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Review Article

Enhancing Androgen Deprivation Therapy (ADT) integration in prostate cancer: Insights for Stereotactic Body Radiotherapy (SBRT) and brachytherapy modalities

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ABSTRACT

The utilization of Androgen Deprivation Therapy (ADT) in conjunction with Stereotactic Body Radiotherapy (SBRT) and Brachytherapy (BT) boost in prostate cancer treatment is a subject of ongoing debate and evolving clinical practice. While contemporary trends lean towards underutilizing ADT with these modalities, existing evidence suggests that its omission may lead to potentially inferior oncologic outcomes. Recommendations for ADT use should be patient-centric, considering individual risk profiles and comorbidities, with a focus on achieving optimal oncologic outcomes while minimizing potential side effects.

Ongoing clinical trials, such as PACE-C, SPA, SHIP 0804, and SHIP 36B, are anticipated to provide valuable insights into the optimal use and duration of ADT in both SBRT and BT settings. Until new evidence emerges, it is recommended to initiate ADT for unfavorable intermediate-risk and high-risk prostate cancer patients undergoing radiotherapy, with a minimum duration of 6 months for unfavorable intermediate-risk patients and at least 12 months for those with high-risk characteristics. The decision to incorporate ADT into these radiation therapy modalities should be individualized, acknowledging the unique needs of each patient and emphasizing a tailored approach to achieve the best possible oncologic outcomes.

Introduction

Numerous clinical trials have examined the integration of Androgen Deprivation Therapy (ADT) with External Beam Radiotherapy (EBRT) and have investigated the optimal strategies for ADT duration and sequencing in this combined treatment approach [1]. These trials have shown that the addition of ADT to EBRT improves cancer specific survival (CSS), biochemical control and overall survival (OS), and this is also true in the era of dose escalation in EBRT [2]. For this reason, the use of ADT in combination with normo and hypofractionated EBRT is endorsed by clinical guidelines in patients with intermediate and high risk localized prostate cancer.

Conversely, ADT seems to be associated with a higher cardiovascular (CV) toxicity and, more importantly, CV mortality [3–5]. However, this detrimental effect has been showed on large observational studies but not in RCTs maybe because these events occur in previously comorbid patients who were not included in RCTs.

Prostate radiotherapy is evolving towards extreme dose escalation and ultra-hypofractionation through the means of prostate brachytherapy (BT) boost and Stereotactic Body Radiation Therapy (SBRT). However, there is a lack of evidence clarifying the role of ADT in the context of these modern radiotherapy modalities.

Prostate BT boost serves as a form of extreme local treatment intensification that recent SBRT protocols are trying to emulate (HypoFLAME II) although with lower equivalent doses [6]. Level I evidence shows that BT boost improves biochemical and local control [7] and large national databases suggest a potential benefit in CSS and [8]. It has been theorized that the addition of ADT to extreme dose escalation in patients with intermediate and high-risk disease may have a less significant impact and could be shortened or even omitted [9,10].

The goal of this article is to review the use an impact of ADT in combination with prostate BT boost or SBRT to ascertain what is the

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current ideal use of these treatment strategies.

Methods and materials

Literature review

A comprehensive search of pertinent literature was conducted across major medical databases including PubMed/MEDLINE, Embase, Cochrane Library, Web of Science, and Scopus. The search strategy employed a combination of Medical Subject Headings (MeSH) terms and keywords related to "androgen deprivation therapy," "brachytherapy," "SBRT (stereotactic body radiation therapy)," and their pertinent synonyms. The search strategy was not limited by publication date but focused on articles available up to the date of this review (Month, Year).

Inclusion and exclusion criteria

Studies were considered eligible if they explored the utilization, efficacy, safety, or outcomes associated with androgen deprivation therapy in conjunction with either brachytherapy or SBRT in the context of various androgen-sensitive conditions. English language publications involving human subjects and clinical trials, observational studies, systematic reviews, meta-analyses, and relevant guidelines were included. Conversely, studies not meeting these criteria, non-English articles, animal studies, and case reports were excluded from this review.

Data extraction and synthesis

Following the literature search, identified articles were independently screened by two reviewers based on titles, abstracts, and full texts, as necessary, to assess their relevance and adherence to the inclusion criteria. Discrepancies were resolved by consensus or consultation with a third reviewer when necessary.

Data extraction encompassed study characteristics, patient demographics, interventions, primary outcomes, and pertinent findings related to the efficacy, safety, and overall impact of androgen deprivation therapy in conjunction with brachytherapy or SBRT. A narrative synthesis was employed to summarize and interpret the collective evidence gleaned from the selected studies.

Results

Stereotactic body radiotherapy and androgen deprivation

Available evidence

Observational evidence and Phase I/II trials. The utilization of ADT in the context of high-risk prostate cancer remains highly variable across published studies that investigate the efficacy of Stereotactic Body Radiotherapy (SBRT), both with and without elective pelvic irradiation. This significant heterogeneity among the studies hinders the formulation of evidence-based recommendations. It is noteworthy that there is a notable absence of phase III Randomized Controlled Trials (RCTs) in the literature, which have specifically examined the role of SBRT in the management of intermediate and high-risk prostate cancer.

When examining published studies that investigate the role of SBRT combined with elective nodal irradiation in high-risk prostate cancer cases, the duration of ADT exhibits considerable variation. Notably, in the FASTR trial [11], ADT is administered for a duration of 1 year, while in the SATURN trial [12], it spans from 12 to 18 months. In the Mumbai cohort [13], patients without lymph node involvement receive a 2-year ADT regimen, while those with positive lymph nodes are recommended an indefinite course.

The variability in research studies that focus specifically on prostate SBRT, especially in the context of intermediate and high-risk patients, is even more pronounced. These studies frequently employ shorter durations of ADT. In a comprehensive analysis pooling data from a US multi-institutional phase II series, comprising 30 % of intermediate-risk patients and 11 % of high-risk patients, neoadjuvant and concurrent ADT were administered to 15 % and 28 % of patients, respectively, with a median ADT duration of 4 months [14].

In contrast, in accordance with contemporary standards, a phase II clinical trial conducted by Zilli T et al. adopted a uniform 6-month ADT regimen (including 2 months of neoadjuvant ADT) for all patients presenting with two or more of the following tumor characteristics: $\geq$T2c, Gleason score 4 + 3, PSA levels exceeding 10 ng/mL, perineural invasion, and/or more than one-third of positive biopsy cores [15].

Despite the absence of robust empirical support for minimizing the utilization of ADT in conjunction with SBRT for intermediate and high-risk prostate cancer, clinical observational studies demonstrate that this pattern is reflected in routine clinical practice. The prevalence of ADT administration increases progressively in accordance with the risk group of patients undergoing SBRT (low-risk, 4.1 %; favorable intermediate-risk, 10.7 %; unfavorable intermediate-risk, 20.3 %; and high-risk, 33.2 %; $p = 0.04$). Nevertheless, these rates remain lower than those observed in patients treated with conventional normofractionated radiation regimens (low-risk, 9.5 %; favorable intermediate-risk, 24.7 %; unfavorable intermediate-risk, 48.2 %; and high-risk, 76.6 %; $p = 0.02$) [16]. These findings have been corroborated by an extensive analysis conducted by Royce et al. utilizing the USA National Database. Their study included 7,559 patients who underwent SBRT and 133,825 patients who were treated with conventional normofractionated and moderate hypofractionated radiotherapy regimens. Their analysis revealed a statistically significant decrease in the utilization of ADT in patients treated with SBRT compared to those receiving other forms of radiotherapy across all risk categories ($p < 0.001$). In this report, the majority of patients receiving SBRT, specifically those classified as having unfavorable intermediate-risk (80.8 %) and high-risk (58.5 %), did not receive concurrent ADT [17]. Also, additional analyses conducted using the same database did not reveal any disparities in the estimated six-year overall survival when comparing normofractionated or moderate hypofractionated radiotherapy regimens with concurrent ADT to SBRT in conjunction with ADT, irrespective of the patients' risk group [18]. Nevertheless, it is essential to emphasize that this evidence is neither derived from randomized trials nor prospective studies and is, therefore, susceptible to potential biases.

Recently, the outcomes of a pooled analysis were presented by van Dams et al., drawing data from seven phase II prospective trials. This analysis focused on 344 patients with high-risk prostate cancer who were subjected to SBRT. Interestingly, 72 % of these patients were administered ADT with a median duration of 9 months, and 19 % received elective nodal radiation therapy. With a median follow-up period of 49.5 months, it was observed that patients who received ADT exhibited a significantly improved biochemical recurrence-free survival (BRFS) ($p = 0.009$). However, no significant differences were detected in distant metastasis-free survival (DMFS) ($p = 0.097$) [19]. The estimated 4-year BRFS at 81.7 % is comparable to the findings reported in the ASCENDE-RT study. In the ASCENDE-RT study, high-risk patients achieved five-year BRFS rates of 85.5 % when a BT boost was administered or 83.6 % when receiving dose-escalated conventionally fractionated radiation therapy alone, combined with 12 months of ADT [20]. It is important to consider that with longer follow-up, the disparities in BRFS have continued to widen, ultimately reaching differences of nearly 20 % in favor of the group that received the BT boost [21].

Randomized evidence and meta-analysis. As of now, all Phase III trials that have compared UHRT to normo-fractionated EBRT, such as the HYPO-RT-PC trial and the PACE-B trial, have not permitted the concurrent administration of ADT with SBRT. Notably, some of these participants may have met the current standards for concurrent ADT, as 11

% of patients in the HYPO-RT-PC trial were diagnosed with high-risk disease [22,23].

However, Jackson et al. conducted a meta-analysis encompassing 6,116 patients who received ultra-hypofractionated RT. Within the analyzed studies, 92 %, 78 %, and 38 % of patients had low-, intermediate-, and high-risk prostate cancer, respectively. While ADT was concurrently employed in 15 % of these patients, there was insufficient available data for quantitative assessment of ADT's impact, ADT duration was inconsistently specified, pelvic irradiation was infrequently utilized, and its potential benefits in the context of prostate SBRT remain uncertain [24].

Ongoing trials

Several ongoing clinical trials, such as the PACE-C trial and the SPA trial, which compare hypofractionated radiotherapy plus ADT versus SBRT plus ADT in intermediate- and high-risk patients, may shed further light on this matter (see Table 1).

Due to the lack of randomized trials investigating the potential benefits and optimal duration of ADT in combination with ultra-hypofractionated RT and the apparent reduction of use of ADT with UHRT, there are currently no evidence-based recommendations available. In fact, as opposed to what happens in normofractionated or moderate hypofractionated radiotherapy regimen, we cannot establish the true role of ADT, the optimal duration of its use or the most appropriate timing of the administration of this systemic treatment in patients undergoing SBRT on the primary tumor [17,19,25]. For this reason, patients who are being considered for ultra-hypofractionated regimens should be enrolled in relevant clinical trials that assess the potential benefits of combining additional ADT with ultra-hypofractionated EBRT.

Contemporary clinical practice reveals a tendency to less commonly use ADT in combination with SBRT, despite the absence of robust high-quality evidence to support this practice. One potential rationale for the omission or reduction of ADT may stem from patient or physician preferences influenced by concerns regarding its adverse effects [26]. However, the omission of ADT may result in inferior oncologic outcomes, and randomized trials are needed to establish the safety of omitting ADT with SBRT for higher risk prostate cancer.

Brachytherapy

Uncertainties persist regarding the clinical advantages of incorporating ADT into dose-escalated EBRT. Current practice patterns for managing intermediate-risk and high-risk prostate cancer patients are a subject of controversy. There has been a suggestion that ADT use could be minimized, or the duration shortened when a BT boost is employed [10]. Indeed, this idea appears to influence clinical practice, as observed in the study by Mohiuddin JJ in 2019 [27].

Numerous randomized trials have demonstrated that the incorporation of a BT boost into EBRT reduces the likelihood of local recurrence and enhances biochemical control. Nevertheless, it has not been shown to significantly reduce the incidence of metastatic disease or improve overall survival [7].

In patients with unfavorable intermediate-, high-, or very-high-risk prostate cancer who are undergoing curative treatment, the option of incorporating a BT boost, whether low-dose rate (LDR) or high-dose rate (HDR), alongside EBRT and ADT is considered [28].

Available evidence

Observational evidence. The outcome of trimodality treatment is excellent, with 9-year progression-free-survival and DFS reaching 87 % and 91 %, respectively [29]. However, it remains unclear whether the ADT component contributes to the outcome improvement. D'Amico and colleagues studied a cohort of 1342 patients with PSA over 20 ng/mL and clinical T3/T4 and/or Gleason score 8 to 10 disease. The addition of either EBRT or ADT to BT did not confer an advantage over BT alone. However, the use of all three modalities reduced prostate cancer-specific mortality compared to BT alone (adjusted HR, 0.32; 95 % CI, 0.14–0.73) [30].

On the other hand, retrospective data suggest less benefit from the addition of ADT in the setting of dose-escalated definitive radiation for prostate cancer, especially when a combination of EBRT and BT approaches are used. Keyes et al. performed a systematic literature review studying 260 men with unfavorable IR prostate cancer treated with low-dose-rate BT, with or without 6 months of ADT without EBRT, 53 % did not receive ADT. They observed that bNED (Phoenix definition) rates with and without ADT at 5 years were 86 % and 85 % (p: 0.52), respectively, with no differences in death from prostate cancer or in overall survival [10]. Apparently, this idea influences clinical practice and a retrospective analysis of the US National Cancer Database found that patients with unfavorable intermediate- and high-risk prostate cancer were significantly less likely to receive ADT if they underwent dose escalation with a combination of EBRT and BT (OR 0.67, p 0.0001)

Table 1
Selected ongoing clinicals trials testing SBRT and ADT in localized prostate cancer. An advanced search of ClinicalTrials.gov was performed in July 2023 for "SBRT and ADT in prostate cancer" (retrieved 101 records). These were reviewed and selected based on the design of the study to analyse the role of ADT + SBRT in localized prostate cancer.

TRIAL (NCT number)	STUDY TYPE	n	RISK GROUPS	TREATMENT PROTOCOL	ADT PLANNED	PRIMARY OUTCOME	RECRUITMENT STATUS
SPA TRIAL (NCT05019846)	Phase III	310	Intermediate unfavorable risk High risk	5 × 7,25 Gy	6 months LhRH analogue	5-year Biochemical disease free survival	Recruiting
PACE TRIAL (NCT01584258)	Phase III	1182	Intermediate risk High risk	5 × 7,25 Gy	6–12 months LhRH analogue	Biochemical disease free survival	Recruiting
NCT03056638	Phase III	120	Intermediate risk	5 × 8 Gy	6 monthsGnRH antagonist	2-year biopsy positivity rate	Active, not recruiting
NCT01985828	Phase II	72	Intermediate risk High risk	5 × 7,27 Gy 45–50,4Gy IMRT + 3 × 7 Gy	Intermediate risk 4–6 months High risk 6–36 months LhRH analogue	5- year Biochemical disease free survival	Recruiting
PBS TRIAL (NCT03380806)	Phase II	100	High risk	45 Gy IMRT + 30–35 Gy 45 Gy IMRT + 3 × 6,5–7 Gy	36 months LhRH analogue	6- months Quality of Life	Recruiting
NCT02296229	Phase II	220	High risk	5 × 7,25–8 Gy	Up to 9 months LhRH analogue	3- year Biochemical disease free survival	Active, not recruiting

Abbreviations: ADT; androgen deprivation therapy, GnRH; Gonadotropin-releasing hormone, LhRH; luteinizing hormone releasing hormone, RT; radiotherapy.

suggesting a potential underutilization of ADT in patients at higher risk of advanced disease [27].

Randomized evidence. To date, 3 randomized clinical trials have shown improved biochemical control with a BT boost over EBRT alone in patients with IR and HR disease but with higher toxicity. The use of ADT is inhomogeneous in these trials.

In the trial lead by Sathya JR. et al, 104 males with clinical T2 or T3 prostate cancer were randomly assigned to EBRT alone (66 Gy in 2 Gy fractions) or EBRT (40 Gy) preceded by a single, transperineal, temporary implantation of iridium-192 BT (35 Gy) given over 48 h. At a median follow-up of eight years, the rate of biochemical or clinical failure was significantly lower in the BT plus EBRT group (29 versus 61 %). The improvement in biochemical control was maintained at a median follow-up of 14 years (hazard ratio [HR] 0.53, 95 % CI 0.31–0.88). However, there was no statistically significant difference in overall survival. It should also be noted that the EBRT regimen of conventionally fractionated 66 Gy in 33 fractions is considered suboptimal. No ADT was prescribed in this trial [31].

In the Hoskin's trial, 218 patients (44 % intermediate and 54 % high-risk in the BT arm) were randomly assigned to EBRT alone (55 Gy in 20 fractions over four weeks) or EBRT (35.75 Gy in 13 fractions over 2.5 weeks) plus HDR BT (17 Gy divided into two fractions over 24 h). Neoadjuvant ADT was administered to 76 % of patients. The intention was to administer ADT for 6 months in low/intermediate risk, and up to 3-years in high-risk patients. Long term results with follow-up exceeding 12 years proved that relapse free survival was significantly longer with the combined treatment and incidence of severe late urinary and bowel morbidity was similar regardless of assigned treatment, but there was no improvement in overall survival [32].

The randomized ASCENDE-RT trial compared two methods of dose escalation in 398 patients with intermediate- or high-risk prostate cancer: dose-escalated EBRT boost to 78 Gy or LDR BT boost [20]. All patients were initially treated with 12 months of ADT and pelvic EBRT to 46 Gy. An intention-to-treat analysis found that the primary endpoint of biochemical PFS was 89 % versus 84 % at 5 years; 86 % versus 75 % at 7 years; and 83 % versus 62 % at 9 years for the LDR versus EBRT boost arms (log-rank $P < 0.001$) [33].

There are 5 randomized clinical trials (RCT), completed or ongoing, addressing the role of ADT in combination with PB in IR and HR patients (Table 2). So far, only two completed RCT at least indirectly addresses the role of ADT in BT [34,35].

In the Australian multicentre TROG 03.04 RADAR 2 × 2 factorial RCT 1071 men with locally advanced PC were randomized to receive ADT for 6 or 18 months with dose escalated EBRT (66 Gy, 70 Gy, 74 Gy or 46 Gy + HDR 19.5 Gy in three fractions) and randomized between 0 or 18 months of zoledronic acid. Initially, the primary end point was BRFS and subsequently changed to prostate cancer specific mortality (PCSM). With a median follow-up of 7.4 years, there was no significant difference in PCSM or OS between arms. Subsequent publication showed the cumulative and composite estimates of BRFS stratified by duration of ADT (6 vs. 18 months). Longer ADT had a positive effect on the PSA and local control outcome on all EBRT dose levels with greater benefit in lower doses, but no effect was seen in patients treated with HDR boost (absolute difference 3 %). This data suggests minimal if any benefit to longer ADT with the use of prostate BT, however it does not answer the question of whether ADT is needed with prostate BT at all [34].

Recently RTOG 0815 phase III prospective randomized study has been published [35]. A total of 1,492 patients with stage T2b-T2c, Gleason score 7, PSA > 10 and ≤20 ng/mL were randomized to dose escalated RT alone (arm 1) or dose escalated RT + ADT (arm 2). ADT consisted in 6 months of luteinizing hormone–releasing hormone agonist/antagonist therapy plus antiandrogen whereas RT modalities were EBRT alone to 79.2 Gy or EBRT (45 Gy) with a BT boost. The primary end point was overall survival (OS). Secondary end points included PCSM, non-PCSM, distant metastases (DMs), PSA failure, and rates of salvage therapy. With a median follow-up of 6.3 years, 5-y OS estimates were 90 % versus 91 %, respectively (hazard ratio [HR], 0.85; 95 % CI, 0.65 to 1.11]; p 0.22). ADT exhibited a modest impact on reducing PSA failure ($p < 0.001$). However, the observed benefit for distant metastasis ($p < 0.001$), prostate cancer-specific mortality ($p = 0.007$) and salvage therapy use (p 0.025), although significant, was modest. Other-cause deaths were not significantly different (p 0.56). Unfortunately, patients treated with BT were significantly underrepresented in the clinical trial, as only 12 % of the patients received this treatment. Therefore, definitive conclusions regarding the impact of BT on the duration of hormonal treatment in localized prostate cancer cannot be drawn.

Table 2
Selected phase III clinicals trials testing BT and ADT in localized prostate cancer.

RCT	STUDY TYPE	n	RISK GROUPS	TREATMENT PROTOCOL	ADT	PRIMARY OUTCOME	STATUS	OUTCOME
ASCENDE-RT [38]	Phase III, 2 arm	398	IR or HR	12 m ADT + 46 Gy WPRT then:→LDR boost (115 Gy I-125) vs EBRT boost (78 Gy)	12 m	bPFS	Closed	No difference in OS, CSS, or DM. BPFS improved. 10-yr OS ~ 75 %, not different. Worse toxicity with LDR
TROG 03.04_RADAR [39]	2 × 2 factorial	1071	IR or HR	Dose escalated EBRT (66 Gy, 70 Gy, 74 Gy or 46 Gy + HDR 19.5 Gy in three fractions). 0–18 m of Zoledronic Acid	6 or 18 m	bPFS/PCSM	Closed	No significant difference in PCSM or OS between the arms
RTOG 08–15 [40]	Phase III	1538	IR Exclusions: all three risk factors or ≥50 % cores positive"	79.2 Gy vs. 79 Gy + 6 m ADT. 45 Gy + brachytherapy boost also allowed (12 %)	6 m	OS	Closed	Short term ADT added to dose escalated radiation improves PCSM and DM, but not OS.
SHIP 0804 [41]	Phase III	420	IR	Brachytherapy + Neoadjuvant ADT 3 m, then 0 vs 9 m ADT	0 vs 9 m	10 y bPFS	Ongoing	
SHIP 36B [42]	Phase III	340	HR	EBRT + Brachytherapy + ADT 6 m, then randomized 0 vs 24 m ADT	0 vs 24 m	bPFS	Closed	
RTOG 0924	Phase III	2580	Unfavourable IR or favourable HR	IMRT, or IMRT + HDR or LDR boost and randomized into IMRT to prostate or pelvis	Stratified 6 vs 32 m	OS	Ongoing	

Abbreviations: ADT; androgen deprivation therapy, LDR; low-dose rate, HDR; high-dose rate, EBRT; external beam radiotherapy, IMRT; intensity-modulated radiation therapy, IR; intermediate risk, HR; high risk, bPFS; biochemical progression-free survival, PCSM; prostate cancer specific mortality, OS; overall survival, DM; distant metastasis, CSS; cancer specific mortality.

In the context of toxicity, patients receiving RT plus ADT exhibited higher incidences of acute AEs in endocrine symptoms, sexual/reproductive function, constitutional symptoms, gastrointestinal toxicity, renal/genitourinary toxicities, and metabolic/laboratory findings, with all values demonstrating statistical significance ($p < 0.001$). The rates of grade ≥ 3 acute AEs were notably elevated in the group receiving combined treatment (12 %) compared to those treated with dose-escalated RT alone (2 %), indicating a substantial difference in toxicity burden between the two groups (odds ratio: 5.67; 95 % CI: 3.30 to 10.28; $p < 0.001$). Additionally, the incidence of acute grade ≥ 3 general cardiac events appeared slightly higher in patients on arm 2 (RT plus ADT) compared to arm 1 (RT alone) but did not reach statistical significance (Fisher's exact $p = 0.068$).

Meta-analysis. Since none of the published RCTs was designed to establish the ideal use of ADT in combination with prostate BT, a patient level meta-analysis of six trials examining ADT use in conjunction with RT for high- or intermediate-risk prostate cancer was recently performed to elucidate specific ADT duration thresholds associated with improved outcomes when BT boost is in place [8]. Across 5136 patients, (median follow-up 12.9 years), the addition of ADT to RT significantly prolonged metastasis-free survival (HR 0.83, 95 % CI 0.77–0.89), corresponding to a 10-year absolute benefit of 8.6 percent (95 % CI 5.8–11.4). Use of ADT also improved overall survival (HR 0.85, 95 % CI 0.80–0.92), corresponding to an absolute 10-year benefit of 7.7 percent (95 % CI 4.9–10.4). The benefits were seen regardless of risk group, patient age, or radiotherapy dose.

Kishan A., et al published data about the interplay between duration of ADT and EBRT with or without a BT boost in HR prostate cancer based on a patient-level data analysis of 3 cohorts [9]. The study analyzed 1827 patients treated with EBRT and 1108 patients treated with EBRT + BT from the retrospective cohort; 181 treated with EBRT and 203 with EBRT + BT from RADAR study; and 91 patients treated with EBRT from DART trial. The primary outcome was DMFS; secondary outcome was overall survival (OS). The study found a significant interaction between the treatment type (EBRT vs EBRT + BT) and ADT duration (binned to <6, 6 to >18 and ≥ 18 months). Natural cubic spline analysis identified minimum duration thresholds of 26.3 months (95 % CI, 25.4–36.0 months) for EBRT and 12 months (95 % CI, 4.9–36.0 months) for EBRT + BT for optimal effect on DMFS. These cohort study findings suggest that the optimal minimum ADT duration for treatment with high-dose EBRT alone is more than 18 months; and for EBRT + BT, it is 18 months or possibly less.

The sequencing of ADT with radiotherapy for non-metastaic prostate cancer has been studied in an individual patient data from 12 randomized trials that included patients receiving neoadjuvant/concurrent or concurrent/adjuvant short-term ADT (4–6 months) with RT for localized disease. Data were obtained from the Meta-Analysis of Randomized trials in Cancer of the Prostate consortium (MARCAP). Overall, 7,409 patients were included with a median follow-up of 10.2 years. A significant interaction between ADT sequencing and RT field size was observed for all end points except OS. Authors concluded that concurrent/adjuvant ADT should be the standard of care where short-term ADT is indicated in combination with prostate radiotherapy [25].

Ongoing trials

Finally, there are several ongoing trials that might help elucidate the role and optimal duration of ADT in combination with prostate BT boost in different prostate cancer groups. 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. Primary endpoint is 10y bPFS. Secondary endpoints include OS, clinical PFS (local, distant failures) DSS, salvage treatments, IPSS and QOL [36].

SHIP 36B (ClinicalTrials.gov: UMIN000003992) is a RTC including 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 was closed for accrual in 2012. Primary endpoint is bPFS, and secondary endpoints are OS, PFS, CSS, salvage treatments and adverse effects and results are expected soon [37].

RTOG 0924 (NCT01368588) is an ongoing Phase III Randomized Trial of ADT and high dose radiotherapy with or without whole-pelvic radiotherapy in unfavourable IR or favourable HR prostate cancer patients. The groups have been stratified according to ADT duration (6 or 32 months) and RT modality (IMRT vs IMRT + HDR or LDR boost) and randomized into IMRT to prostate only or prostate + pelvis. Target accrual is 2580 patients, and the primary endpoint is OS while bPFS, DM, CSS and HRQL are some of the secondary endpoints. First results will be available in 2024.

The promising data discussed above provide a compelling basis for the evaluation of prostate and pelvic SBRT vs BT boost in a randomized clinical trial. The upcoming phase III ASCENDE-SBRT trial (CCTG PR24), is set to address this need. This multicenter randomized controlled trial (RCT) will enroll 710 patients with unfavorable intermediate-risk (UIR) or high-risk prostate cancer (HRPC) and randomize them into two arms: one receiving elective nodal irradiation (ENI) plus BT, and the other receiving a SBRT boost. The BT arm will undergo conventional fractionated radiation therapy (CFRT) with a dose of 46 Gy delivered in 23 fractions, following a high-dose rate (HDR) of 15 Gy or a low-dose rate (LDR) of 115 Gy using I-125 seeds as a BT boost. The SBRT arm will receive 25 Gy to the pelvis and 40 Gy to the prostate in 5 fractions. Patients in both arms will also receive ADT, with a duration of 4–6 months for UIR patients and 18–36 months for HR patients. The hypothesis of the ASCENDE-SBRT trial is that a prostate boost with SBRT, performed concurrently with ENI, will yield outcomes comparable to a BT boost followed by ENI.

The generalizability to contemporary favorable intermediate-risk disease and unfavorable intermediate-risk disease is unclear. Emerging data suggests that underlying transcriptomic heterogeneity may drive outcomes, and such data were not available for incorporation in this analysis. Future trials, such NRG GU009 and GU010, will test these hypotheses [38,39]. Additionally, imaging modalities such as multiparametric MRI, and PET imaging with prostate-specific tracers such as prostate-specific membrane antigen (PSMA) hold potential to more optimally select patients with IR likely to benefit from adjuvant STAD [40].

ADT added to dose-escalated RT did not improve rates of OS for men with IR prostate cancer compared with patients treated with dose-escalated RT alone. Reductions in PSA failure and DMs should be weighed against the toxicity added by ADT and its overall impact on patients' quality of life. In high risk patients, the data form meta analyses suggest that despite escalating RT dose with BT boost, ADT is needed in a long term scheme.

Discussion

Firstly, the existing body of evidence is heterogeneous and limited in terms of both its design and sample size. Despite several studies conducted, including clinical trials, retrospective analyses, and systematic reviews, many of them feature small or heterogeneous samples, making it challenging to generalize the findings. This has led to a lack of consensus regarding definitive recommendations concerning the duration, sequence, and necessity of ADT in combination with modern radiation therapies such as SBRT and BT.

Studies exploring the combination of ADT with SBRT present a diverse landscape. Some studies have demonstrated significant improvements in Biochemical Recurrence-Free Survival (BRFS) with the use of ADT alongside SBRT, as evidenced in van Dams et al.'s analysis

where ADT administration was associated with enhanced BRFS in high-risk prostate cancer patients. However, no significant differences were observed in Distant Metastasis-Free Survival (DMFS) [19].

While these findings suggest some potential benefit from concurrent ADT use with SBRT, it's crucial to note that most of this data originates from retrospective analyses or observational studies, raising concerns about possible biases and limitations in result interpretation.

Furthermore, evidence from randomized clinical trials regarding the role of ADT in combination with BT also presents challenges. Results from trials like ASCENDE-RT have shown improvements in BRFS with the use of BT as a boost to external radiotherapy, but without significant differences in overall survival [21,31,32].

Despite these conclusions, the optimal duration of ADT in the context of BT remains unclear. Some studies suggest that adding ADT to escalated doses of radiotherapy does not enhance overall survival rates in intermediate-risk prostate cancer patients [10,27]. This raises questions about the true utility and appropriate duration of ADT in this specific scenario.

Another critical aspect is the lack of direct and well-designed studies exploring the utility and optimal duration of ADT in contexts of extreme radiation therapies like SBRT and BT, particularly in patients with intermediate to high-risk prostate cancer. This leaves physicians and patients in a therapeutic dilemma without clear evidence-based guidance to make informed decisions regarding the use of ADT in combination with these more modern radiation therapies.

Of note, despite the appeal of integrating ADT with SBRT or BT, caution is advised due to their potential limited efficacy in significantly improving disease outcomes. Recent studies, notably exemplified by RTOG 0815 [35], emphasize the need for cautious approach. The marginal benefits observed in disease control metrics alongside the notable escalation of treatment-related toxicities underscore the necessity for judicious patient selection and careful consideration when contemplating the addition of ADT. For patients with an expected prolonged survival without succumbing to aggressive prostate cancer, the balance between the modest benefits and increased side effects becomes pivotal in treatment decision-making.

Scientific advancements increasingly advocate for the authorization of second-generation anti-androgens in patients with hormone-sensitive prostate cancer, a realm where drugs like Abiraterone, Apalutamide, and Enzalutamide have showcased substantial benefits in disease control and survival [41–46]. The current focus of our discussion in this article lies in exploring the use of ADT alongside SBRT or BT. However, it's noteworthy that the scientific landscape is dynamically evolving. The forthcoming years are anticipated to witness a significant shift due to the emergence of new studies investigating the utilization of novel second-generation anti-androgens in localized prostate cancer and its combination with local radiation therapies.

While existing studies provide some understanding of ADT effectiveness in combination with SBRT and BT, the heterogeneity of the data and the absence of well-designed, large-scale clinical trials pose significant challenges in establishing definitive recommendations. There is an urgent need for further research with rigorous clinical trials to define the role and optimal duration of ADT in combination with modern radiation therapies, enabling better guidance in the management of intermediate and high-risk prostate cancer.

Conclusions

In conclusion, the utilization of ADT in combination with SBRT remains an area of ongoing debate and evolving practice. While in contemporary clinical practice ADT is less commonly used with SBRT, the existing evidence, although limited, suggests that its omission may lead to potentially inferior oncologic outcomes. Recommendations for using ADT in combination with SBRT should be based on individual patient characteristics, including risk profiles and comorbidities. The ongoing clinical trials, such as the PACE-C and SPA trials, should provide valuable insights into the optimal use and duration of ADT in SBRT settings, and the results are eagerly anticipated.

Until new evidence becomes available, the recommendation is to initiate ADT for patients with unfavorable intermediate-risk and high-risk prostate cancer undergoing SBRT. This recommendation is derived from extrapolating information obtained from evidence related to conventional fractionated or moderately hypofractionated radiotherapy, with a requirement to maintain hormonal treatment for a minimum of six months in unfavorable intermediate-risk patients and 24 months for high-risk disease.“

Similarly, the role of ADT in conjunction with BT boost remains a subject of debate. Existing data indicate the potential benefits of BT boost in improving biochemical control and local control in patients with intermediate and high-risk prostate cancer. However, the addition of ADT to BT remains a contentious issue, with clinical practice influenced by guidelines that recommend minimizing or shortening ADT duration. For patients undergoing BT, the decision to use ADT should consider individualized factors and the specific context of the treatment. The ongoing SHIP 0804 and SHIP 36B trials should provide further clarity on the role of ADT in BT settings and the ideal duration of its use. Until then, the recommendation in terms of ADT duration is to administer 6 months for patients with unfavorable intermediate-risk and at least 12 months for patients with high-risk characteristics.

Ultimately, the decision to incorporate ADT into these radiation therapy modalities should be tailored to the unique needs and characteristics of each patient, with a focus on achieving optimal oncologic outcomes while minimizing potential side effects.

CRediT authorship contribution statement

A. Gomez-Iturriaga: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Visualization, Supervision, Project administration. **D. Büchser:** Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Visualization. **F. Lopez-Campos:** Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Visualization. **X. Maldonado:** Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Visualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors disclose that they have received financial compensation for their involvement in the development and composition of this study by Casen Recordati. This financial support may include consulting fees, honoraria, or other forms of remuneration related to the research and writing process. The authors affirm that this potential conflict of interest has not influenced the objectivity or integrity of the study's findings and conclusions. Transparency is maintained to ensure readers can critically assess the content with this disclosure in mind.

References

[1] Baude J, Caubet M, Defer B, Teyssier CR, Lagneau E, Créhange G, et al. Combining androgen deprivation and radiation therapy in the treatment of localised prostate cancer: Summary of level 1 evidence and current gaps in knowledge. Clin Transl Radiat Oncol 2022;37:1–11.

[2] Zapatero A, Guerrero A, Maldonado X, Álvarez A, San-Segundo CG, Rodríguez MÁC, et al. High-dose radiotherapy and risk-adapted androgen deprivation in localised prostate cancer (DART 01/05): 10-year results of a phase 3 randomised, controlled trial. Lancet Oncol 2022;23(5):671–81.

[3] Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 2006;24(27):4448–56.

[4] Saigal CS, Gore JL, Krupski TL, Hanley J, Schonlau M, Litwin MS, et al. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. Cancer 2007;110(7):1493–500.

[5] D'Amico AV, Chen MH, Renshaw A, Loffredo M, Kantoff PW. Long-term follow-up of a randomized trial of radiation with or without androgen deprivation therapy for localized prostate cancer. JAMA 2015;314(12):1291–3.
[6] Draulans C, van der Heide UA, Haustermans K, Pos FJ, van der Voort van Zyp J, De Boer H, et al. Primary endpoint analysis of the multicentre phase II hypo-FLAME trial for intermediate and high risk prostate cancer. Radiother Oncol 2020;147:92–8.
[7] Gomez-Iturriaga A, Keyes M, Martin J, Spratt DE. Should brachytherapy be added to external beam radiotherapy for prostate cancer? Lancet Oncol 2022;23(1):23–5.
[8] Kishan AU, Sun Y, Hartman H, Pisansky TM, Bolla M, Neven A, et al. Androgen deprivation therapy use and duration with definitive radiotherapy for localised prostate cancer: an individual patient data meta-analysis. Lancet Oncol 2022;23(2):304–16.
[9] Kishan AU, Steigler A, Denham JW, Zapatero A, Guerrero A, Joseph D, et al. Interplay between duration of androgen deprivation therapy and external beam radiotherapy with or without a brachytherapy boost for optimal treatment of high-risk prostate cancer: A patient-level data analysis of 3 cohorts. JAMA Oncol 2022;8(3):e216871.
[10] Keyes M, Merrick G, Frank SJ, Grimm P, Zelefsky MJ. American Brachytherapy Society Task Group Report: Use of androgen deprivation therapy with prostate brachytherapy-A systematic literature review. Brachytherapy 2017;16(2):245–65.
[11] Callan L, Bauman G, Chen J, Lock M, Sexton T, D'Souza D, et al. A phase I/II trial of fairly brief androgen suppression and stereotactic radiation therapy for high-risk prostate cancer (FASTR-2): preliminary results and toxicity analysis. Adv Radiat Oncol 2019;4(4):668–73.
[12] Musunuru HB, D'Alimonte L, Davidson M, Ho L, Cheung P, Vesprini D, et al. Phase 1–2 study of stereotactic ablative radiotherapy including regional lymph node irradiation in patients with high-risk prostate cancer (SATURN): early toxicity and quality of Life. Int J Radiat Oncol Biol Phys 2018;102(5):1438–47.
[13] Murthy V, Mallick I, Gavarraju A, Sinha S, Krishnatry R, Telkhade T, et al. Study protocol of a randomised controlled trial of prostate radiotherapy in high-risk and node-positive disease comparing moderate and extreme hypofractionation (PRIME TRIAL). BMJ Open 2020;10(2):e034623.
[14] King CR, Freeman D, Kaplan I, Fuller D, Bolzicco G, Collins S, et al. Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. Radiother Oncol 2013;109(2):217–21.
[15] Zilli T, Jorcano S, Bral S, Rubio C, Bruynzeel AME, Oliveira A, et al. Once-a-week or every-other-day urethra-sparing prostate cancer stereotactic body radiotherapy, a randomized phase II trial: 18 months follow-up results. Cancer Med 2020;9(9):3097–106.
[16] Mahase SS, D'Angelo D, Kang J, Hu JC, Barbieri CE, Nagar H. Trends in the use of stereotactic body radiotherapy for treatment of prostate cancer in the United States. JAMA Netw Open 2020;3(2):e1920471.
[17] Royce TJ, Switchenko JM, Zhang C, Spratt DE, Chen RC, Jani AB, et al. Utilization of androgen deprivation therapy (ADT) and stereotactic body radiation therapy (SBRT) for localized prostate cancer (PC) in the United States (US). JCO 2020;38(6_suppl). 370–370.
[18] Patel SA, Switchenko JM, Fischer-Valuck B, Zhang C, Rose BS, Chen RC, et al. Stereotactic body radiotherapy versus conventional/moderate fractionated radiation therapy with androgen deprivation therapy for unfavorable risk prostate cancer. Radiat Oncol 2020;15(1):217.
[19] van Dams R, Jiang NY, Fuller DB, Loblaw A, Jiang T, Katz AJ, et al. Stereotactic body radiotherapy for high-risk localized carcinoma of the prostate (SHARP) Consortium: analysis of 344 prospectively treated patients. Int J Radiat Oncol Biol Phys 2021;110(3):731–7.
[20] Morris WJ, Tyldesley S, Rodda S, Halperin R, Pai H, McKenzie M, et al. Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): An analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys 2017;98(2):275–85.
[21] Oh J, Tyldesley S, Pai H, McKenzie M, Halperin R, Duncan G, et al. An updated analysis of the survival endpoints of ASCENDE-RT. Int J Radiat Oncol Biol Phys 2023 Apr 1;115(5):1061–70.
[22] Widmark A, Gunnlaugsson A, Beckman L, Thellenberg-Karlsson C, Hoyer M, Lagerlund M, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. Lancet 2019;394(10196):385–95.
[23] Tree AC, Ostler P, van der Voet H, Chu W, Loblaw A, Ford D, et al. Intensity-modulated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): 2-year toxicity results from an open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol 2022;23(10):1308–20.
[24] Jackson WC, Silva J, Hartman HE, Dess RT, Kishan AU, Beeler WH, et al. Stereotactic body radiation therapy for localized prostate cancer: A systematic review and meta-analysis of over 6,000 patients treated on prospective studies. Int J Radiat Oncol Biol Phys 2019;104(4):778–89.
[25] Ma TM, Sun Y, Malone S, Roach M, Dearnaley D, Pisansky TM, et al. Sequencing of androgen-deprivation therapy of short duration with radiotherapy for nonmetastatic prostate cancer (SANDSTORM): A pooled analysis of 12 randomized trials. J Clin Oncol 2023;41(4):881–92.
[26] Chen YW, Muralidhar V, Mahal BA, Nezolosky MD, Beard CJ, Choueiri TK, et al. Factors associated with the omission of androgen deprivation therapy in radiation-managed high-risk prostate cancer. Brachytherapy 2016;15(6):695–700.
[27] Mohiuddin JJ, Narayan V, Venigalla S, Vapiwala N. Variations in patterns of concurrent androgen deprivation therapy use based on dose escalation with external beam radiotherapy vs. brachytherapy boost for prostate cancer. Brachytherapy 2019;18(3):322–31.
[28] Fang FM, Wang YM, Wang CJ, Huang HY, Chiang PH. Comparison of the outcome and morbidity for localized or locally advanced prostate cancer treated by high-dose-rate brachytherapy plus external beam radiotherapy (EBRT) versus EBRT alone. Jpn J Clin Oncol 2008;38(7):474–9.
[29] Martínez-Monge R, Moreno M, Ciérvide R, Cambeiro M, Pérez-Gracia JL, Gil-Bazo I, et al. External-beam radiation therapy and high-dose rate brachytherapy combined with long-term androgen deprivation therapy in high and very high prostate cancer: preliminary data on clinical outcome. Int J Radiat Oncol Biol Phys 2012;82(3):e469–76.
[30] D'Amico AV, Moran BJ, Braccioforte MH, Dosoretz D, Salenius S, Katin M, et al. Risk of death from prostate cancer after brachytherapy alone or with radiation, androgen suppression therapy, or both in men with high-risk disease. J Clin Oncol 2009;27(24):3923–8.
[31] Sathya JR, Davis IR, Julian JA, Guo Q, Daya D, Dayes IS, et al. Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. J Clin Oncol 2005;23(6):1192–9.
[32] Hoskin PJ, Rojas AM, Ostler PJ, Bryant L, Lowe GJ. Randomised trial of external-beam radiotherapy alone or with high-dose-rate brachytherapy for prostate cancer: Mature 12-year results. Radiother Oncol 2020;2(154):214–9.
[33] Rodda S, Tyldesley S, Morris WJ, Keyes M, Halperin R, Pai H, et al. ASCENDE-RT: An analysis of treatment-related morbidity for a randomized trial comparing a low-dose-rate brachytherapy boost with a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys 2017;98(2):286–95.
[34] Denham JW, Joseph D, Lamb DS, Spry NA, Duchesne G, Matthews J, et al. Short-term androgen suppression and radiotherapy versus intermediate-term androgen suppression and radiotherapy, with or without zoledronic acid, in men with locally advanced prostate cancer (TROG 03.04 RADAR): 10-year results from a randomised, phase 3, factorial trial. Lancet Oncol 2019;20(2):267–81.
[35] Krauss DJ, Karrison T, Martinez AA, Morton G, Yan D, Bruner DW, et al. Dose-escalated radiotherapy alone or in combination with short-term androgen deprivation for intermediate-risk prostate cancer: results of a phase III multi-institutional trial. J Clin Oncol 2023;41(17):3203–16.
[36] Miki K, Kiba T, Sasaki H, Kido M, Aoki M, Takahashi H, et al. Transperineal prostate brachytherapy, using I-125 seed with or without adjuvant androgen deprivation, in patients with intermediate-risk prostate cancer: study protocol for a phase III, multicenter, randomized, controlled trial. BMC Cancer 2010;21(10):572.
[37] Konaka H, Egawa S, Saito S, Yorozu A, Takahashi H, Miyakoda K, et al. Tri-Modality therapy with I-125 brachytherapy, external beam radiation therapy, and short- or long-term hormone therapy for high-risk localized prostate cancer (TRIP): study protocol for a phase III, multicenter, randomized, controlled trial. BMC Cancer 2012;22(12):110.
[38] Spratt DE, Zhang J, Santiago-Jiménez M, Dess RT, Davis JW, Den RB, et al. Development and validation of a novel integrated clinical-genomic risk group classification for localized prostate cancer. J Clin Oncol 2018;36(6):581–90.
[39] Feng FY, Huang HC, Spratt DE, Zhao SG, Sandler HM, Simko JP, et al. Validation of a 22-gene genomic classifier in patients with recurrent prostate cancer: an ancillary study of the NRG/RTOG 9601 randomized clinical trial. JAMA Oncol 2021;7(4):544–52.
[40] Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet 2020;395(10231):1208–16.
[41] Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. Lancet Oncol 2019;20(5):686–700.
[42] Chi KN, Chowdhury S, Bjartell A, Chung BH, de Santana P, Gomes AJ, et al. Apalutamide in patients with metastatic castration-sensitive prostate cancer: final survival analysis of the randomized, double-blind, phase III TITAN study. J Clin Oncol 2021;39(20):2294–303.
[43] Sweeney CJ, Martin AJ, Stockler MR, Begbie S, Cheung L, Chi KN, et al. Testosterone suppression plus enzalutamide versus testosterone suppression plus standard antiandrogen therapy for metastatic hormone-sensitive prostate cancer (ENZAMET): an international, open-label, randomised, phase 3 trial. Lancet Oncol 2023;24(4):323–34.
[44] Attard G, Murphy L, Clarke NW, Cross W, Jones RJ, Parker CC, et al. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. Lancet 2022;399(10323):447–60.
[45] Freedland SJ, de Almeida LM, De Giorgi U, Gleave M, Gotto GT, Pieczonka CM, et al. Improved outcomes with enzalutamide in biochemically recurrent prostate cancer. N Engl J Med 2023;389(16):1453–65.
[46] Armstrong AJ, Azad AA, Iguchi T, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, et al. Improved survival with enzalutamide in patients with metastatic hormone-sensitive prostate cancer. J Clin Oncol 2022;40(15):1616–22.