, DE-EBRT, and LDR studies. We included 2 studies of HDR in low- and intermediate-risk patients[24,25] in this graphic to correlate results because the selected HDR HR patient studies did not include data about nPSA. nPSA was similar in SBRT boost studies and HDR studies; however, it tended to be slightly lower in LDR boost studies than SBRT studies.

Toxicity

The toxicity was reported in different manners and varied among studies; some used common terminology

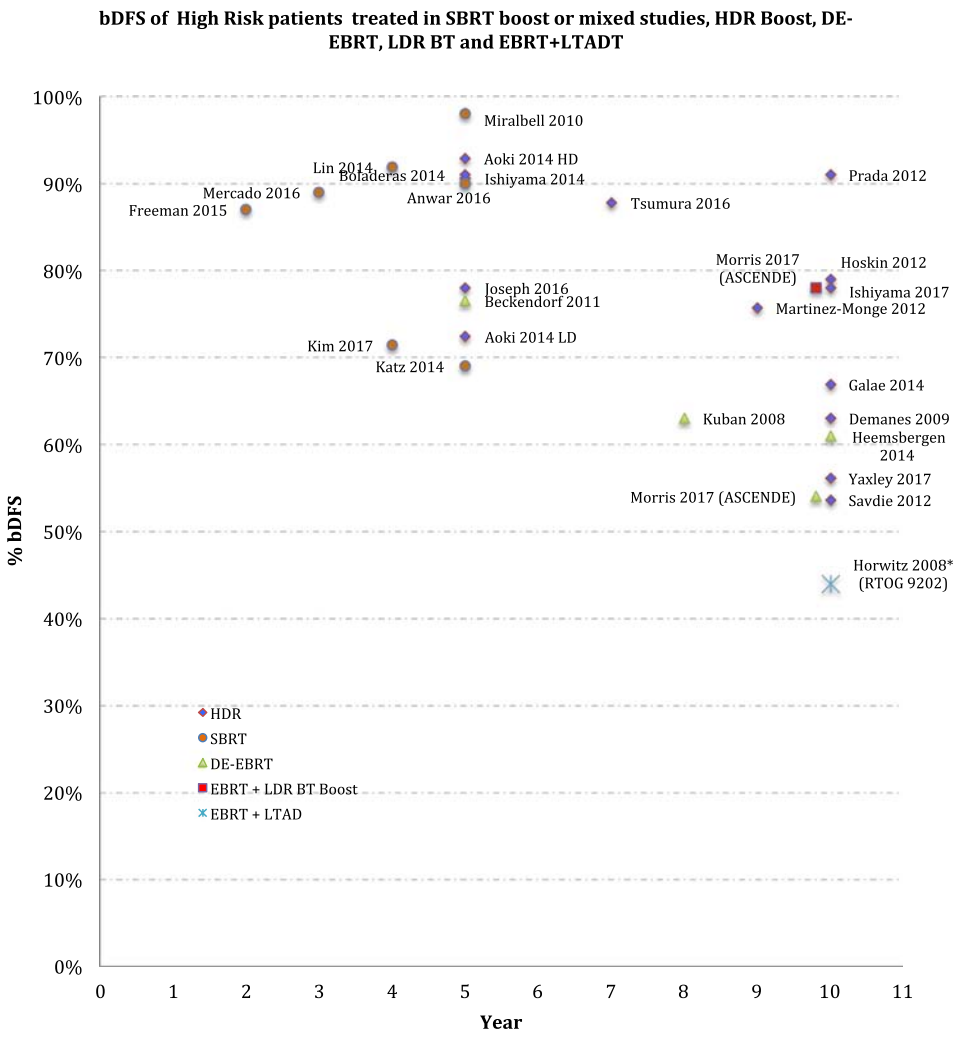

Figure 3 Biochemical disease-free survival (bDFS) (Phoenix) of high-risk (HR) patients treated with stereotactic body radiation therapy (SBRT) boost, high-dose-rate (HDR) boost, external beam radiation therapy plus long-term androgen deprivation therapy (EBRT + LTADT), dose-escalated external beam radiation therapy (DE-EBRT), dose rate prostate brachytherapy (LDR BT) arm of ASCENDE-RT trial. Data from the ASCENDE-RT trial were estimated from the Kaplan-Meier curve of bDFS for HR patients. Data for Radiation Therapy Oncology Group (RTOG 920)2 (EBRT + LTADT) were estimated from biochemical rate reported. *RTOG 9202 used the American Society for Therapeutic Radiology and Oncology definition for biochemical failure. **DE-EBRT arm of the ASCENDE-RT trial received 8 months of neoadjuvant ADT.

criteria for adverse events (CTCAE), and others used the Radiation Therapy Oncology Group (RTOG) scale. Tables 1 through 4 and Fig 5 provide details of toxicity among studies and correlation with HDR, DE-EBRT, and LDR studies.

All SBRT monotherapy studies but 1 reported at least 1 kind of toxicity. Six studies reported an incidence of acute grade 2 (RTOG or CTCAE) genitourinary (GU) and gastrointestinal (GI) toxicity that ranged from 4.4% to 38% and from 0% to 18%, respectively. Eight studies reported late grade 2 (RTOG or CTCAE) GU or GI toxicity that ranged from 3% to 16% and from 0% to 11%, respectively. Nine studies reported an incidence of late grade 3 (RTOG or CTCAE) GU toxicity that ranged from 0% to 4.4%. In the SBRT boost and mixed studies, the CTCAE scale was used to evaluate toxicity in all but 2 studies, which used the RTOG scale. Four studies reported an incidence of acute grade 2 (RTOG or CTCAE) GU and GI toxicity that ranged from 23.8% to 46% and from 8% to 19%, respectively. Six studies reported an incidence of late grade 2 (RTOG or CTCAE) GU that ranged from 2.3% to 25%. Six studies reported an incidence of late grade 3 (RTOG or CTCAE) GU and GI toxicity that ranged from 0% to 2.3% and from 0% to 10%, respectively.

Discussion

SBRT is increasingly being considered an alternative to conventionally fractionated radiation therapy in clinics

Table 3 Selected series of HR patients treated with HDR brachytherapy as a monotherapy

Author, year, origin	No. patients (HR patients)	HR definition	Dose	Median FU (y)	ADT/duration
Zamboglou 2013, Germany[47]	718 (146)	MSKCC group definition	9.5 Gy ×4 11.5 Gy ×3	4.4	87 HR patients/ median: 9 mo
Yoshida 2014, Japan[48]	48 (48)	NCCN	6 Gy ≥9 7 Gy ≥7 9.5 ≥4	5.9	All patients/8 mo
Ashida 2016, Japan[49]	68 (42)	NCCN	13.5 Gy ×2	2.5	76.9% of patients/3-6 mo
Yoshioka 2017, Japan[51]	524 (244)	PSA >20 ng/mL, GS >8, or CS T3-T4	14 Gy ×2 6.5 Gy ×7 7 Gy ×7 6 Gy ×9 6.75 ×8	5.9	91% of HR patients/52% ≥1 y; 19% >3 y
Hoskin 2017, UK[50, c]	293 (147)	NS	(A): 19 Gy ×1 and 20 Gy ×1 (B): 13 Gy ×2 (C): 10.5 ×3	A: 4 B: 5.2 C: 9	% of patients A 74% B 76% C 87%/NS

(*Continued*)

with appropriate equipment, resources, and clinical expertise. The American Society for Therapeutic Radiology and Oncology (ASTRO) model policy updated in 2013 stated: "It is ASTRO's opinion that data supporting the use of SBRT for prostate cancer have matured to a point where SBRT could be considered an appropriate alternative for select patients with low- to intermediate-risk disease."[68] SBRT for HR patients has not yet been adequately studied, however. In this review of HR patients, we were somewhat surprised to find more studies that used SBRT in HR patients as a monotherapy[27-39] rather than as a boost.[40-44] We suspect that these patients represented highly selected patients and not the typical HR patients who might be likely to receive a combined approach as might be recommended in accordance with NCCN guidelines.

In the SBRT boost studies reported here, the BED calculated ($\alpha/\beta = 1.4$) ranged from 201 to 281 Gy for the combination of EBRT and SBRT boost. In the SBRT monotherapy studies reported here, the BED calculated ($\alpha/\beta = 1.4$) ranged from 114 to 268 Gy. Dose escalated EBRT studies[8,10,17] used to reach a dose of 78 to 80 Gy to a BED ($\alpha/\beta = 1.4$) that ranged from 181 to 194 Gy. Zaorsky et al[69] 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 >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[70] reported a 10-year bDFS of 81.1% in patients who received a dose to a BED > 268 Gy ($\alpha/\beta = 1.2$) compared with a 10-year bDFS of 56.9% in patients who received a dose to a BED < 268 Gy ($\alpha/\beta = 1.2$). Similarly, the clinical failure rate and distant metastases were statistically significantly better in patients treated to a BED >268 Gy ($\alpha/\beta = 1.2$). SBRT boost can obtain BED similar to that with HDR boost[40,41]; the studies reviewed here showed comparable biochemical outcomes between SBRT boost and HDR boost in HR patients. Hypofractionation studies in prostate cancer and assumptions about low α/β have been questioned[71]; thus, more studies of α/β are required.

The bDFS in HR patients in the SBRT monotherapy and the SBRT boost studies correlate favorably to those reported in dose escalated EBRT studies that report a 5-year bDFS that ranged from 57% to 69%.[8,10,11] The 5-year bDFS in the SBRT boost studies (69%-98%) was comparable to the results reported in HDR boost studies (72%-93%) and DE-EBRT plus ADT studies (75%-90%).[72-74] In the Androgen Suppression Combined With Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) trial[12] that compared DE-EBRT against LDR BT in intermediate and HR patients, both arms with ADT reported a 5- and 10-year bDFS for HR patients (estimated from the Kaplan-Meier curve) of 85% and 78%; 83% and 55% were reported in the LDR BT arm and the DE-EBRT arm, respectively. Results from SBRT boost studies correlate favorably to the ASCENDE-RT trial. The ASCENDE-RT trial is a randomized and prospective trial, however, which makes the results more reliable. The nPSA has been related to bDFS,[75-78] and nPSA levels <0.5 ng/mL have been associated with better biochemical outcomes and improved distant metastases-free survival.[77] The ASCENDE-RT trial[12] reported an nPSA of 0.01 and 0.25 ng/mL in the LDR BT arm and the DE-EBRT arm, respectively. In the SBRT studies reviewed here, the nPSA appears to be higher than in the LDR BT arm in the ASCENDE-RT trial. nPSA after SBRT

Table 3 (*continued*)

Toxicity (scale)	Outcomes for HR patients [a]	Comments and conclusions
Acute grade 3 GU and GI: 5.4% and 0.2%. Late grade 3 GU and GI: 3.5% and 1.6% [b]	5-y bDFS 93%	4 patients: ≥T3a, 12 patients: GS ≥8, 7 patients: PSA ≥20. Relatively favorable patients. Risk group definition led to superior outcomes. More fx, less reproducible treatment.
Late GU grades 2 and 3: 10% and 4% Late GI grades 2 and 3: 2% and 2% [b]	5-y bDFS: 87%	Multiple fractions in a single application. Caution with displacements of needles and thrombosis. 19 patients: T3-4. 20 patients: GS >8. PSA ≥20: 32. MRI for stage. Authors concluded "HDR-BT + ADT: Promising biochemical control."
Acute grade 2 GU frequency: 12.3%. Late grade 3 GU: 1.5% [b]	3-y bDFS: 91.6% and 88% in HR and VHR	Short FU. Quality control before the Second fraction. 33.8% patients: T3-4, GS ≥8: 44.6% , PSA ≥20: 27.7%
Acute: GU grade 3: 1%; cumulative incidence late GU and GI grade 2-3 at 5-y: 19% and 3% [b]	5-y bDFS: 89%	Heterogeneity of fx. Retrospective multicenter study. Could be bias for reporting of toxicity. High % received ADT. 25% patients: T3-4, 25% patients GS ≥8, 26% patients PSA >20
Kaplan-Meier 4 y: GU grade 3: 2% (A and B) and 11%; (C) GI grade 3: 0% (A and B) and 1% (C) [c,d]	5-y bDFS: 85%	No criteria for HR specified. Patients ≥T3: 33-36%, GS ≥8: 6%-18%, PSA >20: 14%-25%. Single dose achieves good bDFS and no excess of late morbidity compared with 2 or 3 fx

CS, clinical stage; HDR, high dose rate; MSKCC, Memorial Sloan Kettering Cancer Center. Other abbreviations as in Tables 1 and 2.
[a] At least otherwise specified.
[b] Common Terminology Criteria for Adverse Events, version 3-4.
[c] This study used 3 groups (A, B, and C) according to dose received.
[d] Radiation Therapy Oncology Group.

treatment can decay continuously in time, however,[79] and it is possible that with longer follow-up the nPSA of SBRT could be lower and nearer to the nPSA reported with LDR BT.

The biochemical results of the SBRT monotherapy studies found in this review are provocative; however, these data should be interpreted cautiously because there are no randomized studies, and studies exclusively involving HR patients treated by SBRT monotherapy were not found. Although there are more data supporting HDR monotherapy for HR patients, it is not currently recommended by the American Brachytherapy Society or in the NCCN guidelines.[80,81] SBRT boost results appear to be comparable to HDR boost results at 5 years, however, with the latter already being an accepted treatment for HR patients.[80,81] Although these 5-year results are encouraging, it is noteworthy that in the ASCENDE-RT trial[12] the 5-year bDFS results of DE-EBRT and LDR BT were similar and significantly different at 10 years. For this reason, a 10-year follow-up would be highly desirable to evaluate how SBRT boost results compared with HDR in the long term.

This review has several limitations. All of the studies included were observational studies. Few studies included HR patients only. The HR definition was variable within studies, the follow-up was short, the number of patients was low, and the use of ADT differed among studies. The duration and use of ADT between the SBRT studies were variable. Most of the studies used ADT, but not all specified the percentage of HR patients who received ADT. The variable use of ADT could affect the bDFS outcomes, especially those with a short follow-up. The nPSA in HDR studies selected was not reported. The unknown use of ADT in many studies influence the nPSA; for a reliable comparison of the nPSA between SBRT and HDR or LDR, measures without ADT are required. There was a lack of complete data reported regarding the technique of SBRT and EBRT used across studies. Different planning constraints were used. The dose and fractionation used in SBRT and HDR series were variable. Although the technique of SBRT is not the focus of this review, this issue adds to the heterogeneity of data and caution should be used to interpret the results. Many studies did not report a bDFS for HR patients. The bDFS results of SBRT patients with longer follow-up could be different from the bDFS of HDR. Although HDR studies were selected from previous revisions, an extensive literature search was not performed. A statistical comparison between radiation therapy techniques was not carried out because of a lack of confidence in the comparability of patients in the studies. We acknowledge that data on patients in the series by Katz et al[32] or Bolzicco et al[27] could be double-counted in the series by King et al,[33] although King et al[33] stated that nearly half of the patients represent new data. The total number of HR patients treated with SBRT monotherapy in this review could be lower. Also, the series of Freeman et al[46] could have double-counted data from other series. The short follow-up of this series precludes using their findings in the conclusions, however.

Table 4 Selected series of High risk patients treated with EBRT + HDR boost

Author, year, origin	No. patients (HR patients)	HR definition	Dose HDR	Median FU (y)	ADT/duration
Demanes 2009, USA[52]	411 (113)	T3, GS 8-10 or PSA >20	EBRT: 36-39.6 Gy + boost: 5.5-6 Gy ×4	6.4	32% HR patients/NS
Prada 2012, Spain[55]	313 (294)	D'Amico or 2-3 intermediate risk FA	EBRT: 46 Gy/23 fx + boost: 11.5 Gy ×2	5.6	70% of all patients ADT for 1 y
Savdie 2012, Australia[56]	90 (90)	D'Amico	EBRT: 45 Gy/25 fx + boost 5.5 Gy ×3	7.8	Yes/12 mo
Martinez-Monge 2012, Spain[54]	190 (90)	NCCN	EBRT: 54 Gy/30 fx + boost 4.75 Gy ×4	3.7	95%: 2 y of ADT
Hoskin 2012, UK[53]	218 (116)	NCCN	A2**:** EBRT: 35.75 Gy/13 fx + boost 8.5 Gy ×2 [c]	7	92% of A2
Aoki 2014, Japan[57]	123 (123) [d]	D'Amico	LD: EBRT: 45 Gy/15 fx + boost 5-6 Gy ×2. HD: EBRT: 40 Gy/16 fx + boost: 9 Gy ×2	5	Yes/24 mo
Ishiyama 2014, Japan[60]	178 (178)	NCCN	EBRT: 30 Gy/10 fx + boost 7.5 Gy ×5	5	All/36 mo
Galalae 2014, Germany[59]	122 (55)	T3 or iPSA ≥35 or HT grade	EBRT: 50 Gy/25 fx + boost 9 Gy ×2	9.7 [f]	Yes/NS
Boladeras 2014, Spain[58]	377 (347)	D'Amico	EBRT: 60 Gy/30 fx + boost 9-15 Gy ×1	4.1	94% patients/36 mo
Schiffmann 2015, Germany[61]	392 (211)	D'Amico	EBRT: 50.4 Gy/28 fx + boost 9 Gy ×2	4	56% patients/NS
Tsumura 2016, Japan[63]	216 (216)	D'Amico	EBRT: 30 Gy/10 fx + boost 7.5 Gy x 5	7	All/36 mo
Joseph 2016, UK[62]	95 (61)	D'Amico	EBRT: 37.5 Gy/15 fx + boost 12.5 Gy ×1	5.4	97%/35 ≥2 y
Yaxley 2017, Australia[65]	507 (338)	PSA >20, GS >7, or ≥T3	EBRT: 46 Gy/23 fx + boost 5.5-6.5 ×3	10.3	Yes/11 HR patients 12-24 mo
Ishiyama 2017, Japan/ Singapore[64]	3424 (2180)	NCCN	EBRT: 39 Gy/13 fx + boost 18 Gy ×2 [g]	5.5	49%/NS

(*Continued*)

Furthermore, toxicity comparisons between studies in HR patients is problematic because most studies treated patients of all risks and had variable proportions of HR patients and the studies did not use the uniform toxicity assessment tools. Many of these series were not recruited prospectively and the toxicity collection was not formalized. Also, acute toxicity could be not measured at relevant time points for SBRT. Despite all of these limitations, from all SBRT studies reported here, which covered 2386 patients in mixed and boost series and 3043 patients in monotherapy series. The acute and late grade 2 GU and GI toxicity of SBRT studies may be slightly worse than HDR toxicity (although formal statistical comparisons were not made), whereas the late grade 3 GU toxicity of SBRT boost studies may be slightly better than HDR boost studies and LDR BT results of the ASCENDE-RT trial. Given the multitude of variables and differences in patient selection, we do not believe that formal statistical comparison analysis would be

Table 4 (*continued*)

Toxicity (scale)	Outcomes for HR patients [a]	Comments and conclusions
NS	10-y bDFS: 63%	Risk of selection bias. 38 patients: T3. 54 patients GS ≥8. 43 patients GS ≥20. Good results with long FU
6 patients had urethral stricture. No late grade ≥3 [b]	10-y bDFS: 91%, 88%, and 79%: 2 intermediate risk, 1 HR, and 2-3 HR FA	Risk definition led to superior outcomes. Number of ≥T3 not reported. Patients with GS ≥7: 24%. Patients PSA >20: 39%. Favorable results. BED dose: 292-366 Gy
NS	10-y bDFS: 53.6%	Only HR. Patients T3: 25%, GS ≥8: 40%, PSA >20: 38.9%. Selection bias. Better results with EBRT + HDR than expected with Kattan normogram
Late GU grades 2 and 3: 18% and 55%. Late GI grades 2and 3: 9% and 1.5% [b]	9-y bDFS: 75.7%	Only HR patients Long use of ADT. Short FU to report bDFS at 5 and 9 y. No repositioning of needles before each treatment
KM incidence at 5- and 7-y A2: GU, 26% and 31%; GI, 7% and 7% (Dische)	7-y bDFS: A1: 48% A2: 66%	Nearly 50% of HR Only randomized trial. Patients with T3: 31%. Patients with GS ≥8: 18%, PSA >20: 27%. Higher incidence of toxicity with longer FU
NS	5-y bDFS: HD, 92.9%; LD, 72.4%	No T reported. Patients GS ≥8: 81. Pre-HDR PSA ≤0.1 improved bDFS. Better result with 9 Gy ×2
Acute GU and GI grade 2: 11% and 0%. Late GU grade 2 and 3: 7% and 9.6%. Late GI grade 2: 2.8% [e]	5-y bDFS: 90.6% (97.8% and 81.9% for HR and VHR)	T3: 92 patients. 68 patients with GS ≥8. 50% patients had >30% risk of lymph involvement. 50% of patients neo. ≥12 mo. Long w aiting for treatment. Authors considered "Japanese sensitivity to ADT" as a factor of good response to treatment. Selection bias
Late GU and GI grade >3: 4.9% and 2.5% (NS)	10-y bDFS: 66.9%	Long FU. Low number of HR patients. Patients T3: 32%. PSA >40: 11.5%. Few local recurrences. Lower bDFS with Phoenix than previously
Acute GU/GI grade 2-3: 10% and 6%. Late GU/GI grade 2/3:13% and 6.6% [b]	271 patients with FU ≥26 mo: 5-y bDFS: 91%	High number of HR. PSA >20: 32% patients. GS 8-10: 35.8% patients. T3: 70% patients
NS	10-y bDFS +ADT: 50% vs 39% –ADT	PSA >20: 17.6% patients. GS >8: 14.8% patients. >T3: 19.6% patients. This series favors use of trimodality therapy
Acute GU grade 2 and 3: 14.8% and 4.6%. Late GU and GI grade 2: 9.7% and 2.8% [e]	7-Yr-bDFS: 87.8%	GS 8-10: 42% patients. T3-4: 52% patients. Post-radiation therapy nPSA value ≤0.02 ng/mL was associated with better long-term biochemical response
NS	5-y bDFS: 78%	GS >7: 35% patients. T3: 38%patients. PSA ≥20: 39% patients. Lower bDFS than other series
Urethral stricture rate: 13.6%, after 2005: 4.2% (NS)	10-y bDFS: 56.1%	PSA >20: 16%; GS ≥37%; T3-4: 46% patients. Long FU. Urethral constraints after 2005. Nodes not treated. Used 3D-CRT
10-y cumulative rate GU and GI grade ≥2: 26.8% and 4.1% [b]	10-y bDFS 78.1% and 70.6%: HR and VHR	Heterogeneous fractionation. Multiple constraints. Underreporting. Different treatment fields. Neo and adj ADT improved OS in HR. Results could change in other races

Adj, adjuvant; HD, high dose; HT, high tumor; LD, low dose; KM, Kaplan Meier; neo, neoadjuvant. Other abbreviations as in Tables 1 and 2.

[a] At least otherwise specified.

[b] Common Terminology Criteria for Adverse Events, version 3-4 scale.

[c] This study has 2 arms, arm 1: Only EBRT and arm 2: EBRT +HDR.

[d] Study has 2 arms (low-dose arm and high-dose arm).

[e] Radiation Therapy Oncology Group scale.

[f] Mean.

[g] Median dose and fractionation.

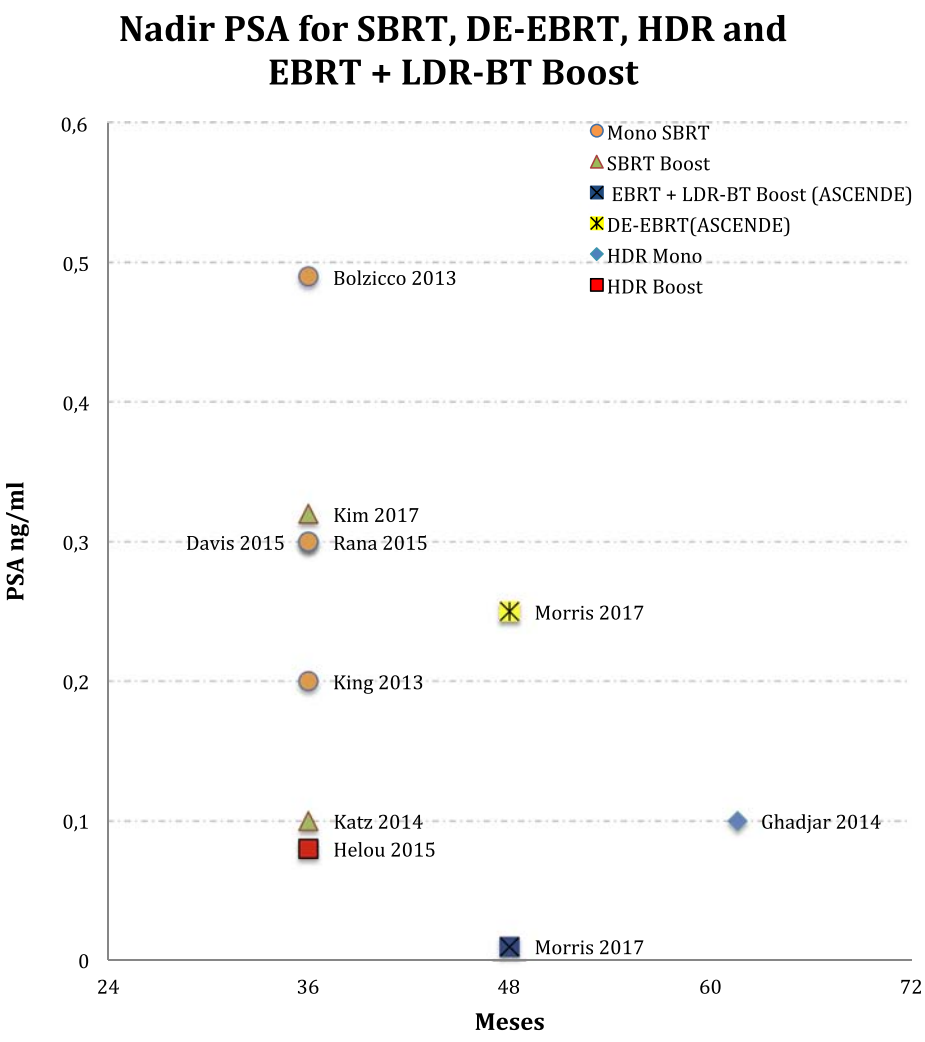

Figure 4 Acute and late toxicity reported in stereotactic body radiation therapy (SBRT), high-dose-rate (HDR), dose-escalated external beam radiation therapy (DE-EBRT), and dose rate prostate brachytherapy (LDR BT) studies. Not all SBRT and HDR studies reported toxicity data. Three scales were used in 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; however, they were plotted together in the figure.

appropriate. Further prospective studies comparing toxicity between radiation techniques are warranted.

A number of observations reached as a result of this review, however:

1. The currently available evidence is limited by observational studies with a relatively low number of patients and short follow-up.
2. None of the studies using SBRT monotherapy studies focus exclusively on HR patients, with most designed primarily for intermediate- and low-risk patients. The results of SBRT monotherapy studies should be interpreted cautiously, with the surprisingly favorable outcomes most likely to be explained by selection bias. Just how these patients should be selected, and whether these results will hold up with longer follow-up, remains unclear. More studies to clarify the role of ADT and pelvic radiation therapy in HR patients are required before the acceptance of SBRT monotherapy for HR patients. Outside of a clinical trial, we do not favor SBRT monotherapy unless fractionated IMRT and ADT are contraindicated.
3. The studies with SBRT boost showed similar bDFS and nPSA results to HDR boost, but follow-up of more than 5 years is required.
4. The acute and late toxicity grade 2 GU and GI may be slightly higher in series using SBRT boost studies than HDR boost studies, but the late grade 3 GU and GI toxicity appears to be similar (but could be lower).
5. SBRT is technically less complex for practitioners and less invasive for patients than BT. SBRT should be considered an option in the absence of expertise in BT or for patients who are not candidates for BT

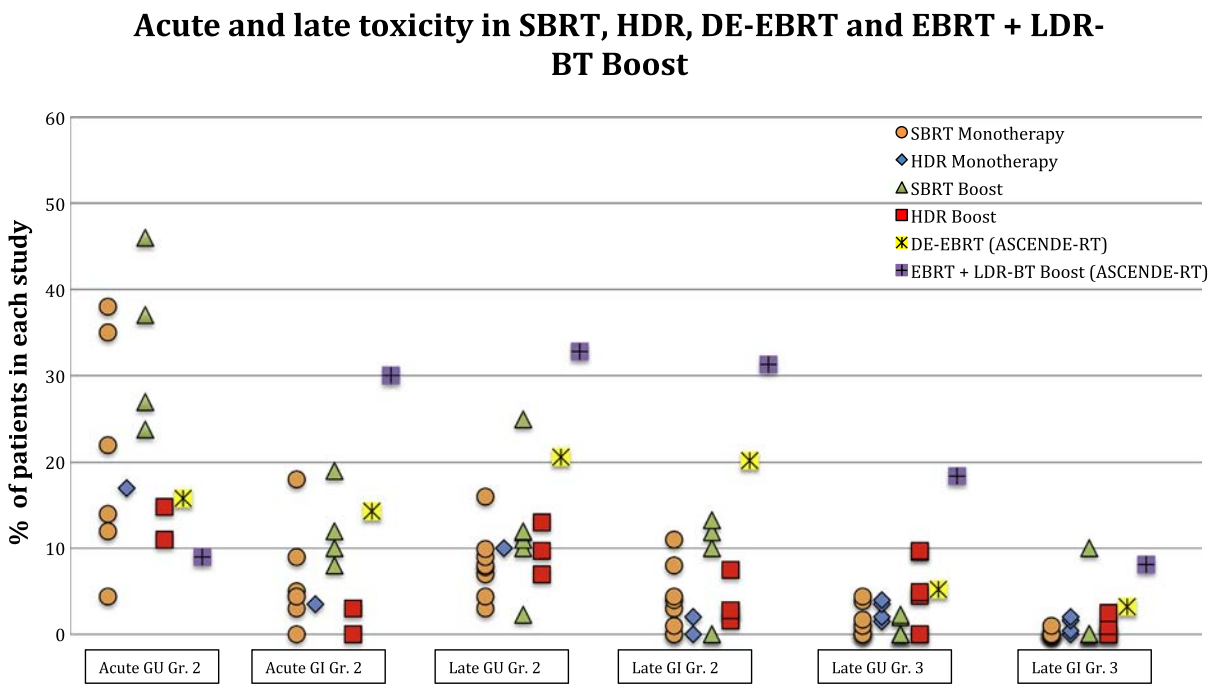

Figure 5 The median prostate-specific antigen nadir (nPSA) reached for stereotactic body radiation therapy (SBRT), high-dose-rate (HDR), dose-escalated external beam radiation therapy (DE-EBRT), and dose rate prostate brachytherapy (LDR BT). Studies with a median nPSA <36 months were not reported.

(eg, anticoagulation, not a candidate for anesthesia) or if a patient strongly prefers this approach.

Conclusion

The evidence for SBRT in HR patients in this review 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 boost and are likely to render results at least as good as those reported with DE-EBRT, albeit with the possibility of higher late GU toxicity. SBRT reduces the treatment time for patients and may be preferred over BT given that it is less invasive and requires neither the discontinuation of anticoagulation nor anesthesia. SBRT boost should ideally be validated in clinical trials. Even if it becomes evident that the results are slightly worse than HDR, SBRT is technically less complex for practitioners and may be preferable to patients. In our opinion, with the exception of very highly selected cases, SBRT monotherapy should not be used in HR patients outside of a clinical trial.

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