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Use of Androgen Deprivation Therapy with Prostate Brachytherapy, A Systematic Literature Review

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Abstract

Introduction—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 is 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).

Material and Methods—A literature search was conducted in Medline and Embase covering the years 1996-2016. Selected were articles with >100 patients, minimum follow-up 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 ongoing brachytherapy Randomized Controlled Trials (RCTs).

Results—52 selected studies (43,303 patients) were included in this review; 7 HDR (High Dose Rate), and 45 LDR (Low Dose Rate). Twenty-five studies were multi-institutional and 27 single institution, (retrospective review or prospective data collection) and two were RCTs. The studies

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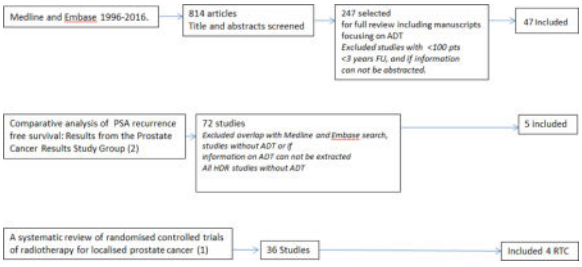
were heterogeneous in patient population, risk categories, risk factors, follow-up time, and treatment administered, including ADT administration and duration (median 3-12 months).

Seventy one percent of the studies reported a lack of benefit, while 28% show improvement in bPFS with addition of ADT to PB. The lack of benefit was seen in LR and favourable IR disease, as well as the majority of HDR studies. A bPFS benefit of up to 15% was seen with ADT use in: patients with suboptimal dosimetry, those with multiple adverse risk factors (unfavourable IR) and most HR studies. Four studies reported very small benefit to CSS (2%). None of the studies showed OS advantage, however 3 studies reported an absolute 5-20% OS detriment with ADT. Literature suggests OS detriment is more likely in older patients or those with pre-existing cardiovascular disease (CVD). Four RCTs with an adequate number of patients and well defined risk stratification are in progress. One RTC will answer the question regarding the role of ADT with PB in favourable IR patients, and the other 3 RTCs will focus on optimal duration of ADT in the unfavourable IR and favourable HR population.

Conclusions—Patients treated with brachytherapy have excellent long-term disease outcomes. Existing evidence shows no benefit of adding ADT to PB in LR and favourable IR patients. Unfavourable IR, 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. In order to minimize morbidity one should exercise caution in prescribing ADT together with PB, in particular to older men and those with existing CVD. 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 unfavourable IR and favourable HR disease.

Graphical abstract



Keywords

Prostate Cancer; Brachytherapy; Androgen Deprivation Therapy; Outcomes; bPFS; CSS; OS

Introduction

Having emerged in the dawn of the PSA era, Prostate Brachytherapy (PB) has gained worldwide acceptance and is currently considered a standard treatment for organ confined prostate cancer. 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 prostate brachytherapy (PB)

both with Low Dose Rate (LDR) and High Dose Rate (HDR), particularly for Intermediate-Risk (IR) and High-Risk (HR) Prostate Cancer (PCa). Data from prospective randomized control trials will not be available for several years.

The purpose of this article is 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 Overall Survival (OS) in Low-Risk (LR) intermediate (IR) and high-risk (HR) risk 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 (RTCs), and reviewed on-going RTCs. We summarize the current available clinical evidence regarding the use of ADT with PB and provided recommendations regarding its use.

Material and Methods

A literature search was conducted in Medline and Embase covering the years 1996-2016. We searched articles on Androgen Deprivation Therapy 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 prostate cancer (2). Fifty-two 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 follow up of <3 years, those where no ADT was given, or where data required could not be extracted (for example, 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)(Graph 1). Factors predictive of bPFS, CSS and OS were extracted from multivariable MVA analysis in 50 out of 52 articles, and are included in the tables.

ABS, ACR, ASTRO, ESTRO/EUE/EORTC and NCCN recommendations regarding use of ADT with PB

Most of the above 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 ABS recommends no ADT in LR, its use in IR is optional and more strongly recommended in HR (3). ABS recommendations for HDR do not refer to use of ADT with HDR, apart from recommending ADT for downsizing (4). ACR 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 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 0-36 months (6). ESTRO/EUE/EORTC (7), GEC/ESTRO-EUE (8) and ASTRO (9) have no specific recommendation or mention the use of ADT with PB.

Androgen Deprivation Therapy in Prostate Cancer

In 1940, Canadian-born Charles Huggins recognized the androgen dependence of prostate cancer. In 1966, he was awarded the 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 prostate cancer (10,11). In 1997, Zietman et al. published another landmark observation that revolutionized treatment of localized prostate cancer (12). The combination of radiation with orchiectomy for Shionogi tumours 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 biological advantage. Several RTCs of ADT and EBRT have reported improvement in not only bPFS and local control, but also in DSS, and OS (2). In order to produce the above-mentioned clinical benefits, ADT must have a biological 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 tumour 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). Prostate cancer is often hypoxic and this drives endothelial growth factor (VEGF) 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 (VEGF) expression and angiogenesis (18). New discovery suggests that androgen receptor(AR) regulates a transcriptional program of DNA repair genes, and with that, AR promotes prostate cancer radio resistance, adding yet another potential mechanism by which ADT increase radio -sensitivity, by deactivating AR and with that DNA repair mechanism, in an experimental setting (19)".

Therefore, if given prior to EBRT in experimental setting, anti-angiogenesis effect may "normalize" the vasculature and lead to better tissue perfusion, increase in oxygenation, radiation tumour 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 MRSI (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 intra-prostatic tumour control is indicative of a positive therapeutic effect of the higher biological dose given with PB vs. EBRT. This observation is supported by clinical results from 3 RCTs of dose escalation using EBRT vs. EBRT and PB (22,23)(24). All 3 RCTs showed significantly higher bPFS with use of PB in addition to EBRT vs. EBRT alone. Therefore the benefits of ADT reported even with dose-escalated EBRT (78-81 Gy) may be due to compensation for suboptimal radiation dose and less effective local therapy. Due to very high intra prostatic dose and excellent disease control, ADT is likely to have less biological 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 Intermediate Risk (IR) and High Risk (HR) patients has been shown to significantly decrease 2 year post PB positive biopsy rate from 14% to 3.5% (p=0.002) (27). While it is unclear whether the difference seen would have translated in to difference in PSA outcomes with further follow up (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 tumour target. Therefore, increase in radiation dose should in fact increase the tumour eradication and cure. Five dose escalation RCTs have so far shown improved bPFS of average 15% at 5-10 years with dose increase from 65-78Gy (28). No CSS or OS benefit was observed, in part due to a variety of factors including underpowered studies, the long natural history of prostate cancer, improved treatment of metastatic disease, competing causes of death, and the fact that any effect on OS may be very small or even non-existent (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, EORTC 22863, TROG 96-01, RTOG 92-02, RTOG 94-08, Harvard/DFCI, EORTC 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 (MFS) and OS in patients with intermediate and high risk 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 prostate cancer comparing EBRT (78Gy) with EBRT and brachytherapy boost in high and high tier-intermediate risk prostate cancer indicate further improvement of PSA RFS (20-30% at 7-10years)(22,23)(24), with no documented CSS or OS benefit. Recent publications using large national databases indicate an increase in CSS (35) and OS (36) in prostate cancer patients treated with any form of brachytherapy. Brachytherapy results in superior disease outcomes, particularly bPFS (24)(22,23,35,36) 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 Androgen Deprivation Therapy

The use of even short term ADT has deleterious effects to 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 one 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 of 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 HR of 1.16 ($p < .004$) (40). Several studies have documented a decrease in OS in patients with localized prostate cancer treated with ADT and brachytherapy (39)(49,50). Therefore, even with short duration of only 3 months ADT can negatively impacts on 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 due to 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 non-fatal 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 follow-up of 5.4 years primary cause of death in 1,354 patients treated with PB + EBRT + ADT is CVD (42% of all deaths) followed by other cancers (30%) and prostate cancer representing only 8.7% of deaths. Even though MVA analysis 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 when compared to 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 comorbidity. After a median follow-up of 5.1 years, Nanda et al. reported that neoadjuvant ADT use was significantly associated with an increased risk of all-cause mortality only in the subgroup of patients with pre-existing CVD (including heart failure and MI). In their study, mortality had increased from 11% in ADT naïve, to 26% in ADT patients (HR of 1.9, 95%CI 1.04-3.71. p=0.04) (58). Similarly, Nguyen et al. found a significant increase in all-cause mortality (ACM) (adjusted HR 1.76 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) (59). Ziehr et al. reported a 5% absolute excess in cardiac specific mortality in men with a history of congestive heart failure (CHF) or myocardial infarction (MI) who received ADT for minimum 4 months (60).

A recent publication from Memorial Sloan-Kettering presented long term follow-up results on 2211 patients treated with EBRT± PB, who received neoadjuvant or adjuvant (45%) or salvage ADT (16%). With median follow-up 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. reported a decrease in OS with ADT in men with low baseline testosterone (62).

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

PCa Risk stratification

The National Comprehensive Cancer Network (NCCN) risk stratification criteria are perhaps the most commonly cited and represent the standard for most modern clinical trials (6). Even though 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 favourable and unfavourable 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 (81Gy) and with median follow-up of 71 months. Unfavorable IR was defined as: primary Gleason pattern of 4, >50% PPC, or multiple intermediate-risk factors (cT2b/c, PSA 10–20, or GS 7). Patients with unfavorable IR (uIR) disease had inferior bPFS (HR: 2.37; $p < 0.0001$), higher risk of Distant Metastasis (DM) (HR: 4.34; $p = 0.0003$), and worse Prostate Cancer Specific Mortality (PCSM) (HR: 7.39; $p = 0.007$) compared with those with favorable IR (fIR) disease, despite being more likely to receive neoadjuvant ADT together with 81Gy EBRT. Nguyen et al 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/mL/y)(67). 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. Prostate cancer deaths as a proportion of all deaths was 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 a*nd* PSA >20) and unfavorable HR (all others) (68). Only men with unfavourable 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 follow-up of only 3.6 years, conclusions are premature.

The Genito-Urinary Oncologists of Canada (GUROC) have proposed new, refined risk stratification based on recursive partitioning analysis (RPA) analyses of the ProCaRS database (7974 patients from four Canadian Institutions) with long-term follow-up 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 favourable LR and LR based on PSA <6 and PSA >6. IR was sub-classified into favourable and unfavourable IR (PSA ≥10 *and, either* T2b/c, *or* T1T2a *and* GS 7) and the HR group was divided into favourable HR and extreme-risk (ER) group (HR *and* positive cores >87.5% *or* PSA >30). Most importantly, unfavourable IR and favourable HR have the same long-term PSA outcomes, when treated with minimum 74Gy EBRT or brachytherapy alone. Furthermore, extreme risk patients had significantly worse long term outcomes when

compared to patients with favourable HR disease. Two ongoing RCTs (see below) stratify patients into favourable IR, unfavourable IR and favourable HR 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. Out 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 combination LDR-PB with EBRT, all with or without ADT. Only 9 HDR studies are included in this report, as the majority of 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 prior to PB (Table 1 and 2). Higher risk patients and patients with multiple risk factors tended to receive ADT more often, and also for a longer duration (Table 4 and 5). Factors predictive of outcomes (bPFS, CSS and OS) were extracted from multivariable (MVA) analysis in all but two studies.

Low Risk and Intermediate Risk Disease (Table 1)

Five studies were identified describing outcomes with LR and IR patients, treated with LDR ±ADT in 4, or LDR±ADT±EBRT in one. Three studies were multi-institutional (one included matched pair analysis) (71), 2 were Canadian single institution series. A total of 5182 patients were included. Median follow-up ranged from 4-7.5 years. ADT was used in 27-65% of the patients for a median duration of 3-6 months. ADT was most often prescribed to downsize prostate prior to 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 favourable IR disease (fIR)(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, iPSA, D90 and risk groups. OS was associated with age, PSA, GS and Clinical Stage (CS) (table 1).

Intermediate Risk Disease (Table 2)

Six studies with 5854 patients were identified describing outcomes in IR patients using LDR + ADT or LDR±EBRT±ADT. Two were multi-institutional and 4 single institution series. Median follow-up ranged from 4.5-7.8 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 out of 6 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 unfavourable IR subgroup (78). Ho et al. reported a benefit to ADT only if BED was <150Gy(77). 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 unfavourable IR patients. OS was associated with age, diabetes, tobacco use and CAD (table 2).

Intermediate Risk and High Risk Disease (Table 3)

Eight studies were identified describing outcomes in 3,485 patients with IR and HR disease; six using LDR, one HDR and one with both LDR and HDR. 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. 44Gy EBRT or 0 vs. 20 vs. 44 Gy EBRT) (84,86) and 4 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 follow-up ranged from 3.5-10.5 years. ADT was used in 32-66 % of the patients for a median duration of 6 months (range 4-28mo). Overall bPFS was 68-95%, CSS 95-98% and OS 77-80%.

Six out of eight studies reported no benefit of ADT to bPFS, apart from ADT improving bPFS by 25%, only in patients with low D90 (81). One HDR study reported 12% and 20% bPFS benefit to adding ADT in IR and HR disease respectively (88). Kraus et al. 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 (FFCF) in patients with GS≥8 and bulky local disease (87). None of the studies showed overall benefit to CSS or OS with ADT. Storm et al did show a non-significant 12% improvement in OS only in HR patients with the addition of ADT (82). Factors associated with bPFS included iPSA, CS, GS, PAP and prostate volume. Factors associated with bPFS included: ADT, Risk Stratification, iPSA, D90 in ADT naïve patients, PAP and prostate volume. Factors associated with CSS included: CS, risk groups, PPC and prostate volume, and with OS: iPSA, age, diabetes and tobacco use (table 3).

High Risk (Table 4)

Eleven studies with a total of 5602 patients were identified describing outcomes in patients with HR disease, ten using EBRT with LDR, one with HDR, all treated with or without ADT. Only one study had patients treated with LDR monotherapy (91). Nine studies were multi-institutional, and 2 were single institutions (1 LDR and 1 HDR). Median follow-up ranged from 4.3-7.8 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 Favourable HR patients with 1-2 HR features.

Nine studies reported an association between ADT and bPFS, 3 showed no benefit and six showed (55,56,90,93–95) benefit to ADT. One HDR study found 6% non-significant increase in bPFS with ADT (97). Bittner et al. and Lissa et al. reported up to 13% benefit to longer ADT duration (56,95). Merrick at 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 3 found a benefit to ADT (56,91,92).

D'Amico et al. found a benefit to CSS with triple therapy vs. LDR+EBRT or LDR monotherapy (92). Similarly Watson et al. reported better CSS for "triple therapy" (LDR+ ADT + EBRT) vs. LDR or LDR+EBRT without ADT (91). None of the 5 studies found any increase in OS with ADT; however Fung et al. reported a non-significant detriment in OS in fIR patients (96).

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 (WPRT) in ADT naïve patients (90)

All risk categories (Table 5)

Twenty two studies with 23,180 patients were identified describing outcomes in all risk categories including LR, IR and HR disease, sixteen using LDR (20,991 patents), five using HDR (2,189 patients) and one with both. Patients were treated using monotherapy LDR or HDR ± EBRT, all with or without ADT. Eight studies were multi-institutional, and 14 are single institution series, with 4 are from the single institution (26,49,98,100). Median follow-up ranged from 3.8-10 years. ADT was used in 18-83% of the patients for median duration of 3-9months. 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 5 HDR studies), 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 <150Gy (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 with the addition of ADT in IR disease (108). None of the 7 studies showed an increase in CSS with ADT. Six studies assessed the impact of ADT on OS; 3 showed no impact on OS with ADT, and 3 showed a statistically significant detriment to OS with the use of ADT (39,49,50), one showed a trend to worse OS(96). The most dramatic OS detriment was reported by Bayer at al. with a median follow-up 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 (39). Stone at al (49) reported a 5% OS detriment at 15 years post treatment with ADT, and Dosoretz et al. found an OS detriment in men >73y age (50).

Other factors associated with bPFS included: iPSA, GS, PPC, risk stratification, BED, treatment year, CAD, 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 prior to implant using LHRH agonists. None of the studies where ADT was used for downsizing showed an improved oncological outcome (70–74). Merrick et al. reported that instead of

LHRH agonists, downsizing can be achieved with use of Dutasteride and Bicalutamide (115). This was confirmed in a recent RCT where 61 patients were randomized to receive either LHRH antagonists or Dutasteride with Bicalutamide to downsize prostate prior to 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 non-inferior to LHRH agonist for prostate volume reduction. Due to the potential impairment of quality of life associated with ADT, in selected cases, one may consider the less toxic combination of 5alpha reductase inhibitors and oral anti-testosterone for cytoreduction instead of LHRH agonists.

Randomized Controlled Trials: ADT and Brachytherapy (Table 6)

There are 6 ongoing RCTs addressing the question of the role of ADT with PB in IR and HR patients. So far, only one completed RCT at least indirectly addresses the role of ADT in Brachytherapy (121). Denham at al published an Australian multicentre TROG 03.04 RADAR 2×2 factorial RCT in men with locally advanced prostate cancer. 1071 men were randomized to receive ADT for 6 or 18 months with dose escalated EBRT (66Gy, 70Gy, 74Gy or 46Gy+HDR 19.5Gy in three fractions), and also randomized between 0-18 months of Zoledronic Acid (4mg IV Q3 months). The primary end point of bPFS subsequently changed to a PCSM. With a median follow-up 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%). This data suggest minimal if any benefit to longer ADT with the use of PB, however it does not answer the question of whether ADT in needed with PB at all (122). Three other completed Brachytherapy RCTs do not provide information on the role of ADT with dose-escalated radiation using PB (22,23)(24). Results of the 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 to EBRT alone (78Gy)(83% vs 62% bPFS at 9 years in favour 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. published results of 2 RTC of supplemental EBRT in addition to LDR-PB in IR patients randomized to 20 vs. 44 Gy EBRT (n=247) or 0 vs. 20Gy EBRT (n=383). ADT (<6mo) was given for downsizing or adverse features in 32% of the patients in 20/44Gy trial and 7.6% in 0/20Gy trial. The results showed a very high bPFS, and CSS for both 20/44Gy and 0/20Gy 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 follow-up 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 (123).

Ongoing RCTs (Table 6)

SHIP 0804

SHIP 0804 (Seed and Hormone for Intermediate–Risk Prostate Cancer, ClinicalTrials.gov NCT00664456) is an ongoing multi-institutional Japanese RTC, 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. The study began recruiting in April 2008. Planned completion is March 2011. Primary endpoint is 10y bPFS. Secondary end-points include OS, clinical PFS (local, distant failures) DSS, salvage treatments, IPSS and QOL (117).

SHIP 36B

SHIP 36B (ClinicalTrials.gov: UMIN000003992) is a RTC of 340 patients with high-risk localized prostate cancer, 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 secondary endpoints are OS, PFS, CSS, salvage treatments and adverse effects. Results are expected in 2022 (118).

RTOG 0815

RTOG 0815 is a recently closed phase III Prospective Randomized Trial of dose-escalated radiotherapy (EBRT to 79.2Gy, or HDR or LDR) with or without 6 months ADT for patients with IR PCa. Planned accrual was 1520 pts. Primary endpoint is OS while bPFS and HRQL are some of the secondary endpoints. Patients with 3 intermediate-risk features (T2b-T2c disease, PSA >10 but ≤20, and GS 7 and with ≥ 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 *unfavourable* IR patients. However, patients have been stratified by Adult Comorbidity Evaluation-27 score (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

RTOG 0924 is an ongoing Phase III Prospective Randomized Trial of ADT and high dose radiotherapy with or without whole-pelvic radiotherapy in unfavourable IR or favourable HR PCa. Patients are stratified, given either ADT for 6 or 32 months, treated with IMRT, or IMRT +HDR or LDR boost and randomized into IMRT to prostate or pelvis. Target accrual is 2580 pts, 1175 patients have been accrued. Primary endpoint is OS while bPFS, DM, CSS and HRQL are some of the secondary endpoints. Results will be available in 2024 (63,82).

The Spanish RCT trial

The Spanish RCT trial in “unfavourable” IR and HR prostate cancer of EBRT+ HDR ± ADT has been reported in abstract form only. With median follow-up of 60 months, there was no benefit to ADT for bPFS (83% vs. 90% P = 0.4), and no benefit to loco regional control or distant metastasis (119).

A Chinese RCT

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 (120).

Discussion

This review included 52 studies and 43,303 patients, the majority treated with LDR (n=40,440). Seven HDR studies included 2863 patients. Twenty-five 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 favourably with other treatment modalities (1) (Tables 1–5). For LR and favourable IR, 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, follow-up time, ADT administration and duration. Inherent in all retrospective analysis is unavoidable patient selection and treatment selection bias. This has a potential to impact the results, and the conclusions, as multivariate analysis cannot always overcome the selection bias. For example, Wattson et al. reported that the number of high risk features in 2234 men with HR PCa (1 and 2 vs. 3) is strongly related to adjusted HR for PCSM (HR 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 (55,91–94,96) (75). 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 unfavourable IR and favourable HR have relatively poor outcomes with PB alone (69,99,124), however, some have speculated that with high quality brachytherapy with sufficient margins, this difference may be less significant (123).

The duration of ADT in brachytherapy studies was relatively short (median: LR 3-6 mo, IR 3-9 mo and HR 12 mo). 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 high risk features, as described above. While 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-BP has less impact on bPFS and local control than when combined with EBRT (122). As most of the studies, even those with HR PCa limited ADT to median 12 months; one may consider shorted 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 unfavourable and IR and favourable HR 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 favourable spectrum of HR disease (table 4) (66,67). It may be for this

reason that ADT duration can be limited to only 12 months. Extreme risk (ER) 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 Extreme Risk 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 above, 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 in order to further refine treatment recommendations (66,68,69).

Eighty percent (n=42) of the 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, while 28% reported modest, up to 15% benefit of adding ADT to PB. The lack of benefit was seen in LR and favourable IR (70–74) as well as the majority of HDR studies. Most of patients in these studies received short term ADT in order to downsize the prostate prior to brachytherapy. ADT consistently showed improved in bPFS in patients with lower BED/D90 (26,81,98,106), unfavourable IR (multiple risk factors) and majority of HR patients (55,56,88,90,93–95)(97).

Only 4 studies found a small benefit to CSS with ADT; one in unfavourable IR (78) and 3 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 (123) or ADT (26,81,98,106,123). 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, 3 found an OS detriment with the addition of ADT to brachytherapy (39,49) and in particular in men >73y (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 (119). 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 (63,82,117–120). Unfortunately, RTOG 0815, the only large RTC that has an arm *not* receiving any ADT, excluded patients with unfavourable IR disease and will *not* be able to provide information regarding the role of ADT in unfavourable IR patients. Both Japanese trials (included IR and HR disease) as well as RTOG 0924 (included unfavourable IR and favourable HR 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 unfavourable IR and favourable HR disease are urgently needed.

If there is a potential to achieve up to a 15% increase in bPFS with the use of 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 suggest ADT should be used with caution in older patients (50,125), and 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.

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Abbreviations

PB	Prostate Brachytherapy
EBRT	External Beam Radiation therapy
ADT	Androgen Deprivation Therapy
HDR	High Dose-Rate
LDR	Low Dose Rate
BED	Biologically Effective Dose
D90	Dose covering 90% of the prostate gland
LR	Low Risk Prostate Cancer
IR	Intermediate Risk Prostrate cancer
HR	High Risk Prostate Cancer
IRf	Intermediate Risk feature
uIR	Unfavourable Intermediate Risk
fIR	Favourable Intermediate Risk
uHR	Unfavourable High Risk
fHR	Favourable High Risk
CS	Clinical Stage
PSA	Prostate Specific Antigen

PAP	Prostatic Acid Phosphatase
PPC	Percent Positive Cores
P Vol	Prostate Volume
bPFS	Biochemical Progression Free Survival
CSS	Cause Specific Survival
DMPFS	Distant Metastasis Progression Free survival
DM	Distant Metastasis
PCSS	Prostate Cancer Specific Survival
FFCF	Freedom From Clinical Failure
OS	Overall Survival
IQR	Inter Quartile Range
NR	Not Recorded
CPRPC	Castrate resistant Prostate Cancer
QOL	Quality of Life
Triple therapy	EBRT + PB + ADT
CVD	Cardio Vascular Disease
CHF	Congestive Heart Failure
MI	Myocardial Infarction
BX	Biopsy

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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 favourable IR patients. In unfavourable IR and favourable HR patients, the use and duration of ADT was subject to considerable physician bias. Despite this, ADT was beneficial in improving bPFS in most patients with HR disease using LDR, some patients with unfavourable IR, and patients with low D90 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 3 studies had reported a detriment to OS with the use of ADT. In order 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 unfavourable IR and HR disease, ADT is likely to still play a role through spatial cooperation for suppression of micrometastatic disease. The optimal duration, however, remains to be determined. RCTs testing the role of ADT in unfavourable IR and favourable HR disease are urgently needed.

Table 1

Low Risk (LR) and Intermediate Risk (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 (70)	MultiinstitutionalUS	1996-2001	1668	4y	LR:64% IR:36%	LDR±ADT	37%	6 mo	87.8%	No benefit	NR	NR	NR	NR	NR
Potters (71)	New York Institutions US	1992-2000	1449	6.8y	NR	LDR±EBRT±ADT	27%	5.2 mo (1-24)	77%	No benefit	93%	NR	81%	NR	bPFS (GS, iPSA, D90)
Ohashi (72)	Multiinstitutional Japan	2003-2009	663	5y	LR: 67% fIR: 33%	LDR±ADT	44%	3 mo	95.9%	No benefit	99%	NR	96%	NR	bPFs (D90, risk group)
Morris (73)	British Columbia, Canada	1998-2003	1006	7.5y	LR: 58% fIR: 42%	LDR±ADT	65%	6 mo	95%	No benefit	99%	NR	83%	No benefit	bPFS (log iPSA, D90 in ADT naïve) OS (Age, log iPSA)
Martin (74)	Quebec City Canada	1994-2001	396	5y	LR: 69% fIR: 31%	LDR±ADT	65%	6mo	88.5%	No benefit	NR	NR	NR	NR	bPFS (GS and stage)

Table 2

Intermediate Risk Disease (IR)

IR	Type of the study	Study years	Number of patients	Median FU in years	Sub Group 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 (75)	Chicago	1997-2007	807	4.5y (IQR2.7-6.2y)	NR	LDR±ADT or EBRT+LDR	76%	4mo (2-6 mo)	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 (76)	Multiinstitutional UK	2003-2007	615	5y (0.3-8.3y)	NR	LDR±ADT	17%	4mo	88%	No benefit	NR	NR	NR	NR	bPFS (iPSA)
Ho (77)	Mount Sinai NY 2009	1990-2004	558	5y	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 <150Gy2, 10% benefit to ADT, p=ns)
Keane (78)	Harvard Boston MA	1997-2013	2510	7,8y (IQR5.3-10.5)	fIR: 76% uIR: 24%	LDR±ADT, or EBRT+LDR	33%	4mo	NR	NR	NR	Benefit ADT only in unfavourable IR (HR 0.34 CI .13-.91)	NR	NR	CSS (Year of PB, ADT (uIR and risk stratification)
Bittner (79)	Multiinstitutional US	1995-2001	932	7,4y	90%IR GS 3+4: 58% GS 4+3: 41%	LDR+EBRT,±ADT	29%	6mo	95%	No benefit	98%	No benefit	77%	No benefit	bPFS (GS, iPSA, stage) CSS(nil) OS(age, diabetes, tobacco, CAD)
Stock (80)	Mount Sinai NY	1994-2006	432	4,6y (23-155 mo)	1 IRF: 47% 2IRF: 41% 3IRF: 12%	LDR+EBRT±ADT	81%	4mo (324)	92%	No benefit	NR	NR	NR	NR	bPFS(iPSA, GS, CS, number of risk features)

Table 3

Intermediate Risk (IR) and High Risk (HR) disease

IR and HR	Type of the study/institution	Year of study	Number of patients	Median FU in years	Treatment	Risk Stratification	% ADT	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
LDR															
Lee (81)	Mount Sinai NY	1990-1998	201	3.5y	LDR±ADT	IR: 33% HR: 67%	66%	6mo	68%	Benefit to ADT for low D90	NR	NR	NR	NR	bPFS(ADT, RS, iPSA, D90 in ADT naïve - 25% bPFS benefit to ADT with low D90)
Strom (82)	Tampa FL	2001-2011	120	5.2y	LDR+EBRT±ADT	IR: 76% HR: 24%	45%	IR 4 mo HR 28mo	NR	No benefit	NR	No benefit	NR	No benefit	OS (age, trend for ADT benefit in HR (12% p=NS)
Merrick (83)	Multiinstitutional US	1995-2003	530	5.7y	LDR+EBRT±ADT	IR: 73% HR: 27%	33%	4-7mo (3-36mo)	95.2%	No benefit	95.2%	No benefit	77.3%	No benefit	bPFS (iPSA, CS) CSS(CS) OS (age, diabetes, tobacco)
Merrick (84)	Multiinstitutional US RCT - 20 vs 44Gy EBRT + PB	1999-2004	247	9y	LDR+EBRT±ADT	PSA>10; 15% GS 8-9: 15%	32%	4 and 9 mo	93.2%	No benefit	97.7%	No benefit	80%	No benefit	bPFS (PSA, CS)
Dattoli (85)	Multiinstitutional US	1992-1997	321	10.5y	LDR+EBRT±ADT	IR: 49% HR: 51%	44%	4mo (3–6)	82%	No benefit	NR	NR	NR	NR	bPFS (GS, PAP)
Merrick (86)	Multiinstitutional US RCT - 0 vs.20 vs. 44GyEBRT + PB	1999-2013	630	7.7y	LDR±EBRT±ADT	fIR: 46% uIR: 46% HR: 8%	10-56%	6mo	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)
HDR/LDR															
Kraus (87)	William Beaumont	1991-2004	1044 pts	5y	LDR/HDR±EBRT±ADT	IR: 75% HR: 25%	40%	6 mo	72%	No benefit	98%	No benefit	83%vs79%for+ADT	No benefit	bPFS (iPSA, GS, CS. ADT improved bPFS 11.5% p=0.02 with LDR/HDR monotherapy. ADT improved FFCF with

IR and HR	Type of the study/institution	Year of study	Number of patients	Median FU in years	Treatment	Risk Stratification	% ADT	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
															GS>=8 and bulky local disease
HDR															
Schiffmann (88)	Hamburg Germany	1999-2009	392	4y	LDR±EBRT±ADT	IR:46% HR:53%	56%	3mo	77%/65 % tri vs. bi modality	ADT Benefit (11%-20%)	NR	NR	NR	NR	bPFS (ADT benefit 12% for IR and 20% in HR)

Table 4

High Risk Disease (HR)

HR	Type of the study	Year of the study	Number of patients	Median FU		Treatment	% ADT	Median ADT duration	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
LDR															
Ohashi (89)	Japan	2003-2009	206	5y	1 HRf 90% 2 HRf 9% 3 HRf 0.5%	LDR+EBRT±ADT	4[0-9]%	4mo	84.4%	No benefit	98%	NR	97%	NR	bPFS (PPC and risk features)
Bittner (56)	Multiinstitutional US (very high risk)	1995-2007	131	6.6y	GS 8/9:80% PSA>20:29%	LDR+EBRT±ADT	9[0-9]%	19mo (4–36)	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)
Bittner (90)	Multiinstitutional US	1995-2005	186	6.7y	GS8-10:76% Med iPSA:11	LDR+EBRT (mini vs whole pelvis) ±ADT	7[0-9]%	>6mo (75%)	92/84% WP vs Mini P	ADT benefit	95%/92% WPRT vs MPRT	No benefit	79/67% WPRT vs MPRT	No benefit	bPFS (ADT) OS (age, PPC, WPRT in ADT naïve pts)
Wattson (91)	Multiinstitutional, US	1991+2007	2234	4.3y	1HRf: 83% 2HRf: 14% 3HRf:2%	LDR±EBRT,±ADT	7[0-9]%	4mo	NR	NR	NR	ADT benefit	NR	NR	CSS(ADT, number of high risk factors, triple therapy vs. LDR or LDR +EBRT)
D'Amico (92)	Multiinstitutional US	1991-2005	1342	5.1y	1HRf: 5% 2HRf: 86% 3HRf:8%	LDR±ADT or EBRT+LDR or EBRT+LDR+ADT	6[0-9]%	4mo (IQR 3.4-6.2mo)	NR	NR	84%	Benefit to ADT +EBRT vs LDR alone	NR	NR	CSS (trend for better tri vs. bimodality AHR 0.32 CI 0.14-0.73)
Merrick (93)	Multiinstitutional US	1995-2002	204	7y	Med iPSA 9.9 Med GS8	EBRT+LDR±ADT	4[0-9]%	4 and 12mo (3–36)	89%	ADT benefit (6-16%)	86%	No benefit	68%	No benefit	bPFS (PPC, ADT and ADT duration) CSS (GS) OS (GS, diabetes)
Shilkurt (94)	Multiinstitutional US	1995-2010	448	5.2y	1HRf: 84% 2HRf: 14% 3HRf: 2%	LDR+EBRT±ADT	7[0-9]%	12mo (8–24)	86%	ADT benefit (HR 0.2)	93%	No benefit	NR	NR	From the analysis of 958 pts who received EBRT ±ADT or LDR +EBRT±ADT
Merrick (55)	Multiinstitutional US	1995-2005	284	7.8y	NR	LDR+EBRT±ADT	6[0-9]%	4-12 mo (range 3-36)	89%	ADT benefit if PSA>2 0 (10%)	94%	No benefit	69%	No benefit	bPFS(PPC, ADT) CSS(nil) OS(age, diabetes, PPC)

HR	Type of the study	Year of the study	Number of patients	Median FU		Treatment	% ADT	Median ADT duration	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
Liss (95)	Multiinstitutional US	1998-2008	141	4.7	GS8-10:75% Med iPSA:20 T2b-T4:40%	LDR+EBRT±ADT	8[0-9]%	12 mo	80%	Benefit to ADT>1 2 mo	94	No benefit	88% (with GS5)	No benefit	bPFS (iPSA, ADT, CSS(nil) MFS(iPSA, GS5, ADT OS (iPSA, GS5)
Fang (96)	Multiinstitution al US	1995-2005	174	6.6y	GS 8-10 PSA<15	LDR+EBRT±ADT	6[0-9]%	12mo(3–36)	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 Vol) NS detriment to OS with ADT
HDR															
Prada (97)	Oviedo, Spain	1998-2006	252	6.1y	2 IRf17% 1 HRf 40% 2 HRf 35% 3 HRf8%	HDR+EBRT±ADT	69%	12mo	84%/78% 5 and 10y	No benefit	NR	NR	NR	NR	bPFS (GS, benefit to ADT 6% p=ns)

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	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
LDR															
Stock (98)	Mount Sinai NY	1990-2010	2427	6.5	LR :44% IR : 34% HR :21%	LDR±EBRT±ADT	54%	6mo (3-36mo)	85vs 86% for ±ADT	Benefit if BED <150Gy (24% at 10y)	NR	NR	NR	NR	bPFS (ADT, BED) Post PB Biopsy (benefit to ADT with BED < 200Gy)
Stone (49)	Mount Sinai NY	1990-2007	1669	10 mean	LR :45% IR : 38% HR :16%	LDR±EBRT±ADT	54%	6mo (6–36)	89%/67% 10 and 15 y	NR	94.[0-9]%	No benefit	57%(15y)	OS worse with ADT (5% at 15y)	CSS (stage and GS) OS (age, ADT, smoking, diabetes, emphysema, atrial fib.)
Beyer (39)	Arizona Oncology Services	1998-2001	2378	4.1	LR :47% IR : 33% HR :19%	LDR±EBRT±ADT	19.5[0-9]%	3-6 mo (3-12mo)	NR	NR	88%	No benefit	43%	OS worse with ADT (20%)	OS (ADT, age, GS)
Hinnen (99)	Utrecht Netherlands	1989-2004	921	5.7	LR :25% IR : 40% HR :35%	LDR±ADT	18%	6mo	79%/57% 5 and 10y	No benefit	82%	No benefit	59%	NR	bPFS(year of PB, HR, IR) OS (year of PB, HR)
Burri (100)	multiinstitutional US	1990-2005	1665	5.6	LR :60% IR : 27% HR :12%	LDR±EBRT±ADT	54%	3-9mo	94%/88% 5 and 8 y	No benefit	NR	NR	NR	NR	bPFS (GS, iPSA, BED)
Merrick (101)	multiinstitutional US	1995-2002	938	5.4	LR :35% IR : 35% HR :19%	LDR+EBRT±ADT	40%	7-40mo	96%	Benefit to longer ADT (15%)	96%	No benefit	78%	No benefit	bPFS (PPC, longer ADT) OS(age tobacco),
Tiara (102)	multiinstitutional US	1992-1997	1656	7	LR :35% IR : 36% HR :28%	LDR±EBRT±ADT	37%	<6 and >6 mo	95.6%	No benefit	98.[0-9]%	No benefit	72.6%	No benefit	bPFS (PPC, Risk groups, CAD) CSS (GS, hypertension) OS (age, diabetes, tobacco)
Potters (103)	Multiinstitutional-matched pair analysis	1992-1997	263 (612 all pts)	3.8	NR	LDR±EBRT,±ADT	50%	3.4 mo (3-8mo)	87%/87% for±ADT	No benefit	NR	NR	NR	NR	bPFS (iPSA, GS, stage)
Bittner (57)	Multiinstitutional US	1995-2004	1354	5.4	LR :35% IR : 46% HR :18%	LDR±EBRT,±ADT	39%	6mo (max 36)	NR	NR	97%	No benefit	76.7%	No benefit	CSS(GS, Risk Factor) OS(age, smoking)
Stone (26)	Mt Sinai NY	1990-2005	584	7.1	LR :44% IR : 24% HR :31%	LDR±EBRT,±ADT	48%	6mo (3-9mo)	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)

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	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
Dosoretz (50)	21st Centurut Oncology	1991-2005	2474	4.8	LR :65% IR : 23% HR :12%	LDR ±ADT	69%-83%	3-3.4mo	NR	NR	NR	NR	NR	OS worse with ADT in men >73y	ACM detriment with ADT (AHR 1.24 CI1.01-1.53 p=0.04)
Merrick (104)	Multiinstitutional US	1995-2001	668	4.8	LR :33% IR : 37% HR :28%	LDR±EBRT±ADT	58%	4mo (3–36)	98%/98%-88% LR/IR/HR	ADT benefit only for HR (9-12%)	NR	NR	NR	NR	bPFS (HR, ADT, GS, PPC)
Kollmeier (105)	Mount Sinai NY	1990-1996	243	6.2	LR :61% IR : 47% HR :1.1%	LDR±ADT	60%	6 mo	NR	No benefit	NR	NR	NR	NR	bPFS (iPSA, GS, BED)
Senzaki (106)	Tokushima University Hospital Japan	2004-2012	431	5.3	LR :40% IR : 45% HR : 14%	LDR±ADT	63%	6.5 mo (6–10)	98, 94 and 89% for LR, IR and HR	ADT benefit	NR	NR	NR	NR	bPFS(ADT and BED <180Gy)
Wilson (107)	Sir Charles Gairdner Hospital, Australia	1994-2007	207	7.8	LR :51% IR : 47% HR :1.1%	LDR±ADT	58%	3-6mo	89% at 10y	No benefit	NR	NR	NR	NR	Only 1% was HR
Henry (108)	St. James Hospital Leeds UK	1995-2004	1298	4.9y	LR: 44% IR : 33% HR :14%	LDR±ADT	44%	3-4 (all < 6mo)	79%	Detriment with ADT in IR	95%	NR	95%	NR	bPFS (jPSA, GS, worse with ADT, D90 <140Gy, year of PB)
LDR and HDR															
Zelefsky (109)	Memorial Sloan- Kettering NY US	1998-2009	1466	4y	LR: 57% IR : 38% HR :5%	LDR/HDR±EBRT±ADT	31%	3mo	LR: 98% IR : 95% HR :80%	No benefit	NR	NR	NR	NR	bPFS(iPSA, GS, D90)
HDR															
Tselis (110)	Offenbach Germany	2004-2008	351	4.9	LR: 56% IR : 23% HR :21%	HDR monotherapy ±ADT	19%	9mo	94%	No benefit	98%	NR	98%	NR	bPFS (trend to ADT benefit-5%, p=NS)
Demanes (111)	Oakland CA	1991-1998	411	6.4	LR: 27% IR : 45% HR :27%	HDR+EBRT±ADT	48%	<6mo	81%	No benefit	97%	NR	NR	NR	NR
Galalae (112)	Multiinstitutional US and Germany	1986-2000	611	5 mean	LR:[0-9]% 1 risk factor 31% ≥2 risk factors 60%	HDR+EBRT±ADT	28%	4 mo	77%/73% 5 and 10y	No benefit	96/9 2% 5 and 10y	NR	NR	NR	bPFS (Risk group, iPSA, GS, stage)
Phan (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	86%	No benefit	98%	NR	91%	NR	bPFS (risk group, iPSA)
Martinez (114)	Multiinstitutional US	1986-2000	507	4.8	NR	HDR+EBRT±ADT	35%	6 mo	74%/76% for ± ADT	No benefit	90%/98% for ± ADT	No benefit	81%/76% for ± ADT	No benefit	bPFS (iPSA, GS)

Table 6

Randomised Control Trials (RTCs) s in progress

RCT	Country	Accrual	Randomization	Number of patients	Risk Groups	Primary Endpoint	Secondary Endpoints	Status
SHIP 0804 (120)	Japan	2008- 2011	PB + 3 mo neoadjuvant ADT **Randomization:** 0 vs. 9 mo adjuvant ADT	420	IR	bPFS	OS, PFS, CSS, salvage treatments, IPSS and QOL	Closed
SHIP 36B (121).	Japan	Closed 2012	EBRT+PB +ADT 6mo **Randomization**: 0 vs. 24 mo adjuvant ADT	340	HR	bPFS	OS, PFS, CSS, salvage treatments and adverse effects	Closed
RTOG 0815 (122)	US	2009-2016	EBRT (79.2Gy), or HDR or LDR boost **Randomization**: 0 vs 6 mo ADT	1520 *(Stratified by number of risk factors and comorbidity status)*	Favourable IR *Excluded: T2b-T2c, PSA 10-20, and GS 7 and with > 50% PPC*	OS	bPFS, local and distant RFS, PCSM Salvage, Toxicity, QOL	Closed
RTOG 0924 (83,122).	US	2011-2019?	EBRT ± HDR or LDR boost ± ADT (4,6 or 32mo) **Randomization**: Prostate only vs. whole pelvis RT	Projected 2580 1175 accrued	Unfavourable IR Favourable HR	OS	bPFS, DMFS,CSS, time to CRPC toxicity QOL	Open
Spanish RCT(123)	Spain	2007-2008	EBRT+HDR boost **Randomization**: ADT vs no ADT	62	IR and HR	6ybNED with and without ADT 83% vs.90%, P=ns	DMFS and Local Control - no difference between arms	Reported: Abstract form 2013
Chinese RCT(124)	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

Table 7

Summary of all studies

Total studies 52	**bPFS**	**CSS**	**OS**
	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%)