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American Brachytherapy Society Task Group Report: Use of androgen deprivation therapy with prostate brachytherapy—A systematic literature review

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ABSTRACT

PURPOSE: Prostate brachytherapy (PB) has well-documented excellent long-term outcomes in all risk groups. There are significant uncertainties regarding the role of androgen deprivation therapy (ADT) with brachytherapy. The purpose of this report was to review systemically the published literature and summarize present knowledge regarding the impact of ADT on biochemical progression-free survival (bPFS), cause-specific survival (CSS), and overall survival (OS).

METHODS AND MATERIALS: A literature search was conducted in Medline and Embase covering the years 1996–2016. Selected were articles with >100 patients, minimum followup 3 years, defined risk stratification, and directly examining the role and impact of ADT on bPFS, CSS, and OS. The studies were grouped to reflect disease risk stratification. We also reviewed the impact of ADT on OS, cardiovascular morbidity, mortality, and on-going brachytherapy randomized controlled trials (RCTs).

RESULTS: Fifty-two selected studies (43,303 patients) were included in this review; 7 high-dose rate and 45 low-dose rate; 25 studies were multi-institutional and 27 single institution (retrospective review or prospective data collection) and 2 were RCTs. The studies were heterogeneous in patient population, risk categories, risk factors, followup time, and treatment administered, including ADT administration and duration (median, 3–12 months);71% of the studies reported a lack of benefit, whereas 28% showed improvement in bPFS with addition of ADT to PB. The lack of benefit was seen in low-risk and favorable intermediate-risk (IR) disease and most high–dose rate studies. A bPFS benefit of up to 15% was seen with ADT use in patients with suboptimal dosimetry, those with multiple adverse risk factors (unfavorable IR [uIR]), and most high-risk (HR) studies. Four studies reported very small benefit to CSS (2%). None of the studies showed OS advantage; however, three studies reported an absolute 5–20% OS detriment with ADT. Literature suggests that OS detriment is more likely in older patients or those with pre-existing cardiovascular disease. Four RCTs with an adequate number of patients and well-defined risk stratification are in progress. One RCT will answer the question regarding the role of ADT with PB in favorable IR patients and the other three RCTs will focus on optimal duration of ADT in the uIR and favorable HR population.

CONCLUSIONS: Patients treated with brachytherapy have excellent long-term disease outcomes. Existing evidence shows no benefit of adding ADT to PB in low-risk and favorable IR patients. UIR and HR patients and those with suboptimal dosimetry may have up to 15% improvement in bPFS with addition of 3–12 months of ADT, with uncertain impact on CSS and a potential detriment on OS. To minimize morbidity, one should exercise caution in prescribing ADT together with PB, in

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particular to older men and those with existing cardiovascular disease. Due to the retrospective nature of this evidence, significant selection, and treatment bias, no definitive conclusions are possible. RCT is urgently needed to define the potential role and optimal duration of ADT in uIR and favorable HR disease.

Keywords: Prostate cancer; Brachytherapy; Androgen deprivation therapy; Outcomes; bPFS; CSS; OS

Introduction

Having emerged in the dawn of the prostate-specific antigen (PSA) era, prostate brachytherapy (PB) has gained worldwide acceptance and is currently considered a standard treatment for organ confined prostate cancer (PCa). Excellent long-term results have been published for all risk groups (1). Despite a large body of retrospective and prospective single- or multi-institutional data, significant uncertainties remain regarding the role of androgen deprivation therapy (ADT), external beam radiation (EBRT) or both, in patients treated with PB both with low-dose rate (LDR) and high-dose rate (HDR), particularly for intermediate-risk (IR) and high-risk (HR) PCa. Data from prospective randomized control trials will not be available for several years.

The purpose of this article was to review the published literature systematically and to summarize present knowledge regarding the role of ADT with PB. Clinical trials will be reviewed and future directions for research outlined. The mechanism of interaction between ADT and radiation, adverse effects, and impact on cardiovascular morbidity, mortality, and overall survival (OS) will be described. We separately considered the effects of ADT on biochemical progression-free survival, (bPFS), cause-specific survival (CSS), and OS in low-risk (LR) IR and HR group stratification. We considered both LDR and HDR retrospective institutional and multi-institutional studies, reviewed the limited data on this subject available from randomized controlled trials (RCTs), and reviewed on-going RCTs. We summarize the current available clinical evidence regarding the use of ADT with PB and provided recommendations regarding its use.

Methods and materials

A literature search was conducted in Medline and Embase covering the years 1996–2016. We searched articles on ADT searching under the subject heading ''androgen deprivation therapy'' in Embase and searching the titles of articles in Medline for the words ''androgen'' and ''depriv*''; 814 articles were identified; those directly focused on toxicity or the use of ADT and PB were reviewed in great detail ($n = 247$). Outcome articles were cross-referenced with the systematic outcome analysis (1) and the systematic review of randomized trials in PCa (2); 52 were selected for this review, all with >100 patients, with clearly defined risk stratification and directly examining the role and impact of ADT on primarily bPFS, in addition to CSS and OS where available. Excluded were those with followup of <3 years, those where no ADT was given, or where data required could not be extracted (e.g., studies where results between PB and EBRT alone were compared, but effect of ADT on clinical outcomes was assessed together for PB, and non-PB cohorts) (Fig. 1). Factors predictive of bPFS, CSS, and OS were extracted from multivariable analysis (MVA) in 50 of 52 articles and are included in the tables.

American Brachytherapy Society, American College of Radiology, American Society for Radiation Oncology, European Society for Radiotherapy and Oncology/ European Association of Urology/European Organization for Research and Treatment of Cancer, and National Comprehensive Cancer Network recommendations regarding use of ADT with PB

Most of the earlier mentioned best practice guideline recommendations underline the controversy regarding use of ADT and PB and do not give firm recommendations apart from recommending ADT for downsizing. For example, American Brachytherapy Society recommends no ADT in LR and its use in IR is optional and more strongly recommended in HR (3). American Brachytherapy Society recommendations for HDR do not refer to use of ADT with HDR, apart from recommending ADT for downsizing (4). American College of Radiology similarly states that the use of ADT is ''usually not appropriate'' for LR disease, ''may be appropriate'' for IR disease, and is ''usually appropriate'' for HR disease (5); 2016 National Comprehensive Cancer Network (NCCN) guidelines do not recommend ADT for IR treated with PB. For HR disease, ADT ''may or may not be used'' together with EBRT and PB boost and duration is specified between 0 and 36 months (6). European Society for Radiotherapy and Oncology/European Association of Urology/European Organization for Research and Treatment of Cancer (7), Groupe Europeen de Curetherapie/European Society for Radiotherapy and Oncology-European Association of Urology (8), and American Society for Radiation Oncology (9) have no specific recommendation or mention the use of ADT with PB.

ADT in PCa

In 1940, Canadian-born Charles Huggins recognized the androgen dependence of PCa. In 1966, he was awarded the

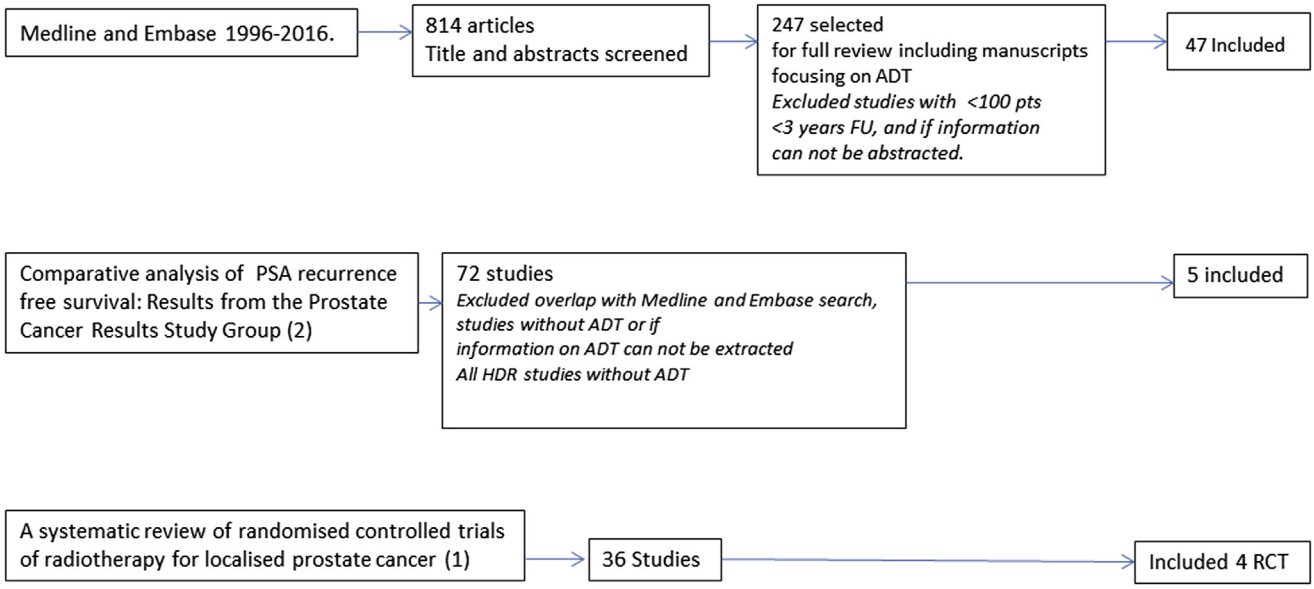

Fig. 1. Literature search. ADT = androgen deprivation therapy; FU = follow-up; HDR = high dose rate; RTC = randomized controlled trials.

Nobel Prize for medicine for his "discoveries concerning hormonal treatment of prostate cancer" (http://www.nobelprize.org/nobel_prizes/medicine/laureates/1966/). This discovery revolutionized the treatment of metastatic PCa (10, 11). In 1997, Zietman *et al.* (12) published another landmark observation that revolutionized treatment of localized PCa.

The combination of radiation with orchiectomy for Shionogi tumors treated *in vivo* resulted in a significant increase in control. In addition, orchiectomy 1–12 days before radiation increased radiation effectiveness, suggesting that not only the combination but also the timing was crucial to maximize treatment effect. Two decades later, several large national and international RCTs confirmed and quantified the therapeutic benefit of ADT in combination with EBRT (2).

When combined with EBRT or brachytherapy, ADT improves the geometry of the prostate target by decreasing the volume juxtaposed to adjacent organs at risk (13). There may also be a synergistic relationship between RT and the concurrent administration of ADT, producing a biologic advantage. Several RCTs of ADT and EBRT have reported improvement in not only bPFS and local control but also in DSS and OS (2). To produce the earlier mentioned clinical benefits, ADT must have a biologic effect on both local and systemic disease. Clinical evidence supports the hypothesis that ADT can eliminate subclinical micro-metastasis (14).

Interaction between ADT and radiation

Basic clinical research provides evidence of the profound effect of ADT on the local tumor microenvironment. ADT induces apoptosis in normal epithelial cells through p53 expression and inhibition of bcl-2 and inhibition of cell proliferation and repopulation in tumor cells (15). PCa is often hypoxic, and this drives endothelial growth factor (vascular endothelial growth factor) expression, which in turn stimulates angiogenesis (16, 17). Neo-vasculature is structurally disorganized, highly permeable, and leads to interstitial hypertension and insufficient delivery of nutrients and oxygen. ADT inhibits both endothelial growth factor (vascular endothelial growth factor) expression and angiogenesis (18). New discovery suggests that androgen receptor (AR) regulates a transcriptional program of DNA repair genes, and with that, AR promotes PCa radioresistance, adding yet another potential mechanism by which ADT increases radiosensitivity, by deactivating AR and with that DNA repair mechanism, in an experimental setting (19)."

Therefore, if given before EBRT in experimental setting, anti-angiogenesis effect may "normalize" the vasculature and lead to better tissue perfusion, increase in oxygenation, radiation tumor sensitivity, and ultimately increasing local control. Reducing local failure may consequently reduce second-wave metastatic spread and, thus, improve OS (20).

Brachytherapy increases local control by delivering a higher radiation dose. Studies of metabolic activity using MRI and magnetic resonance spectroscopic imaging showed significantly higher complete prostate metabolic atrophy and lower nadir PSA at 48 months after PB vs. EBRT (21). This higher intraprostatic tumor control is indicative of a positive therapeutic effect of the higher biologic dose given with PB vs. EBRT. This observation is supported by clinical results from three RCTs of dose escalation using EBRT vs. EBRT and PB (22–24). All three RCTs showed significantly higher bPFS using PB in addition to EBRT vs. EBRT alone. Therefore, the benefits of ADT reported even with dose-escalated EBRT (78–81 Gy) may be because of compensation for suboptimal radiation dose and less

effective local therapy. Because of very high intraprostatic dose and excellent disease control, ADT is likely to have less biologic effect with PB, except perhaps in cases with very high-volume local disease or through spatial cooperation for suppression of micrometastatic disease (25, 26). Addition of ADT to LDR-PB in IR and HR patients has been shown to significantly decrease 2-year post–PB-positive biopsy rate from 14% to 3.5% ($p = 0.002$) (27). Although it is unclear whether the difference seen would have translated in to difference in PSA outcomes with further followup (due to testosterone recovery in ADT arm and presence of indeterminate biopsies), the results are intriguing. Taken all together, these somewhat contradictory observations suggest possible benefits of ADT even with high doses of radiation.

EBRT, dose escalation, and ADT

If we disregard normal tissues tolerance for a moment, one can speculate that any truly localized cancer can be cured with radiation alone, given sufficiently high radiation dose and ensuring complete coverage of the tumor target. Therefore, increase in radiation dose should in fact increase the tumor eradication and cure. Five dose escalation RCTs have so far shown improved bPFS of average 15% at 5–10 years with dose increase from 65 to 78 Gy (28). No CSS or OS benefit was observed, in part because of a variety of factors including underpowered studies, the long natural history of PCa, improved treatment of metastatic disease, competing causes of death, and the fact that any effect on OS may be very small or even nonexistent (29).

EBRT, ADT, and improved OS in IR and HR PCa

With addition of ADT to EBRT, RCTs have shown benefit in improving OS, CSS, and bPFS in HR (RTOG 85-31, RTOG 86-10, European Organization for Research and Treatment of Cancer 22863, TROG 96-01, RTOG 92-02, RTOG 94-08, Harvard/DFCI, European Organization for Research and Treatment of Cancer 22961) (2, 29) and IR (RTOG 94-08, Harvard/DFCI 95–096) (2, 30, 31) for a duration of 4–36 months, using conventional doses of radiation. A recently published Spanish RCT showed that even in setting the dose escalation to 78 Gy, 24 vs. 4 months of ADT improves bPFS, metastatic-free survival, and OS in patients with IR and HR disease (32). Hence, it is clear that ADT has an additive effect on improving disease outcomes with EBRT even to high doses of 78 (32) and 81 Gy (33). Despite toxicity concerns, patients who get ADT live longer and, therefore, should be treated with ADT, with exception of perhaps those with significant cardiac history. The optimal ADT duration with EBRT for each risk category has not been established.

Dose escalation with brachytherapy

Brachytherapy for any disease site is considered as the ultimate dose escalation modality, with clearly documented OS benefit in cervical cancer over EBRT alone (34). Randomized trials in PCa comparing EBRT (78 Gy) with EBRT and brachytherapy boost in high and high-tier IR PCa indicate further improvement of PSA recurrence free survival (20–30% at 7–10 years) (22–24), with no documented CSS or OS benefit. Recent publications using large national databases indicate an increase in CSS (35) and OS (36) in PCa patients treated with any form of brachytherapy. Brachytherapy results in superior disease outcomes, particularly bPFS (22–24, 35, 36), higher complete prostate metabolic atrophy, and lower nadir PSA (21). For these reasons, addition of ADT to either brachytherapy monotherapy or a boost may have less impact on outcomes than when ADT is combined with EBRT.

Side effects of ADT

The use of even short-term ADT has deleterious effects to quality of life (QOL) (37, 38) and may increase morbidity and mortality (39, 40). Initially recognized and well-documented side effects of ADT include sexual dysfunction, loss of libido, and hot flashes, fatigue, anemia, and decreased muscle mass. Cognitive dysfunction and depression have also been documented (41) where up to 27% of patients on ADT may suffer psychiatric illness during their treatment (42). As experience grew, the more ominous systemic and metabolic effects were documented (43). There is an increased risk of osteoporosis with 23% increase in incidence of fractures. The incidence of metabolic syndrome is 50% for men with ADT vs. 20% in general population, even with 1 year of ADT. Central and peripheral obesity is common with 9–11% increase in fat mass after 1 year of ADT (44), total cholesterol is elevated by 9%, triglycerides by 27%, and HDL decreased by 11% after only 3 months of ADT (40, 44–46). In addition, ADT is documented to elevate blood pressure, elevate fasting glucose and fasting insulin by 26%, decrease insulin sensitivity by 13%, and increase diabetes by 44% (40, 42, 47). All these changes act to increase the risk of cardiovascular events 12–60 months after starting ADT (24 vs. 18%; $p < 0.001$) (48) and sudden cardiac death by adjusted hazard ratio [AHR] of 1.16 ($p < 0.004$) (40). Several studies have documented a decrease in OS in patients with localized PCa treated with ADT and brachytherapy (39, 49, 50). Therefore, even with short duration of only 3 months, ADT can negatively impact quality of life and increase morbidity and mortality (48).

ADT, cardiovascular morbidity, mortality, and OS

The cardiovascular morbidity and excess mortality (3.5–6%) has been reported in observational studies (40,

48, 51, 52) but not confirmed in RCTs that used ADT (37, 53, 54). This discrepancy between randomized and non-randomized data may be because of several factors. Older and less healthy men are more likely to be included in observational rather than RCTs studies (40, 48, 52). In addition, observational data included nonfatal cardiovascular events, which have been considered a more sensitive outcome than fatal cardiovascular events (52).

The primary cause of death in men with PCa treated with brachytherapy is cardiovascular disease (55, 56). This is well illustrated in a report from Bittner *et al.* (57). With median followup of 5.4 years, primary cause of death in 1354 patients treated with PB + EBRT + ADT is cardiovascular disease (CVD; 42% of all deaths) followed by other cancers (30%) and PCa representing only 8.7% of deaths. Although MVA shows no association between use of ADT and risk of cardiovascular death, CSS, or OS, it remains unclear why HR patients had double the risk of dying from CVD compared with IR and LR patients (19.8% vs. 9.3% vs. 8.7% for HR, IR, and LR, respectively) (57).

Recent evidence suggests that excess cardiovascular morbidity and mortality is seen predominantly in patients with pre-existing cardiovascular co-morbidity. After a median followup of 5.1 years, Nanda *et al.* (58) reported that neoadjuvant ADT use was significantly associated with an increased risk of all-cause mortality (ACM) only in the subgroup of patients with pre-existing CVD (including heart failure and myocardial infarction [MI]). In their study, mortality had increased from 11% in ADT naive, to 26% in ADT patients (hazard ratio, 1.9; 95% CI, 1.04–3.71; $p = 0.04$). Similarly, Nguyen *et al.* (59) found a significant increase in ACM (AHR, 1.76; 95% CI, 1.32–2.34; $p = 0.001$) in 1378 men with a history of congestive heart failure or MI treated with PB-based radiation with or without median 4 months of ADT (ACM 22.7% vs. 11.6% with and without ADT). Ziehr *et al.* (60) reported a 5% absolute excess in cardiac-specific mortality in men with a history of congestive heart failure or MI who received ADT for minimum 4 months.

A recent publication from Memorial Sloan-Kettering presented long-term followup results on 2211 patients treated with EBRT ± PB, who received neoadjuvant or adjuvant (45%) or salvage ADT (16%). With median followup of 9.3 years, short course of ADT was associated with an increased risk of cardiovascular morbidity (absolute increase 5.3% at 10 years or increase from 14.3% to 19.6%). The authors also presented nomograms to quantify the risk of cardiovascular death for patients (61). In addition to pre-existing comorbidity as a predictor of inferior OS, Tiara *et al.* (62) reported a decrease in OS with ADT in men with low baseline testosterone.

Further information regarding impact of pre-existing co-morbidity on risk of cardiovascular morbidity and mortality with ADT will be available form an ongoing RCT (RTOG 08-15) that randomizes patients between 0 and 6 months of ADT and stratifies patients by Adult Comorbidity Evaluation-27 score (ACE-27) (63). Based on a re-analysis of six RCTs, Albertsen *et al.* (64, 65) speculated that the increase in cardiovascular morbidity and cardiovascular mortality might be an luteinizing hormone-releasing hormone agonists (LHRH) agonist class effect. The authors have reported significantly less CVD events in men treated with LHRH antagonists vs. LHRH agonists (hazard ratio, 0.44; 95% CI, 0.26–0.74; $p = 0.002$). More information will be available on completion of the RCT comparing major cardiovascular events with LHRH agonists vs. antagonists in patients with pre-existing cardiovascular comorbidity (PRONOUNCE NCT02663908).

PCa risk stratification

The NCCN risk stratification criteria are perhaps the most commonly cited and represent the standard for most modern clinical trials (6). Although studies included in this report were grouped based on risk stratification, the risk stratification used is not very clear or uniform, apart from a clear definition of LR disease. Evidence suggests that IR and HR PCa are rather heterogeneous disease. Recent publications propose subdividing each risk group (LR, IR, and HR) into favorable and unfavorable risk, based on actual patient outcomes. Understanding the new proposed risk stratification and its impact on clinical outcomes is critical when interpreting the literature, formulating treatment decisions and evidence-based recommendations. Hence, this issue has been reviewed here in some detail.

Zumsteg *et al.* (66) supported this concept with their report on 1024 patients treated with high-dose EBRT (81 Gy) and with median followup of 71 months. Unfavorable IR (uIR) was defined as: primary Gleason pattern of 4, >50% percent positive cores (PPC), or multiple IR factors (cT2b/c, PSA 10–20, or Gleason score [GS] 7). Patients with uIR disease had inferior bPFS (hazard ratio, 2.37; $p < 0.0001$), higher risk of distant metastasis (hazard ratio, 4.34; $p = 0.0003$), and worse PCa-specific mortality (PCSM) (hazard ratio, 7.39; $p = 0.007$) compared with those with favorable IR (fIR) disease, despite being more likely to receive neoadjuvant ADT together with 81 Gy EBRT. Nguyen *et al.* (67) reported outcomes on 1063 patients treated with radical prostatectomy, or with EBRT, with or without ADT and stratified by the number of risk features in both IR and HR disease (PSA > 10 ng/mL, GS > 7, ≥T2b, pre-treatment PSA velocity > 2.0 $ng \cdot mL^{-1} \cdot y^{-1}$). The 5-year cumulative incidence of PCSM was 2.4% for one factor, 2.4% for two factors, 7.0% for three factors, and 14.7% for all four factors. PCa deaths as a proportion of all deaths were 19% for one factor, 33% for two factors, 53% for three factors, and 80% for four factors. Recent data on outcomes on PCSM in HR disease from the SEER database (45,078 patients treated with EBRT with or without PB boost) further outline efforts in redefining risk stratification. HR disease was divided into favorable (T1c, GS4 + 4, and PSA

< 10 or T1C, GS6, and PSA > 20) and unfavorable HR (all others) (68). Only men with unfavorable HR had a significantly reduced PCSM with EBRT alone vs. EBRT + PB boost (3.9% vs. 5.3% AHR, 0.73; 95% CI, 0.55–0.59; $p = 0.022$). Unfortunately, with median followup of only 3.6 years, conclusions are premature.

The Genitourinary Oncologists of Canada have proposed new, refined risk stratification based on recursive partitioning analysis of the ProCaRS database (7974 patients from four Canadian Institutions) with long-term followup of 48–94 months (69). The new risk groups accommodate six separate and statistical unique groups based on differences in long-term bPFS. The LR group has been divided into favorable LR and LR based on PSA < 6 and PSA > 6. IR was subclassified into fIR and uIR (PSA ≥ 10 and either T2b/c or T1T2a and GS 7), and the HR group was divided into favorable HR (fHR) and extreme-risk (ER) group (HR and positive cores > 87.5% or PSA > 30). Most importantly, uIR and fHR have the same long-term PSA outcomes, when treated with minimum 74 Gy EBRT or brachytherapy alone. Furthermore, ER patients had significantly worse long-term outcomes compared with those with fHR disease. Two ongoing RCTs (as given subsequently) stratify patients into fIR, uIR, and fHR groups.

Review of the published literature on ADT and PB

The summary of all studies is given in Tables 1–5. For the purpose of this review, studies were grouped based on risk stratification. Of 52 studies, 36 (68%) included a mixture of risk groups (Tables 1, 3, and 5) and 17 (32%) report on single-risk group (Tables 2 and 4). Almost half of the studies are multi-institutional (47%). The treatment varied widely between patients, and the majority were treated with LDR-PB monotherapy or a combination of LDR-PB with EBRT, all with or without ADT. Only 9 HDR studies are included in this report as most institutions do not give ADT with HDR. Risk stratification is extracted from the studies where possible and included in the tables. For LR and IR patients, ADT was most often prescribed to downsize the prostate before PB (Tables 1 and 2). Higher risk patients and those with multiple risk factors tended to receive ADT more often and also for a longer duration (Tables 4 and 5). Factors predictive of outcomes (bPFS, CSS, and OS) were extracted from MVA in all but two studies.

LR and IR disease

Five studies were identified describing outcomes with LR and IR patients, treated with LDR ± ADT in four, or LDR ± ADT ± EBRT in one (Table 1). Three studies were multi-institutional (one included matched pair analysis) (71) and two were Canadian single-institution series. A total of 5182 patients were included. Median followup ranged from 4 to 7.5 years. ADT was used in 27–65% of the

Table 1
LR and IR disease

LR and IR	Type of study/ institution	Year of study	Number of patients	Median FU	Risk stratification	Treatment	% On ADT	Median ADT duration (range)	Overall bPFS (%)	ADT benefit for bPFS	Overall CSS	ADT benefit for CSS	Overall OS	ADT benefit for OS	Comments and factors predictive of outcome bPFS, CSS, and OS
LDR															
Ciezki *et al.* (70)	Multi-institutional, USA	1996–2001	1668	4 y	LR: 64% IR: 36%	LDR ± ADT	37	6 mo	87.8	No benefit	NR	NR	NR	NR	NR
Potters *et al.* (71)	New York Institutions, USA	1992–2000	1449	6.8 y	NR	LDR ± EBRT ± ADT	27	5.2 mo (1–24)	77	No benefit	93%	NR	81%	NR	bPFS (GS, iPSA, D_{90})
Ohashi *et al.* (72)	Multi-institutional Japan	2003–2009	663	5 y	LR: 67% fIR: 33%	LDR ± ADT	44	3 mo	95.9	No benefit	99%	NR	96%	NR	bPFs (D_{90}, risk group)
Morris *et al.* (73)	British Columbia, Canada	1998–2003	1006	7.5 y	LR: 58% fIR: 42%	LDR ± ADT	65	6 mo	95	No benefit	99%	NR	83%	No benefit	bPFS (log iPSA, D_{90} in ADT naive) OS (age, log iPSA)
Martin *et al.* (74)	Quebec City Canada	1994–2001	396	5 y	LR: 69% fIR: 31%	LDR ± ADT	65	6 mo	88.5	No benefit	NR	NR	NR	NR	bPFS (GS and stage)

ADT = androgen deprivation therapy; bPFS = biochemical progression-free survival; CSS = cause-specific survival; EBRT = external beam radiation therapy; fIR = favorable intermediate risk; FU = followup; GS = Gleason score; iPSA = initial PSA; IR = intermediate risk; LR = low risk; LDR = low-dose rate; NR = not recorded; OS = overall survival.

Table 2
IR disease

IR	Type of the study	Study years	Number of patients	Median FU	Subgroup risk stratification	Treatment	% On ADT	Median ADT duration	Overall bPFS	ADT benefit to bPFS	Overall CSS	ADT benefit to CSS	Overall OS	ADT benefit to OS	Comments/factors predictive of outcome
LDR															
Rosenberg *et al.* (75)	Chicago	1997–2007	807	4.5 y (IQR 2.7–6.2 y)	NR	LDR ± ADT or EBRT + LDR	76	4 mo (2–6)	NR	NR	98%	Benefit to ADT (2%)	NR	NR	PCSM (3.3 vs. 1.1% EBRT + PB vs. PB + ADT) CSS (iPSA, GS4 + 3, no ADT)
Tran *et al.* (76)	Multi-institutional, UK	2003–2007	615	5 y (0.3–8.3 y)	NR	LDR ± ADT	17	4 mo	88%	No benefit	NR	NR	NR	NR	bPFS (iPSA)
Ho *et al.* (77)	Mount Sinai, NY	1990–2004	558	5 y	1 IRf: 68% 2 IRf: 26% 3 IRf: 5%	LDR ± EBRT ± ADT	74	3–9 mo	86%	No benefit	NR	NR	NR	NR	bPFS (BED <150 Gy^2, 10% benefit to ADT, p = NS)
Keane *et al.* (78)	Harvard, Boston, MA	1997–2013	2510	7.8 y (IQR 5.3–10.5)	fIR: 76% uIR: 24%	LDR ± ADT, or EBRT + LDR	33	4 mo	NR	NR	NR	Benefit of ADT only in unfavorable IR (HR, 0.34; 95% CI 0.13–0.91)	NR	NR	CSS (year of PB, ADT (uIR and risk stratification)
Bittner *et al.* (79)	Multi-institutional, USA	1995–2001	932	7.4 y	90% IR GS 3 + 4: 58% GS 4 + 3: 41%	LDR ± EBRT, ±ADT	29	6 mo	95%	No benefit	98%	No benefit	77%	No benefit	bPFS (GS, iPSA, stage) CSS (nil) OS (age, diabetes, tobacco, coronary artery disease)
Stock *et al.* (80)	Mount Sinai, NY	1994–2006	432	4.6 y (23–155 mo)	1 IRf: 47% 2 IRf: 41% 3 IRf: 12%	LDR + EBRT ± ADT	81	4 mo (3–24)	92%	No benefit	NR	NR	NR	NR	bPFS (iPSA, GS, CS, number of risk features)

ADT = androgen deprivation therapy; bPFS = biochemical progression-free survival; BED = biologically effective dose; 95% CI = confidence interval; CSS = cause-specific survival; EBRT = external beam radiation therapy; fIR = favorable intermediate risk; FU = followup; GS = Gleason score; iPSA = initial PSA; IR = intermediate risk; IQR = interquartile range; IRf = intermediate-risk feature; LR = low risk; LDR = low-dose rate; NR = not recorded; OS = overall survival; PB = prostate brachytherapy; PCSM = prostate cancer–specific mortality ; uIR = unfavorable intermediate risk.

Table 3
IR and HR disease

IR and HR	Type of the study/ institution	Year of study	Number of patients	Median FU, y	Treatment	Risk stratification	% ADT
LDR							
Lee (81)	Mount Sinai, NY	1990–1998	201	3.5	LDR ± ADT	IR: 33% HR: 67%	66
Strom (82)	Tampa, FL	2001–2011	120	5.2	LDR + EBRT ± ADT	IR: 76% HR: 24%	45
Merrick *et al.* (83)	Multi-institutional, USA	1995–2003	530	5.7	LDR + EBRT ± ADT	IR: 73% HR: 27%	33
Merrick *et al.* (84)	Multi-institutional, USA RCT—20 vs. 44 Gy EBRT + PB	1999–2004	247	9	LDR + EBRT ± ADT	PSA > 10; 15% GS 8–9: 15%	32
Dattoli *et al.* (85)	Multi-institutional, USA	1992–1997	321	10.5	LDR + EBRT ± ADT	IR: 49% HR: 51%	44
Merrick *et al.* (86)	Multi-institutional, USA RCT—0 vs. 20 vs. 44 Gy EBRT + PB	1999–2013	630	7.7	LDR ± EBRT ± ADT	fIR: 46% uIR: 46% HR: 8%	10–56
HDR/LDR							
Kraus *et al.* (87)	William Beaumont	1991–2004	1044 Patients	5	LDR/HDR ± EBRT ± ADT	IR: 75% HR: 25%	40
HDR							
Schiffmann *et al.* (88)	Hamburg Germany	1999–2009	392	4	LDR ± EBRT ± ADT	IR: 46% HR: 53%	56

patients for a median duration of 3–6 months. ADT was most often prescribed to downsize prostate before PB and in one study also for IR features (73). In all but one study, where information could not be extracted (70), IR patients had fIR disease (69). Overall, bPFS was 77–95%, CSS 93–99%, and OS 81–96%. None of the studies, including the matched-pair analysis (71), showed any benefit from ADT to bPFS. The effect of ADT on CSS was not reported in any of the studies and ADT was not associated with improved or detrimental OS in one study (73). On MVA, bPFS was associated with GS, initial PSA (iPSA), D_{90}, and risk groups. OS was associated with age, PSA, GS, and clinical stage (CS) (Table 1).

IR disease

Six studies with 5854 patients were identified describing outcomes in IR patients using LDR ± ADT or LDR ± EBRT ± ADT. Two were multi-institutional and four single-institution series (Table 2). Median followup ranged from 4.5 to 7.8 years. Three studies reported risk stratification. Two studies (both from the Mount Sinai group) (77, 80) stratified patients by number of risk features and study from Harvard (78) stratified patients into fIR and uIR (69). ADT was used in 17–81% of the patients for a median duration of 4 months. Four of six studies reported no overall benefit to bPFS with ADT. Two studies did not report on bPFS. One study reported an absolute 2% benefit to CSS with ADT (75) and one reported benefits in only the uIR subgroup (78). Ho *et al.* (77) reported a benefit to ADT only if biologically effective dose (BED) was <150 Gy. Four studies did not report on an association between ADT and OS and one showed no benefit to OS with ADT (79). On MVA, bPFS was associated with GS, iPSA, BED, CS, and number of risk features. CSS was associated with iPSA, GS, treatment year, and a benefit to ADT in uIR

Median ADT duration	Overall bPFS	ADT benefit to bPFS	Overall CSS	ADT benefit to CSS	Overall OS	ADT benefit to OS	Comments and factors predictive of outcome for bPFS, CSS, and OS
6 mo	68%	Benefit to ADT for low D_{90}	NR	NR	NR	NR	bPFS (ADT, RS, iPSA, D_{90} in ADT naïve - 25% bPFS benefit to ADT with low D_{90})
IR 4 mo HR 28 mo	NR	No benefit	NR	No benefit	NR	No benefit	OS (age, trend for ADT benefit in HR (12% p = NS)
4–7 mo (3–36)	95.2%	No benefit	95.2%	No benefit	77.3%	No benefit	bPFS (iPSA, CS) CSS(CS) OS (age, diabetes, tobacco)
4 and 9 mo	93.2%	No benefit	97.7%	No benefit	80%	No benefit	bPFS (PSA, CS)
4 mo (3–6)	82%	No benefit	NR	NR	NR	NR	bPFS (GS, PAP)
6 mo	99–85% for IR and HR	No benefit	100–95% for IR and HR	No benefit	80–57% for IR and HR	No benefit	bPFS (iPSA, P vol.) CSS (risk groups, PPC, P vol.) OS (age, iPSA, tobacco)
6 mo	72%	No benefit	98%	No benefit	83% vs. 79% for ± ADT	No benefit	bPFS (iPSA, GS, CS. ADT improved bPFS 11.5% p = 0.02 with LDR/HDR monotherapy. ADT improved FFCF with GS ≥ 8 and bulky local disease
3 mo	77%/65% Tri- vs. bi- modality	ADT Benefit (11–20%)	NR	NR	NR	NR	bPFS (ADT benefit 12% for IR and 20% in HR)

patients. OS was associated with age, diabetes, tobacco use, and coronary artery disease (Table 2).

IR and HR disease

Eight studies were identified describing outcomes in 3485 patients with IR and HR disease, six using LDR, one HDR, and one with both LDR and HDR (Table 3). Patients were treated using monotherapy LDR or HDR or with EBRT + LDR or HDR boost, all with or without ADT. Four studies were multi-institutional, including two RCTs (20 vs. 44 Gy EBRT or 0 vs. 20 vs. 44 Gy EBRT) (84, 86) and four were single-institution series. Risk stratification given in Table 3 shows the predominance of IR rather than HR disease in most studies, one of which stratified IR into fIR and uIR (86). Median followup ranged from 3.5 to 10.5 years. ADT was used in 32–66% of the patients for a median duration of 6 months (range, 4–28 months). Overall, bPFS was 68–95%, CSS 95–98%, and OS 77–80%.

Six of eight studies reported no benefit of ADT to bPFS, apart from ADT improving bPFS by 25%, only in patients with low D_{90} (81). One HDR study reported 12% and 20% bPFS benefit to adding ADT in IR and HR disease, respectively (88). Kraus *et al.* (87) reported no overall benefit of ADT on bPFS; however, patients treated with either LDR or HDR monotherapy had 11% improved bPFS if ADT was used. In addition, ADT improved freedom from clinical failure in patients with GS ≥ 8 and bulky local disease. None of the studies showed overall benefit to CSS or OS with ADT. Storm *et al.* (82) did show a nonsignificant 12% improvement in OS only in HR patients with the addition of ADT. Factors associated with bPFS included iPSA, CS, GS, prostatic acid phosphatase, and prostate volume. Factors associated with bPFS included ADT, risk stratification, iPSA, D_{90} in ADT-naive patients, prostatic acid phosphatase, and

Table 4
HR disease

HR	Type of the study	Year of the study	Number of patients	Median FU	Risk stratification	Treatment	% ADT	Median ADT duration
LDR								
Ohashi *et al.* (89)	Japan	2003–2009	206	5 y	1 HRf 90% 2 HRf 9% 3 HRf 0.5%	LDR + EBRT ± ADT	49	4 mo
Bittner *et al.* (56)	Multi-institutional, USA (very high risk)	1995–2007	131	6.6 y	GS 8/9: 80% PSA > 20: 29%	LDR + EBRT ± ADT	91	19 mo (range, 4–36)
Bittner *et al.* (90)	Multi-institutional, USA	1995–2005	186	6.7 y	GS8–10: 76% Med iPSA: 11	LDR + EBRT (mini vs. whole pelvis) ± ADT	73	>6 mo (75%)
Wattson *et al.* (91)	Multi-institutional, USA	1991–2007	2234	4.3 y	1HRf: 83% 2 HRf: 14% 3 HRf: 2%	LDR ± EBRT, ±	79	4 mo
D'Amico *et al.* (92)	Multi-institutional, USA	1991–2005	1342	5.1 y	1 HRf: 5% 2 HRf: 86% 3 HRf: 8%	LDR ± ADT or EBRT + LDR or EBRT + LDR + ADT	67	4 mo (IQR 3.4–6.2)
Merrick *et al.* (93)	Multi-institutional, USA	1995–2002	204	7 y	Med iPSA 9.9 Med GS8	EBRT + LDR ± ADT	40	4 and 12 mo (range, 3–36)
Shilkurt *et al.*(94)	Multi-institutional, USA	1995–2010	448	5.2 y	1 HRf: 84% 2 HRf: 14% 3 HRf: 2%	LDR + EBRT ± ADT	76	12 mo (range, 8–24)
Merrick *et al.* (55)	Multi-institutional, USA	1995–2005	284	7.8 y	NR	LDR + EBRT ± ADT	63	4–12 mo (range, 3–36)
Liss (95)	Multi-institutional, USA	1998–2008	141	4.7 y	GS8-10: 75% Med iPSA: 20 T2b-T4: 40%	LDR + EBRT ± ADT	87	12 mo
Fang *et al.* (96)	Multi-institutional, USA	1995–2005	174	6.6 y	GS8-10 PSA < 15	LDR + EBRT ± ADT	64	12 mo (range, 3–36)
HDR								
Prada *et al.* (97)	Oviedo, Spain	1998–2006	252	6.1 y	2 IRf1 7% 1 HRf 40% 2 HRf 35% 3 HRf 8%	HDR + EBRT ± ADT	69	12 mo

ADT = androgen deprivation therapy; AH = adjusted hazard ratio; bPFS = biochemical progression-free survival; 95% CI = confidence interval; CSS = cause-specific survival; EBRT = external beam radiation therapy; FU = followup; GS = Gleason score; HDR = high-dose rate; HRf = high risk feature; IRf = intermediate risk feature; IQR = interquartile range; LDR = low-dose rate; NR = not recorded; NS = nonsignificant; OS = overall survival; PB = prostate brachytherapy; PPC = percent positive cores; PSA = prostate-specific antigen; WPRT = whole pelvis radiotherapy.

prostate volume. Factors associated with CSS included CS, risk groups, PPC, and prostate volume and with OS included iPSA, age, diabetes, and tobacco use (Table 3).

High risk

Eleven studies with a total of 5602 patients were identified describing outcomes in patients with HR disease, 10 using EBRT with LDR, and 1 with HDR, all treated with or without ADT (Table 4). Only one study had patients treated with LDR monotherapy (91). Nine studies were multi-institutional and two were single institutions (one LDR and one HDR). Median followup ranged from 4.3 to 7.8 years. ADT was used in 40–91% of the patients for a median duration of 3–12 months. Overall bPFS was 65–92%, CSS was 84–98%, and OS was 69–95%. Most patients included fHR patients with 1–2 HR features.

Nine studies reported an association between ADT and bPFS, three showed no benefit, and six showed (55, 56, 90, 93–95) benefit to ADT. One HDR study found 6% nonsignificant increase in bPFS with ADT (97). Bittner *et al.* (56) and Lissa *et al.* (95) reported up to 13% benefit to longer ADT duration. Merrick *et al.* reported a 10% bPFS benefit to patients with PSA > 20 (55) and an overall benefit of 6–16% (93). Nine studies reported an association between ADT and CSS, six found no benefit, and three found a benefit to

Overall bPFS	ADT benefit on bPFS	Overall CSS	ADT benefit on CSS	Overall OS	ADT benefit on OS	Comments and factors predictive of outcome bPFS, CSS, and OS
84.4%	No benefit	98%	NR	97%	NR	bPFS (PPC and risk features)
87%	Benefit to longer ADT (13%)	91%	Benefit with longer ADT	70%	No benefit	bPFS (longer ADT. PPC) CSS (longer ADT, PPC) OS (age, PPC)
92%/84% Whole pelvis vs. mini pelvis	ADT benefit	95%/92% WPRT vs. MPRT	No benefit	79%/67% WPRT vs. MPRT	No benefit	bPFS (ADT) OS (age, PPC, WPRT in ADT-naive pts)
NR	NR	NR	ADT benefit	NR	NR	CSS (ADT, number of high risk factors, triple therapy vs. LDR or LDR + EBRT)
NR	NR	84%	Benefit to ADT + EBRT vs. LDR alone	NR	NR	CSS (trend for better tri vs. bi-modality AHR, 0.32; 95% CI, 0.14–0.73)
89%	ADT benefit (6–16%)	86%	No benefit	68%	No benefit	bPFS (PPC, ADT, and ADT duration) CSS (GS) OS (GS, diabetes)
86%	ADT benefit (HR 0.2)	93%	No benefit	NR	NR	From the analysis of 958 patients who received EBRT ± ADT or LDR + EBRT ± ADT
89%	ADT benefit if PSA > 20 (10%)	94%	No benefit	69%	No benefit	bPFS (PPC, ADT) CSS (nil) OS (age, diabetes, PPC)
80%	Benefit to ADT > 12 mo	94	No benefit	88% (with GS5)	No benefit	bPFS (iPSA, ADT, CSS (nil) MFS (iPSA, GS5, ADT OS (iPSA, GS5)
92%/95% with/without ADT	No benefit	92%/95% with/without ADT	No benefit	66%/75% with/without ADT	No benefit Detriment to OS (p = NS)	bPFS (age) CSS (iPSA, hypertension) OS CS (prostate volume) NS detriment to OS with ADT
84%/78% 5 and 10 y	No benefit	NR	NR	NR	NR	bPFS (GS, benefit to ADT 6%, p = NS)

ADT (56, 91, 92). D'Amico *et al.* (92) found a benefit to CSS with triple therapy vs. LDR + EBRT or LDR monotherapy. Similarly Watson *et al.* (91) reported better CSS for "triple therapy" (LDR + ADT + EBRT) vs. LDR or LDR + EBRT without ADT. None of the five studies found any increase in OS with ADT; however, Fung *et al.* (96) reported a nonsignificant detriment in OS in fIR patients.

Other factors associated with bPFS included iPSA, PPC, risk stratification, and age. Factors associated with CSS included PPC, number of risk factors, GS, hypertension, and prostate volume. Factors associated with OS included age, diabetes, PPC, iPSA, GS, Gleason pattern 5, and whole pelvis radiotherapy in ADT-naive patients (90).

All risk categories

Twenty-two studies with 23,180 patients were identified describing outcomes in all risk categories including LR, IR, and HR disease, 16 using LDR (20,991 patents), 5 using HDR (2189 patients), and 1 with both. Patients were treated using monotherapy LDR or HDR ± EBRT, all with or without ADT (Table 5). Eight studies were multi-institutional and 14 are single-institution series, with 4 from the single institution (26, 49, 98, 100). Median followup ranged from 3.8 to 10 years. ADT was used in 18–83% of the patients for median duration of 3–9 months. Overall, 10 y bPFS was 57–95%, CSS 82–98%, and OS 43–98%.

Sixteen studies reported an association between ADT and bPFS, 12 found no benefit (including all five HDR studies),

Table 5
All risk categories

All risk groups	Institution/type of the study	Year of the study	Number of patients	Median FU	Risk stratification	Treatment	% On ADT	Median ADT duration
LDR								
Stock *et al.* (98)	Mount Sinai, NY	1990–2010	2427	6.5	LR: 44% IR: 34% HR: 21%	LDR ± EBRT ± ADT	54	6 mo (3–36)
Stone *et al.* (49)	Mount Sinai, NY	1990–2007	1669	10 mean	LR: 45% IR: 38% HR: 16%	LDR ± EBRT ± ADT	54	6 mo (6–36)
Beyer *et al.* (39)	Arizona Oncology Services	1998–2001	2378	4.1	LR: 47% IR: 33% HR: 19%	LDR ± EBRT ± ADT	19.50	3–6 mo (3–12)
Hinnen *et al.* (99)	Utrecht, The Netherlands	1989–2004	921	5.7	LR: 25% IR: 40% HR: 35%	LDR ± ADT	18	6 mo
Burri *et al.* (100)	Multi-institutional, USA	1990–2005	1665	5.6	LR: 60% IR: 27% HR: 12%	LDR ± EBRT ± ADT	54	3–9 mo
Merrick *et al.* (101)	Multi-institutional, USA	1995–2002	938	5.4	LR: 35% IR: 35% HR: 19%	LDR + EBRT ± ADT	40	7–40 mo
Tiara *et al.* (102)	Multi-institutional, USA	1992–1997	1656	7	LR: 35% IR: 36% HR: 28%	LDR ± EBRT ± ADT	37	<6 and >6 mo
Potters *et al.* (103)	Multi-institutional- matched pair analysis	1992–1997	263 (612 all patients)	3.8	NR	LDR ± EBRT, ± ADT	50	3.4 mo (3–8)
Bittner *et al.* (57)	Multi-institutional, USA	1995–2004	1354	5.4	LR: 35% IR: 46% HR: 18%	LDR ± EBRT, ± ADT	39	6 mo (max 36)
Stone *et al.* (26)	Mt Sinai, NY	1990–2005	584	7.1	LR: 44% IR: 24% HR: 31%	LDR ± EBRT, ± ADT	48	6 mo (3–9)
Dosoretz *et al.* (50)	21st Century Oncology	1991–2005	2474	4.8	LR: 65% IR: 23% HR: 12%	LDR ± ADT	69–83	3–3.4 mo
Merrick *et al.* (104)	Multi-institutional, USA	1995–2001	668	4.8	LR: 33% IR: 37% HR: 28%	LDR ± EBRT ± ADT	58	4 mo (3–36)
Kollmeier *et al.* (105)	Mount Sinai, NY	1990–1996	243	6.2	LR: 61% IR: 47% HR: 1.1%	LDR ± ADT	60	6 mo
Senzaki *et al.* (106)	Tokushima University Hospital, Japan	2004–2012	431	5.3	LR: 40% IR: 45% HR: 14%	LDR ± ADT	63	6.5 mo (6–10)
Wilson *et al.* (107)	Sir Charles Gairdner Hospital, Australia	1994–2007	207	7.8	LR: 51% IR: 47% HR: 1.1%	LDR ± ADT	58	3–6 mo
Henry *et al.* (108)	St. James Hospital Leeds, UK	1995–2004	1298	4.9 y	LR: 44% IR: 33% HR: 14%	LDR ± ADT	44	3–4 (all <6 mo)
LDR and HDR								
Zelefsky *et al.* (109)	Memorial Sloan-Kettering, NY	1998–2009	1466	4y	LR: 57% IR: 38% HR: 5%	LDR/HDR ± EBRT ±ADT	31	3 mo
HDR								
Tselis *et al.* (110)	Offenbach, Germany	2004–2008	351	4.9	LR: 56% IR: 23% HR: 21%	HDR monotherapy ± ADT	19	9 mo
Demanes *et al.* (111)	Oakland, CA	1991–1998	411	6.4	LR: 27% IR: 45% HR: 27%	HDR + EBRT ± ADT	48	<6 mo
Galalae *et al.* (112)	Multi-institutional, USA and Germany	1986–2000	611	5 mean	LR: 8% 1 Risk factor 31% ≥2 Risk factors 60%	HDR + EBRT ± ADT	28	4 mo
Phan *et al.* (113)	University Of California-Irvine	1996–2003	309	4.9	LR: 21% 1 Risk factor 35% ≥2 Risk factors 43%	HDR + EBRT ± ADT	36	3 mo
Martinez *et al.* (114)	Multi-institutional, USA	1986–2000	507	4.8	NR	HDR + EBRT ± ADT	35	6 mo

ADT = androgen deprivation therapy; bPFS = biochemical progression-free survival; BED = biologically effective dose; bx = biopsy; 95% CI = confidence interval; CAD = coronary artery disease; EBRT = external beam radiation therapy; FU = followup; GS = Gleason score; IR = intermediate risk; LR = low risk; LDR = low-dose rate; NR = not recorded; OS = overall survival; PB = prostate brachytherapy; PPC = percent positive cores.

and 4 found benefit to bPFS with addition of ADT. One study reported a 15% benefit only with longer ADT duration (101). One reported a 24% benefit to ADT at 10 years, only if BED was <150 Gy (98), and yet another showed a 9–15% benefit with ADT only in HR disease (104). Counterintuitively, a study from the UK showed a detriment to bPFS

Overall bPFS	ADT benefit to bPFS	Overall CSS	ADT benefit to CSS	Overall OS	ADT benefit to OS	Comments and factors predictive of outcome bPFS, CSS, and OS
85 vs. 86% for ± ADT	Benefit if BED < 150 Gy (24% at 10 y)	NR	NR	NR	NR	bPFS (ADT, BED) Post-PB biopsy (benefit to ADT with BED < 200 Gy)
89%/67% 10 and 15 y	NR	94.1%	No benefit	57% (15 y)	OS worse with ADT (5% at 15 y)	CSS (stage and GS) OS (age, ADT, smoking, diabetes, emphysema, atrial fibrillation)
NR	NR	88%	No benefit	43%	OS worse with ADT (20%)	OS (ADT, age, GS)
79%/57% 5 and 10 y	No benefit -	82%	No benefit	59%	NR	bPFS (year of PB, HR, and IR) OS (year of PB, HR)
94%/88% 5 and 8 y	No benefit	NR	NR	NR	NR	bPFS (GS, iPSA, BED)
96%	Benefit to longer ADT (15%)	96%	No benefit	78%	No benefit	bPFS (PPC, longer ADT) OS (age tobacco),
95.6%	No benefit	98.2%	No benefit	72.6%	No benefit	bPFS (PPC, risk groups, CAD) CSS (GS, hypertension) OS (age, diabetes, tobacco)
87%/87% for ±ADT	No benefit	NR	NR	NR	NR	bPFS (iPSA, GS, stage)
NR	NR	97%	No benefit	76.7%	No benefit	CSS (GS, risk factor) OS (age, smoking)
85%/59% for positive vs. negative bx	No benefit	99%/87% for positive vs. negative bx	No benefit	NR	NR	bPFS (GS, iPSA BED, bx) CSS (BED, positive bx) Results: (ADT benefit in IR)
NR	NR	NR	NR	NR	OS worse with ADT in men >73 y	ACM detriment with ADT (AHR, 1.24; 95% CI, 1.01–1.53; $p = 0.04$)
98%/98%–88% LR/IR/HR	ADT benefit only for HR (9–12%)	NR	NR	NR	NR	bPFS (HR, ADT, GS, PPC)
NR	No benefit	NR	NR	NR	NR	bPFS (iPSA, GS, BED)
98%, 94%, and 89% for LR, IR, and HR	ADT benefit	NR	NR	NR	NR	bPFS (ADT and BED < 180 Gy)
89% at 10 y	No benefit	NR	NR	NR	NR	Only 1% was HR
79%	Detriment with ADT in IR	95%	NR	95%	NR	bPFS (jPSA, GS, worse with ADT, D_{90} < 140 Gy, year of PB)
LR: 98% IR: 95% HR: 80%	No benefit	NR	NR	NR	NR	bPFS (iPSA, GS, D_{90})
94%	No benefit	98%	NR	98%	NR	bPFS (trend to ADT benefit-5%, p = NS)
81%	No benefit	97%	NR	NR	NR	NR
77%/73% 5 and 10 y	No benefit	96/92% 5 and 10 y	NR	NR	NR	bPFS (risk group, iPSA, GS, stage)
86%	No benefit	98%	NR	91%	NR	bPFS (risk group, iPSA)
74%/76% for ±ADT	No benefit	90%/98% for ±ADT	No benefit	81%/76% for ±ADT	No benefit	bPFS (iPSA, GS)

with the addition of ADT in IR disease (108). None of the seven studies showed an increase in CSS with ADT. Six studies assessed the impact of ADT on OS, three showed no impact on OS with ADT, three showed a statistically significant detriment to OS using ADT (39, 49, 50), and one showed a trend to worse OS (96). The most dramatic OS

detriment was reported by Beyer *et al.* (39) with a median followup of only 4.1 years; a 20% decrease in OS was seen in those patients treated with LDR PB with up to 12 months of ADT. Worth noting is the small number of patients in analyses at the end of the OS curves, which brings into question the validity of the magnitude in OS detriment with ADT. Stone *et al.* (49) reported a 5% OS detriment at 15 years post-treatment with ADT, and Dosoretz *et al.* (50) found an OS detriment in men >73 years.

Other factors associated with bPFS included iPSA, GS, PPC, risk stratification, BED, treatment year, coronary artery disease, and positive post-treatment biopsy. Factors associated with CSS included: CS, GS, BED, positive post-treatment biopsy, and hypertension, and OS: age, diabetes, tobacco use, CVD, and treatment year.

ADT for cytoreduction before PB

Since the introduction of PB, it has been a common practice to downsize the prostate before implant using LHRH agonists. None of the studies where ADT was used for downsizing showed an improved oncologic outcome (70–74). Merrick *et al.* (115) reported that instead of LHRH agonists, downsizing can be achieved using dutasteride and bicalutamide. This was confirmed in a recent RCT where 61 patients were randomized to receive either LHRH antagonists or dutasteride with bicalutamide to downsize prostate before brachytherapy (116). Gaudet *et al.* reported a mean relative prostate volume reduction of 35.5% (SD 8.9) in the LHRH group and 34.6 (SD 17.2) in dutasteride and bicalutamide group, suggesting that 3 months of dutasteride and bicalutamide is noninferior to LHRH agonist for prostate volume reduction. Because of the potential impairment of quality of life associated with ADT, in selected cases, one may consider the less toxic combination of 5-alpha reductase inhibitors and oral antitestosterone for cytoreduction instead of LHRH agonists.

RCTs: ADT and brachytherapy

There are six ongoing RCTs addressing the question of the role of ADT with PB in IR and HR patients (Table 6). So far, only one completed RCT at least indirectly addresses the role of ADT in brachytherapy (118). Denham *et al.* published an Australian multicenter TROG 03.04 RADAR 2 × 2 factorial RCT in men with locally advanced PCa; 1071 men were randomized to receive ADT for 6 or 18 months with dose-escalated EBRT (66, 70, 74, or 46 Gy + HDR 19.5 Gy in three fractions) and also randomized between 0 and 18 months of zoledronic acid (4 mg i.v. Q3 months). The primary end point of bPFS subsequently changed to a PCSM. With a median followup of 7.4 years, there was no significant difference in PCSM or OS between the arms. Subsequent publication shows the cumulative and composite estimates of bPFS and local control for all EBRT dose levels (n = 814) and HDR boost patients (n = 237) stratified by duration of ADT (6 vs. 18 months); 18 months of ADT had a positive effect on the PSA and local control outcome on all EBRT dose levels with greater benefit is seen in lower doses and had almost no effect for patients treated with HDR boost (absolute difference 3%). These data suggest minimal if any benefit to longer ADT using PB; however, it does not answer the question of whether ADT is needed with PB at all (119). Three other completed brachytherapy RCTs do not provide information on the role of ADT with dose-escalated radiation using PB (22–24). Results of the Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE RT) trial (22) indicate that when combined with 12 months of ADT, patients treated with EBRT plus LDR boost have a significantly better bPFS compared with EBRT alone (78 Gy) (83% vs. 62% bPFS at 9 years in favor of PB boost arm). Two other RCTs likewise showed the superiority of dose escalation with HDR + EBRT vs. EBRT, but both used radiation alone without ADT (23, 24).

Recently, Merrick *et al.* (120) published results of two RCTs of supplemental EBRT in addition to LDR-PB in IR patients randomized to 20 vs. 44 Gy EBRT (n = 247) or 0 vs. 20 Gy EBRT (n = 383). ADT (<6 months) was given for downsizing or adverse features in 32% of the patients in 20/44 Gy trial and 7.6% in 0/20 Gy trial. The results showed a very high bPFS and CSM for both 20/44 Gy and 0/20 Gy trials (biochemical failure 7.7% and 8.2% at 8 and 13 years and CSS of 2% and 2.4% at 8 and 13 years followup, respectively). Predictors of PSA failure were PPC and prostate volume. The trial showed no benefit of supplemental EBRT on bPFS and PCSM with high-quality implants. ADT was not associated with improved outcomes. The reason for association between prostate volume and outcome is unclear.

Ongoing RCTs

SHIP 0804 (Seed and Hormone for Intermediate-Risk Prostate Cancer, ClinicalTrials.gov NCT00664456) is an ongoing multi-institutional Japanese RCT that will be reporting outcomes on 420 IR patients treated with PB and neoadjuvant ADT for 3 months, randomized to 0 vs. 9 months adjuvant ADT (Table 6). The study began recruiting in April 2008. Planned completion is March 2011. Primary end point is 10 years bPFS. Secondary end points include OS, clinical PFS (local, distant failures) DSS, salvage treatments, International Prostate Symptom Score, and QOL (122).

SHIP 36B (ClinicalTrials.gov: UMIN000003992) is an RCT of 340 patients with HR localized PCa, all treated with EBRT + PB + ADT for 6 months, randomized between additional 0 vs. 24 months of adjuvant ADT. The trial is closed for accrual in 2012. Primary endpoint is bPFS, and

Table 6
RCTs in progress

RCT	Country	Accrual	Randomization	Number of patients	Risk groups	Primary end point	Secondary end points	Status
SHIP 0804 (117)	Japan	2008−2011	PB + 3 mo neoadjuvant ADT Randomization: 0 vs. 9 mo adjuvant ADT	420	IR	bPFS	OS, PFS, CSS, salvage treatments, International Prostate Symptom Score and QOL	Closed
SHIP 36B (118)	Japan	Closed 2012	EBRT + PB + ADT 6 mo Randomization: 0 vs. 24 mo adjuvant ADT	340	HR	bPFS	OS, PFS, CSS, salvage treatments and adverse effects	Closed
RTOG 0815 (119)	US	2009−2016	EBRT (79.2 Gy), or HDR or LDR boost Randomization: 0 vs. 6 mo ADT	1520 (Stratified by number of risk factors and comorbidity status)	Favorable IR Excluded: T2b-T2c, PSA 10−20, and GS 7 and with ≥50% PPC	OS	bPFS, local and distant recurrence free survival, PCSM salvage, toxicity, QOL	Closed
RTOG 0924 (83, 119).	US	2011−2019?	EBRT ± HDR or LDR boost + ADT (4, 6, or 32 mo) Randomization: Prostate only vs. Whole pelvis RT	Projected 2580 1175 accrued	Unfavorable IR Favorable HR	OS	bPFS, DMFS, CSS, time to CRPC toxicity, QOL	Open
Spanish RCT (120)	Spain	2007−2008	EBRT +HDR boost Randomization: ADT vs. no ADT	62	IR and HR	6 y bNED with and without ADT 83% vs. 90%, p = NS	DMFS and local control—no difference between arms	Reported: Abstract form 2013
Chinese RCT (121)	China	NR	LDR PB Randomization: 0 vs. 3 mo neoadjuvant ADT	165	T1c-T3b (PSA 3.5−150) (all risk groups)	bNED toxicity	NR	Reported: Abstract form 2012

ADT = androgen deprivation therapy; bPFS = biochemical progression-free survival; CRPC = castrate resistant prostate cancer; CSS = cause-specific survival; DMFS = distant metastatic free survival; HR = high risk; IPSS = International Prostate Symptom Score; IR = intermediate risk; NS = nonsignificant; OS = overall survival; PB = prostate brachytherapy; PCSM = prostate cancer−specific mortality; PFS = progression free survival; QOL = quality of life; RCT = randomized controlled trials.

Table 7
Summary of all studies

	bPFS	CSS	OS
Total studies 52	Reported in 42 studies (80%)	Reported in 24 studies (46%)	Reported in 19 studies (36%)
Benefit to ADT	12 (28%)	4 (16%)	0
No benefit	30 (71%)	19 (79%)	16 (84%)
Detriment with ADT	1 (2%)	—	3 (15%)

ADT = androgen deprivation therapy; bPFS = biochemical progression-free survival; CSS = cause-specific survival; OS = overall survival.

secondary endpoints are OS, PFS, CSS, salvage treatments, and adverse effects. Results are expected in 2022 (123).

RTOG 0815 is a recently closed Phase 3 Prospective Randomized Trial of dose-escalated radiotherapy (EBRT to 79.2 Gy or HDR or LDR) with or without 6 months ADT for patients with IR PCa. Planned accrual was 1520 patients. Primary end point is OS, whereas bPFS and health related quality of life are some of the secondary end points. Patients with three IR features (T2b-T2c disease, PSA $>$ 10 but $\leq$20, and GS 7 and with $\geq$50% PPC) were excluded from this study. Therefore, the study will not be able to answer the question whether ADT is required with dose-escalated RT in uIR patients. However, patients have been stratified by ACE-27, and the results will further clarify the role that comorbidity may play in risk of cardiovascular events with ADT. The study has met its target accrual and closed on March 7, 2016 (63).

RTOG 0924 is an ongoing Phase 3 Prospective Randomized Trial of ADT and high-dose radiotherapy with or without whole-pelvic radiotherapy in uIR or fHR PCa. Patients are stratified, given ADT for 6 or 32 months, treated with IMRT, IMRT + HDR, or LDR boost, and randomized into IMRT to prostate or pelvis. Target accrual is 2580 patients, and 1175 patients have been accrued. Primary end point is OS, whereas bPFS, distant metastasis, CSS, and health related quality of life are some of the secondary end points. Results will be available in 2024 (63, 82).

The Spanish RCT trial in "uIR" and HR PCa of EBRT + HDR ± ADT has been reported in abstract form only. With median followup of 60 months, there was no benefit to ADT for bPFS (83% vs. 90%; $p = 0.4$) and no benefit to locoregional control or distant metastasis (124).

A Chinese RCT investigated LDR monotherapy in all risk stratifications with or without ADT. The trial has been reported in abstract form only, and there are no available disease outcomes published yet (117).

Discussion

This review included 52 studies and 43,303 patients, the majority treated with LDR (n = 40,440). Seven HDR studies included 2863 patients; 25 studies are multi-institutional and 27 are single institution. Studies are mostly retrospective in nature and most included prospective data collection with exception of two RCTs.

Overall, patients treated with brachytherapy have exceptionally good long-term disease outcomes and compare favorably with other treatment modalities (1) (Tables 1–5). For LR and fIR, bPFS, CSS, and OS are 77–95%, 93–99%, and 81–96%, respectively. For IR, bPFS, CSS, and OS are 88–95%, 98%, and 77%, respectively. For IR and HR, bPFS, CSS, and OS are 68–95%, 95–98%, and 57–79%, respectively. For HR, bPFS, CSS, and OS are 80–92%, 86–98%, and 68–97%, respectively.

The literature review shows significant heterogeneity of patient populations, risk categories, risk factors, followup time, ADT administration, and duration. Inherent in all retrospective analysis is unavoidable patient selection and treatment selection bias. This has a potential to affect the results, and the conclusions, as multivariate analysis, cannot always overcome the selection bias. For example, Wattson *et al.* reported that the number of HR features in 2234 men with HR PCa (1 and 2 vs. 3) is strongly related to AHR for PCSM (hazard ratio, 0.5; 95% CI, 0.2–0.9; p = 0.03). In many studies, patients with worse risk factors have been selected not only to receive ADT (82, 83, 85, 86) but also to receive ADT for longer duration (55, 75, 91–94, 96). In addition, patients with higher risk factors are expected to do less well overall. The fact that they did have similar outcomes to patients with lower risk or fewer risk factors may indicate overall ADT benefit. It has been reported that patients with uIR and fHR have relatively poor outcomes with PB alone (69, 99, 121); however, some have speculated that with high-quality brachytherapy with sufficient margins, this difference may be less significant (120).

The duration of ADT in brachytherapy studies was relatively short (median, LR 3–6, IR 3–9, and HR 12 months). Patients in LR and IR most often received ADT to downsize the prostate, and in some IR and most HR studies, ADT was given for HR features, as described earlier. Although optimal duration of ADT cannot be determined from this review, TROG 03.04 RADAR has provided some evidence that duration of ADT together with HDR-BT has less impact on bPFS and local control than when combined with EBRT (119). As most of the studies, even those with HR PCa limited ADT to median 12 months; one may consider shortened duration of ADT if PB boost is to be used (up to 12 months). This is also supported by excellent results from recently reported ASCENDE RT trial where uIR and fHR patients received triple therapy with 12 months of neoadjuvant and adjuvant ADT. It is also worth noting that HR patients treated with PB tend to be in the more favorable spectrum of HR disease (Table 4) (66, 67). It may be for this reason that ADT duration can be limited

to only 12 months. Unfavourable HR patients or HR with multiple high risk features are few in number in the studies reviewed as they are less likely to be offered brachytherapy boost. In studies that included unfavourable HR patients, ADT was given for up to 36 months (104).

The studies were grouped to reflect disease risk stratification. Advances in refining the risk stratification have been included in this review. As mentioned earlier, treatment selection bias is present in almost all studies presented in this review. It is clear that physicians seem to take into account the presence of multiple adverse factors and recommend more aggressive treatments, including addition of EBRT and ADT and using ADT for longer duration (55, 75, 91–94, 96). It is clear that further advances in refining group stratification are urgently needed to further refine treatment recommendations (66, 68, 69).

Eighty percent ($n = 42$) studies have information on the effect of ADT on bPFS, 46% ($n = 24$) on CSS, and 36% ($n = 19$) on OS (Table 7). Seventy-one percent studies report no bPFS benefit with addition of ADT, whereas 28% reported modest, up to 15% benefit of adding ADT to PB. The lack of benefit was seen in LR and fIR (70–74) and the majority of HDR studies. Most patients in these studies received short-term ADT to downsize the prostate before brachytherapy. ADT consistently showed improved in bPFS in patients with lower BED/D_{90} (26, 81, 98, 106), uIR (multiple risk factors), and majority of HR patients (55, 56, 88, 90, 93–95, 97).

Only four studies found a small benefit to CSS with ADT: one in uIR (78) and three in HR PCa (56, 91, 92), where increase in CSS was reported with "triple therapy" vs. monotherapy or vs. EBRT + PB without ADT (91, 92). Others reported that high-quality implants may derive less benefit from supplemental EBRT (120) or ADT (26, 81, 98, 106, 120). The impact of ADT on OS has not been studied well as only 19 studies (36%) reported association of ADT and OS. Overall, 16 studies found no OS benefit with ADT; however, three found an OS detriment with the addition of ADT to brachytherapy (39, 49) and in particular in men >73 years (50).

In general, most HDR studies (87, 97, 110–114) found no benefit to addition of ADT. The preliminary results of the Spanish HDR RCT reported no benefit to ADT (124). Only one HDR study reported 11% and 20% improved bPFS with ADT for IR and HR patients (88). Results of RCTs in progress may provide more information on the role of ADT with HDR.

Six RCTs are in progress to further assess the role of ADT with PB (63, 82, 117, 122–124). Unfortunately, RTOG 0815, the only large RCT that has an arm not receiving any ADT, excluded patients with uIR disease and will not be able to provide information regarding the role of ADT in uIR patients. Both Japanese trials (included IR and HR disease) and RTOG 0924 (included uIR and fHR disease) do not have arm treated without ADT. Therefore, they will primarily test the hypothesis regarding duration of ADT, rather than whether ADT is of any benefit together with brachytherapy. RCTs that test not only the duration but whether there is any role for ADT in uIR and fHR disease are urgently needed.

If there is a potential to achieve up to a 15% increase in bPFS using ADT in some IR and HR patients without significant impact on CSS, will this improvement come at a price of diminished QOL, potentially increase in cardiovascular morbidity and diminished OS? Literature suggests ADT should be used with caution in older patients (50, 125) and in those with CVD (48, 51, 52, 58, 60). In addition, ADT may have detriment to long-term OS in brachytherapy patients (39, 49, 50). Therefore, ADT should be prescribed only to patients likely to benefit from it. In addition, significant efforts should be directed to reducing and managing ADT side effects including appropriate life style changes, smoking cession, and referral to a family doctor or a specialist experienced in the management of CVD.

Summary

The inherent selection bias in retrospective studies, unclear risk stratification, inconsistent use and duration of ADT, and inconsistent treatment allocation precludes any definitive conclusions regarding use of ADT in brachytherapy-treated patients. Despite these significant limitations, we can deduce that there is no clinical or biochemical benefits from addition of ADT in LR and fIR patients. In uIR and fHR patients, the use and duration of ADT were subject to considerable physician bias. Despite this, ADT was beneficial in improving bPFS in most patients with HR disease using LDR, some patients with uIR, and patients with low D_{90} or low BED. The very small absolute benefit (2%) to CSS was found in only few studies and was seen predominantly with tri-modality treatment vs. PB monotherapy. No OS survival benefit was found in any study; however, three studies had reported a detriment to OS using ADT. To minimize morbidity and potentially excess mortality, one should exercise caution in prescribing ADT to older patients and those with existing cardiovascular disease. With high-quality brachytherapy, the radiation dose is sufficient that any synergistic local effect of ADT with radiation is likely to be of little benefit except, perhaps in cases with very high-volume local disease. In uIR and HR disease, ADT is likely to still play a role through spatial co-operation for suppression of micrometastatic disease. The optimal duration, however, remains to be determined. RCTs testing the role of ADT in uIR and fHR disease are urgently needed.

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