Androgen Deprivation Therapy

Subjects: Urology & Nephrology
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Androgen deprivation therapy alone is commonly performed for metastatic prostate cancer but is generally not recommended for the treatment of high-risk localized or locally advanced prostate cancer.

prostate cancer androgen deprivation therapy

1. Introduction

Prostate cancer (PC) is the most common cancer in men and the leading cause of cancer-related deaths in developed countries [1][2]. Most PC deaths are caused by metastatic disease [3]. Approximately 10% of new PC cases are diagnosed with distant metastasis [4][5][6]. The development and dissemination of prostate-specific antigen (PSA) screening have contributed to early PC detection, which in turn has reduced PC-related mortality [7][8][9][10]. However, approximately 15% of newly diagnosed PCs are high-risk PCs [11]. While localized PC generally has a good prognosis, high-risk PC has a significantly worse prognosis than low- and intermediate-risk PC, with a 15-year PC-specific mortality rate of 22–38% [11][12][13]. Guidelines differ slightly in their definition of high-risk PC, including locally advanced PC (**Table 1**). In the D'Amico risk classification, the European Association of Urology (EAU) guidelines, and European Society for Medical Oncology (ESMO) guidelines, patients are classified as high-risk if they meet clinical stage T2c or a PSA level of ≥20 ng/mL or Gleason score of 8–10, while the National Comprehensive Cancer Network (NCCN) guidelines classify patients as high-risk at clinical stage T3 or higher [14][15][16][17]. The EAU guidelines classify locally advanced PC at clinical stage T3 or higher or clinical stage N1, and the NCCN guidelines classify very high-risk at clinical stage T3b or higher or primary Gleason pattern 5 or >4 cores with grade group 4 or 5 [15][16]. Briefly, patients with clinical stage T2c, a PSA level of ≥20 ng/mL, or a Gleason score of 8–10 are considered to have high-risk PC. Although each guideline differs slightly, radical prostatectomy (RP) + extended pelvic lymph node dissection (ePLND) or radiation therapy (RT) + long-term androgen deprivation therapy (ADT) is recommended for the treatment of high-risk or locally advanced PC, and ADT alone is currently indicated in a few cases [15][16][17]. However, ADT has been used aggressively for localized PC in Japan. According to data from 10,280 PC patients diagnosed in Japan in 2004, 41% of non-metastatic castration-sensitive prostate cancer (nmCSPC) patients received ADT as initial treatment [5].

Table 1. Definition of high-risk prostate cancer.

	Risk	Clinical Stage		Initial PSA		Gleason Score	References
D'Amico	High	≥T2c	or	>20	or	≥8	[14]

	Risk	Clinical Stage		Initial PSA		Gleason Score			References
et al.				ng/mL					
NCCN 2021	High	T3a	or	>20 ng/mL	or	Grade Group 4 or Grade Group 5			[15]
	Very high	T3b/T4	or		or	Primary Gleason pattern 5 or > 4 cores with Grade Group 4 or 5	or	2 or 3 high-risk features	
EAU 2020	High	T2c	or	>20 ng/mL	or	≥8			[16]
	Locally advanced	T3/T4 or N1	and	Any	and	Any			
ESMO 2020	High	≥T2c	or	>20 ng/mL	or	≥8			[17]

PSA = Prostate specific antigen; NCCN = National Comprehensive Cancer Network; EAU = European Association of Urology; ESMO = European Society for Medical Oncology.

2. ADT

2.1. History of ADT

After Huggins and Hodges reported the efficacy of castration therapy, ADT became the gold standard for advanced PC [18]. Surgical castration had been the only method of castration, but Schally and Guillemin elucidated the structure of GnRH, which led to the development of GnRH agonists, and medical castration became possible [19]. Studies have reported the efficacy and tolerability of GnRH agonists as a first-line treatment for advanced PC and concluded that the survival rate, disease progression, and time to treatment failure are comparable between GnRH agonist therapy and orchiectomy [20][21][22][23]. Surgical castration is a simple and cost-effective outpatient procedure, while the advantage of medical castration is the avoidance of surgery [20][21][22][23][24]. In recent years, the rate of surgical castration has been reported to be less than 9% [24]. Although castration reduces serum testosterone levels by approximately 90%, 20–40% of dihydrotestosterone (DHT) remains in human PC tissue [25][26][27]. As this residual androgen may cause inadequate treatment of PC or relapse, CAB therapy, which combines ADT with an antiandrogen drug, has been proposed [28][29][30]. Recently, GnRH antagonists are developed. GnRH agonists have been reported to result in a transient increase in testosterone levels that occurs early in the administration, which is called a testosterone surge that can cause urinary tract obstruction and spinal cord compression [31][32][33]. GnRH antagonists do not cause testosterone surges, and testosterone levels reach castration levels early, so they may be particularly useful in patients with symptomatic metastatic PC [34]. In

addition, ADT has made progress with the development of the new androgen receptor signaling-targeted agent (ARSTs), such as enzalutamide, abiraterone acetate, apalutamide, and darolutamide [35][36][37][38]. The effects of ADT are generally not permanent and eventually lead to castration-resistant PC (CRPC) [6]. The treatment for CRPC includes alternative ADT [39], ARST [35][36][37][38], and chemotherapy such as docetaxel [40][41] and cabazitaxel [42][43].

ADT is effective in improving patients' quality of life by reducing bone pain, pathological fractures, spinal cord compression, and ureteral obstruction, which are symptoms specific to advanced PC, such as bone metastases or local enlargement of PC [18][44][45]. However, ADT has various adverse effects, such as hot flashes [46][47][48][49][50], sexual dysfunction [46][49][50][51][52], breast enlargement [48][49][53][54], depression [49][55], dementia [56][57][58][59][60][61], osteoporosis [62][63][64][65][66], obesity [46][67], diabetes [68][69][70][71][72][73], and cardiovascular (CV) toxicity [68][74][75][76][77][78][79][80].

Dementia, osteoporosis, and CV toxicity are important side effects of ADT in older patients. Researchers summarize these AEs for older patients with PC in the next section.

2.2. ADT for High-Risk Localized and Locally Advanced PC

Various guidelines do not recommend ADT alone as an initial treatment for high-risk or locally advanced PC [15][16][17]. However, in clinical practice, some patients, especially older ones, are treated with ADT alone as the initial therapy. In the USA, the use of GnRH agonists has increased since the 1990s [81], and as of 2009, 22% of patients with localized PC aged >66 years were being treated with ADT alone [82]. In Japan, approximately 30% of patients with localized PC were treated with ADT alone [5]. As shown in **Table 2** and **Table 3**, many studies have reported on the efficacy of ADT alone for localized PC, but worldwide, there are more negative reports.

Table 2. Negative data of ADT for high-risk localized and locally advanced prostate cancer.

Study	Study Specification	Patient Characteristics	Size	Findings	References
Merglen et al. (2007)	retrospective cohort study	Patients with localized PC treated with either total prostatectomy, radiation therapy, watchful waiting, hormone therapy, or other treatment	844	Patients who received ADT alone already had an increased risk of PCSM at 5 years (HR 3.5, 95% CI 1.4–8.7)	[83]
Lee et al. (2018)	retrospective study	Patients diagnosed with localized PC who underwent ADT or treatment-free follow-up	340	In clinically unfavorable localized intermediate- and high-risk PC, initiation of ADT within 12 months of diagnosis was not associated with improved 5-year all-cause mortality or PCSM compared	[84]

Study	Study Specification	Patient Characteristics	Size	Findings	References
				with patients who received no conservative treatment	
Lu-Yao et al. (2008)	retrospective cohort study	Patients diagnosed with localized PC who underwent ADT or treatment-free follow-up	19,271	ADT is not associated with improved survival among the majority of elderly men with localized prostate cancer when compared with conservative management	[85]
Potosky et al. (2014)	retrospective cohort study	Newly diagnosed patients with localized PC	15,170	ADT was associated with neither a risk of all-cause mortality (HR 1.04, 95% CI 0.97–1.11) nor PCSM (HR 1.03, 95% CI 0.89–1.19).	[86]
Lu-Yao et al. (2014)	retrospective cohort study	Patients aged 66 years or older with localized PC who did not receive curative treatment	66,717	ADT is not associated with improved long-term overall or disease-specific survival for men with localized PC.	[87]
Sammon et al. (2015)	retrospective cohort study	Newly diagnosed patients with locally advanced or localized PC	46,376	There was an increased risk of all-cause mortality in the ADT group compared to the observation group (HR 1.37, 95% CI 1.20–1.56)	[82]

ADT = Androgen deprivation therapy; PC = Prostate cancer; PCSM = Prostate cancer specific mortality; HR = Hazard ratio; CI = Confidence interval.

Table 3. Positive data of ADT for high-risk localized and locally advanced prostate cancer.

Study	Study Specification	Patient Characteristics	Size	Findings	References
Labrie et al. (2002)	prospective study	Patients with newly diagnosed locally advanced or localized PC who have undergone CAB	57	In patients with stage T2–T3 cancer who continued CAB for more than 6.5 years and discontinued treatment there were only two cases of PSA elevation. Long-term continuous CAB was suggested to be a possibility for long-term control or cure of localized PC	[88]
Akaza et al. (2006)	prospective cohort study	Patients with newly diagnosed locally advanced or	151	In men with localized or locally advanced PC, primary ADT inhibited PC	[89]

Study	Study Specification	Patient Characteristics	Size	Findings	References
		localized PC who have undergone ADT		progression and resulted in a life expectancy similar to that of the normal population	
Kawakami et al. (2006)	retrospective cohort study	Newly diagnosed localized PC patients with or without ADT	7044	The use of ADT therapy appeared to control disease in the majority of patients who received it, at least for an intermediate period	[90]
Akaza et al. (2010)	retrospective cohort study	Patients with newly diagnosed locally advanced or localized PC who have undergone ADT	15,461	ADT resulted in a long-term survival rate comparable to the general population	[91]
Matsumoto et al. (2014)	retrospective cohort study	Patients with newly diagnosed locally PC at intermediate to high risk who have undergone ADT	410	When prostate cancer with no capsular invasion and a GS of less than 8 was treated with ADT, the expected survival rate was similar to that of the general population	[92]
Studer et al. (2014)	randomized controlled trial	PC patients without distant metastasis treated with immediate or delayed ADT	985	Deferred ADT was inferior to immediate ADT in terms of overall survival (HR 1.21; 95% CI 1.05–1.39)	[93]
Nguyen et al. (2011)	meta-analysis of randomized controlled trial	Patients diagnosed with PC	4141	ADT was associated with lower PCSM (443/2527 vs. 552/2278 events; RR, 0.69; 95% CI, 0.56–0.84; $p <$ 0.001) and lower all-cause mortality (1140/2527 vs. 1213/2278 events; RR, 0.86; 95% CI 0.80–0.93; $p < 0.001$)	[80]

ADT = Androgen deprivation therapy; PC = Prostate cancer; CAB = Combined androgen blockade; PSA = Prostate specific antigen; GS = Gleason score; HR = Hazard ratio; PCSM = Prostate cancer specific mortality; CI = Confidence interval; RR = Relative risk.

2.2.1. Negative Data of ADT for High-Risk Localized and Locally Advanced PC

A cohort study of 844 patients with localized PC who underwent total prostatectomy, RT, watchful waiting, ADT, or other treatment, with data collected from the Geneva Cancer Registry, revealed that patients who received

hormone therapy alone had increased PC-specific mortality at 5 years [83].

A retrospective cohort study of 340 patients diagnosed with localized PC and followed up with ADT or no treatment at a single center in Singapore found no improvement in 5-year all-cause mortality or PC-specific mortality (PCSM) when ADT was initiated within 12 months of diagnosis [84].

A retrospective cohort study comparing 7867 patients who were newly diagnosed with localized PC and received ADT with 11,404 patients who did not receive ADT was selected from the population-based Surveillance, Epidemiology, and End Results (SEER) program database and linked Medicare files. The study showed that ADT was not associated with improved survival for the majority of older men compared with conservative management [85].

A retrospective study of 15,170 patients with newly diagnosed clinically localized PC who were not receiving curative treatment was conducted using data from three integrated healthcare delivery systems within the HMO Cancer Research Network in the USA. The results showed that ADT was not associated with either overall or PCSM risk. However, ADT predominantly reduced the risk of all-cause mortality only in a subgroup of men at high-risk for cancer progression [86].

A retrospective cohort study of 66,717 patients aged ≥66 years with localized PC who did not receive curative treatment, from the National Cancer Institute's SEER program and Medicare data, found that primary ADT was not associated with improved long-term overall survival (OS) or disease-specific survival at 15 years [87].

In a retrospective cohort study of 46,376 patients newly diagnosed with locally advanced or localized PC from the National Cancer Institute's SEER program and Medicare data and not treated with curative intent, ADT was associated with decreased survival compared with observation management [82].

As shown above, many large cohort studies have rejected the efficacy of ADT for localized PC. However, some studies have shown the efficacy of ADT in localized PC.

2.2.2. Positive Data of ADT for High-Risk Localized and Locally Advanced PC

In a previous study, 57 patients with newly diagnosed locally advanced or localized PC who discontinued long-term CAB therapy were followed for at least 5 years. Among 20 patients with stage T2 to T3 cancer who discontinued continuous CAB therapy after 6.5 years, two cases of PSA elevations occurred, with a 90% non-failure rate. This study suggested that long-term and continuous CAB was associated with the possibility of long-term control or cure of localized PC [88].

In a prospective cohort study of 151 patients with newly diagnosed locally advanced or localized PC who underwent ADT from 104 sites in Japan, ADT reduced PC progression, resulting in a life expectancy similar to that of the normal population [89].

A retrospective study of data from The Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) in the USA compared 993 patients with newly diagnosed localized PC who received ADT with 6051 patients who did not receive ADT. The results revealed that ADT use controlled the disease in the majority of patients with PC at an intermediate period of 5 years [90].

In an analysis of the Japan Study Group of Prostate Cancer (J-CaP) surveillance study of 15,461 patients with locally advanced or localized PC in Japan, ADT resulted in long-term survival rates similar to that in the general population [91].

In a report of 410 patients with intermediate- to high-risk localized PC treated with ADT alone from five centers in Japan, the expected survival rate was similar to that of the general population in the absence of capsular invasion and with a Gleason score of ≥8 [92].

In the European Organization for Research and Treatment of Cancer (EORTC) trial 30891, a randomized, prospective study compared 492 patients with PC without distant metastases who received immediate ADT with 493 patients who received delayed ADT. The results indicated that the delayed ADT group had a significantly inferior OS rate to the immediate ADT group [93].

In a pooled analysis of a randomized trial of 4141 patients with unfavorable-risk PC, ADT use was associated with a decreased risk of PCSM and all-cause mortality [80].

As described above, most of the studies demonstrating the efficacy of ADT for localized PC were reported from Japan. However, there have been reports of racial differences in the efficacy of ADT for localized PC.

2.2.3. Differences in the Efficacy of ADT by Race

A retrospective study of 165 patients with PC who underwent ADT at The Queen's Medical Center in Honolulu compared 59 Caucasian men (CM) and 105 Japanese American men (JAM) [94]. Although no significant difference was found in the patient background, JAMs who received ADT had a better prognosis than CMs in terms of both overall and cause-specific survival (p = 0.001 and 0.036, respectively). The multivariate analysis also revealed that race was one of the significant prognostic factors (p = 0.03).

A retrospective study compared data from a total of 15,513 patients with PC who received ADT from the CaPSURE database in the USA and the J-CaP database in Japan [95]. Men who underwent ADT at J-CaP (n = 13,880) were older and had higher risk of disease than men who underwent ADT at CaPSURE (n = 1633) and had a higher rate of CAB (66.9% vs. 46.4%). The multivariate regression showed that the sub-hazard ratio for PCSM was 0.52 (95% confidence interval 0.40–0.68) for J-CaP versus CaPSURE, and the adjusted PCSM for men receiving ADT in Japan was less than half that of men in the USA.

Although further large-scale prospective studies are awaited, Asians, including Japanese, may be expected to benefit more from ADT than Caucasians.

2.2.4. Position of ADT in High-Risk Localized and Locally Advanced PC

The efficacy of RP and RT for localized PC has been recognized [96][97][98]. A randomized clinical trial (RCT) reported that improved survival with long-term ADT plus RT for patients with locally advanced PC has led to the recommendation of combined RT and ADT for high-risk cases [99][100]. RP was not recommended for patients with high-risk PC; however, recent reports have led to a reevaluation. In a meta-analysis including 118,830 patients and comparing the prognosis of RP and RT for localized PC, the prognosis was significantly better with RP, even in the high-risk group [101]. In a retrospective study of 42,765 patients with high-risk PC, the RP group had a significantly better prognosis than the RT plus ADT group [102]. Based on the above, RP plus ePLND or RT plus ADT is recommended for the treatment of high-risk or locally advanced PC [15][16][17]. However, RP is not recommended for patients with an expected life expectancy of ≤5 years, and ADT alone may be an option [15]. Older patients are more likely to have several comorbidities and should be aware of adverse events (AEs) from ADT.

2.3. Evidence of ARST for Castration-Sensitive Prostate Cancer

In recent years, evidence of ARST for castration-sensitive prostate cancer (CSPC) has been accumulating. In the ARCHES trial, in which 1150 patients with metastatic CSPC (mCSPC) were randomized 1:1 to enzalutamide plus ADT or placebo plus ADT, the enzalutamide plus ADT group had significantly longer radiographic progression-free survival than the placebo group (not reached vs. 19.0 months, $p < 0.001$, HR = 0.39) [103]. In the ENZAMET study, in which 1125 patients with mCSPC were randomized to enzalutamide plus ADT or non-steroidal antiandrogen plus ADT, both groups did not reach the median OS; however, the enzalutamide plus ADT group had a significantly longer OS [104]. In the LATITUDE trial, in which 1199 patients with mCSPC were randomized to abiraterone acetate plus prednisone ($n = 597$) or placebo ($n = 602$), the abiraterone acetate plus prednisone group had significantly prolonged OS compared with the placebo group (53.3 vs. 36.5 months, $p < 0.0001$, HR = 0.66) [105]. In the TITAN trial, in which 1052 patients with mCSPC were randomized 1:1 to apalutamide plus ADT or placebo plus ADT, the apalutamide plus ADT group had a significantly longer OS than the placebo group (not reached vs. 52.2 months, $p < 0.0001$, HR = 0.65) [106].

As mentioned above, ARST for mCSPC is effective. However, evidence on ARST for nmCSPC is limited. In the STAMPEDE trial, which randomized 1974 patients with high-risk nmCSPC to ARST plus ADT ($n = 986$) or ADT ($n = 988$), both groups did not reach the median OS; however, the ARST plus ADT group had a significantly longer OS ($p < 0.0001$, HR = 0. 60) [107]. Of the 1974 patients in this study, 774 (39%) had positive lymph nodes and 1684 (85%) received concomitant RT.

There are no reports of ARST being given for nmCSPC rather than in combination with other therapies. At present, ARST for nmCSPC is not recommended.

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