Review Article
Hormonal regulation of male reproduction and hypogonadism

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How Does Androgen Deprivation Therapy Affect Mental Health including Cognitive Dysfunction in Patients with Prostate Cancer?

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Androgen deprivation therapy (ADT) is used to block the release of androgen in prostate cancer to promote the regression of cancer cells, and hence, disease progression. Its indication has been widened from the metastatic setting to the localized setting in prostate cancer. Long-term ADT for suppressing androgen release leads to a rapid decrease in androgen, termed as andropause, resulting in several dose and duration dependent adverse effects, including cognitive dysfunction such as dementia. Many retrospective and prospective studies, as well as meta-analyses, have attempted to confirm the crucial relationship between ADT and cognitive dysfunction, but pro and contrary opinions regarding this issue are ongoing owing to the absence of randomized controlled trials. Additionally, several recent studies have suggested the negative effects of dose- and duration-dependent ADT on cognitive dysfunction, especially in 40–65-year-old patients with prostate cancer, who are currently active workers in the society. This review article discusses several studies examining the influence of ADT on mental health based on diverse significant perspectives, especially cognitive dysfunction.

Keywords: Androgens; Cognition; Dementia; Hormone therapy; Prostatic neoplasms

INTRODUCTION

Prostate cancer (PC) is an androgen-dependent cancer. The main therapeutic objective in PC is either to destroy the primary tumor at the prostate *via* surgery or radiation therapy, or to block androgen production to suppress the proliferation of cancer cells. The currently available androgen blocking agents are gonadotropin-releasing hormone (GnRH) agonists and anti-androgen agents, which are administered to an annual estimate of 25 million patients with PC as androgen deprivation therapy (ADT) [1]. Previously, ADT alone has been used in metastatic PC, until Bolla et al [2] revealed the benefits of ADT in locally advanced PC after radiation therapy. The median survival time and progression-free time were significantly prolonged by about 18–24 months, and cancer-related pain was also significantly delayed in locally advanced PC. As a consequence of this study, ADT has expanded its indication from the metastatic setting to the locally advanced PC resulting in increased numbers of PC patients who receive ADT. However, long-term ADT as well as an abrupt

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interruption of androgen release called andropause can cause adverse effects dependent upon dosage, duration, therapeutic regimen (continuous or intermittent application), and type of drugs [3]. Side effects include obesity, anemia, osteoporosis, gynecomastia, muscular atrophy, depression, and mood change, among others.

Guidelines for cancer treatment are constantly evolving. ADT has been a major component of therapeutic intervention in many PC regimens. The majority of patients have undergone ADT according to treatment guidelines at the time of their diagnosis. As the number of PC patients with long-term ADT increases with prolonged survival, the effects of ADT on mental health, such as cognitive dysfunction and dementia risks, have received more attention [4]. This review article summarizes articles dealing with the association of ADT with cognitive dysfunction, including dementia risks, in PC patients treated with ADT.

MAIN BODY

1. The role of androgen in the brain

ADT has been widely used to treat PC and was designed to block the production of the androgen testosterone that stimulates the proliferation of PC cells. The correlation between testosterone and cognitive function, including dementia, has been revealed *via* a metabolite of testosterone, named dihydortesterone (DHT). Its target receptor (DHT-related androgen receptor) is expressed in the hippocampus, parietal lobe, and pretemporal cortex of the brain, which are key areas of cognitive function [5]. Westlye et al [6] demonstrated the high expression of androgen receptors in the amygdala, brain stem, hypothalamus, and cerebral cortex, which regulate emotion and cognitive function. They also reported the effect of anabolic androgen in reducing the connection between the amygdala and the hippocampus.

Andropause starts in the 30s and 40s with an annual decrease of androgen levels of 0.4%–1.2% and is observed in 90% of men in their 80s [7]. The link between androgen and brain function has been known for a long time, since treating patients with hypogonadism, senescent andropause, or hypogonadism caused by low testosterone levels. The N-terminal transactivation domain of the androgen receptor has been shown to be responsible for the andropause-related symptoms in patients with low testosterone levels and hypogonadal states [8-10]. Supplementation of testosterone levels has been effective in treating andropause-related symptoms. Foland-Ross et al [11] showed that the testosterone analog oxandrolone restored the hippocampus volume to improve spatial memory in boys with Klinefelter Syndrome compared to the placebo group in their 2-year, double-blind, placebo-controlled trial.

2. The association of androgen with neurocognitive diseases and cognitive dysfunction

In the context of neurocognitive diseases such as dementia and Alzheimer's disease (AD), testosterone has been proposed as a protective drug in age-related cognitive decline because multiple observational studies have shown associations not only with andropause-related mood changes but also with cognitive dysfunction including dementia [7,8,12,13]. Two observational long-term follow-up studies [14,15] revealed a significant relationship between age-associated decreases in endogenous serum total testosterone levels and the subsequent development of AD or cognitive dysfunction. In another study, significant metabolic changes in cognitive-function brain areas were observed after the suppression of DHT, resulting in the production of metabolites in AD, cognitive dysfunction, and cerebral ischemic change [16]. Another study revealed a beneficial effect of testosterone supplementation on cognition in a placebo-controlled comparative study using 57 healthy men with normal testosterone levels [17]. However, unfortunately not all patients' testosterone levels and hypogonadal states were reversible with testosterone supplementation even after the cessation of ADT [18]. Some clinical studies also reported negative results of testosterone supplementation for the prevention of early cognitive dysfunction [19]. Thereby, the direct effects of ADT on mental health in patients with PC are challenging to determine because of the multiple factors influencing cognitive function, such as age, marital status, retirement status, number of comorbidities, previous history of depression, and the disease state of PC [18,20].

3. Imaging of androgen deprivation therapy effects on the brain

Many researchers aimed to demonstrate the effects of ADT on the brain using functional magnetic resonance imaging (fMRI) and positron-emission tomogra-

phy. A comparative study analyzing follow-up metabolic imaging changes showed significantly decreased metabolic changes in brain function between ADT and non-ADT PC groups [21], suggesting that ADT as the key element of brain dysfunction in PC patients. However, this study did not show a direct link between ADT and brain dysfunction. In another pilot study [22] the effects of ADT on neuronal activation were assessed for the first time. Five patients with ADT were compared with nine non-ADT subjects which revealed reduced, task-related BOLD-fMRI activation after 9 months of ADT. Another prospective study with nine biochemically recurred PC patients after 9 months of complete ADT with leuprolide and flutamide showed decreased glucose activity from positron-emission tomography scans in multiple brain areas such as the cerebellum, posterior cingulate, and medial thalamus bilaterally [23].

In other prospective comparative cohort studies between ADT and non-ADT groups in non-metastatic PC, fMRI at baseline and at 6 months revealed statistically significant associations between ADT and decreased medial prefrontal cortical activation during cognitive control, suggesting predating clinical manifestations of ADT-induced cognitive impairment from cerebral changes [24]. Another comparative study demonstrated that ADT resulted in structural changes with decreased gray matter volume in several cortical areas [24].

4. Retrospective comparative studies of androgen deprivation therapy in patients with prostate cancer with non-cancer controls studies

Several brain regions have been investigated for a link between changes in blood hormone levels and cognitive function and different types of dementia in ADT PC cohort studies. The representative British OPTIMA study (Oxford Project to Investigate Memory and Aging) showed that the androgen level is a significant independent AD risk factor after age-matching 112 AD patients with healthy controls [25,26]. Decreased androgen levels and its suppression-relating follicle-stimulating hormone level in the AD group were significantly different from those in healthy controls. Spatial resolution ability was improved in an androgen replacement-treated group compared to the placebo-treated control group in a randomized intervention study in healthy aged people [27].

5. Positive association of androgen deprivation therapy with neurodegenerative disease in large-numbered representative studies

Nead et al [28,29] evaluated 16,888 PC patients' medical records (14.2% ADT) for their AD risk during a median follow-up period of 2.7 years. A significant positive association was noted with a hazard ratio (HR) of 1.88 proportional to the ADT duration [28]. In a subgroup analysis of 9,272 patients (19.7% receiving ADT) with a median follow-up of 3.4 years, they also observed a significant correlation between ADT and the risk for all types of dementia with an HR of 2.17 [29].

A population-based SEER-Medicare study using a localized PC cohort from Gilbert et al [13] showed that ADT was associated with a 23% higher risk of depression. The cumulative ADT dose-dependent association of ADT with depression was significant even after adjustment for clinical and demographic variables [20].

Another recently published, retrospective population-based study [30] using 154,089 66-year-old or older patients from the SEER database showed that 2-year ADT exposure was associated with both dementia and AD. ADT-dose dependency was also proportional to the risk of dementia (HR=1.24) and AD (HR=1.19) at the first four doses of ADT, and the risk increased to HR=1.28 for AD and HR=1.24 for dementia for 5–8 doses.

Tully et al [31] used the TRICARE military database to show evidence of a significant correlation between ADT and dementia (HR=1.7) and depression (HR=2.07) in 9,117 40- to 64-year-old patients with localized PC either receiving ADT or not. The authors calculated an overall increased risk of 70% for the patients aged 40–64 years with ADT and 107% of depression compared to the non-ADT group, similar to earlier findings [20,32]. Their subgroup analysis evaluating the patients receiving more than 1 year ADT during the 8.7-year follow-up showed also a significant association between the duration of ADT and dementia risks [33].

6. Negative association of androgen deprivation therapy with neurodegenerative diseases in large-numbered representative studies

In contrast, other large-numbered retrospective stud-

ies reported that ADT does not show any significant correlation with dementia risk. The United Kingdom's Clinical Practice Research Datalink study including 30,903 PC patients showed no higher association in the ADT group with dementia compared to the non-ADT group during a mean follow-up of 4.3 years [32]. Another study [34] with 1.2 million (35% ADT users) Medicare beneficiaries with PC during 14 years reported that ADT did not increase the risk of AD with a subdistributional HR of 0.98, and patients had only a 1% risk of dementia (HR=1.01). The authors concluded that ADT does not increase the AD risk and no meaningful hazard for dementia among men aged 67 years or older could be established. Another study supported these findings using the FDA MedWatch adverse event data, showing no significant relationship between ADT and AD or cognitive dysfunction [35].

Serial Taiwanese population-based studies using the Taiwanese National Health Insurance Database showed [36,37] non-significant differences in the dementia risk between ADT and non-ADT groups with stratified dementia subtypes during a 5-year follow-up in one study (adjusted HR=1.21, 95% confidence interval [CI]=0.82–1.78). These different interpretations originate in different study designs including different baseline enrolled cohorts, ADT agents, duration of the ADT, different primary outcomes, and methodologies to test the association of ADT with cognitive dysfunction [38].

A European population-based study with 17,000 people did also not find an association between ADT and dementia risk [32]. Another study with 4,000 patients treated with medications for AD showed that both the ADT and non-ADT groups had not significantly different risks [36] (adjusted HR=1.76, 95% CI=0.55–5.62), supporting the studies listed above showing no association between ADT and dementia development.

7. Prospective androgen deprivation therapy studies

A first low-numbered prospective study reported that half of the patients with ADT experienced impaired verbal memory and executive function at 6 months of ADT among 82 men with advanced PC compared to a non-ADT group [39]. Two other prospective studies [40,41] also found a significant association of testosterone decline with impaired cognitive function. Almeida et al. revealed an improvement in global cognitive function and word list recall after termination of ADT in patients with 36-week ADT [42]. Another study [43] also demonstrated significantly impaired cognitive performance within 6–12 months of ADT in 58 non-metastatic or asymptomatic patients with PC compared to 84 non-ADT patients with prostatectomy and to 88 non-PC healthy men. Gunlusoy et al [44] found that only certain domains of cognitive function were affected by ADT in their 78 advanced PC patients with ADT after prostatectomy, such as language ability, short-term memory, mental flexibility, and inhibitory control [45]. Yang et al [46] also showed that a specific memory function was affected by ADT.

A representative large-numbered prospective study between 1994 and 2013 applied an exact interval and dosage with the same duration to both the ADT and non-ADT groups to test for differential cognitive functional change [47]. The authors showed an absolute increased dementia risk of 4.4% in the ADT group (3.5% in the non-ADT *vs.* 7.9% in the ADT group). Wu et al [48] showed in an intervention study with a computerized cognitive training program in patients with at least 3 months ADT with mild cognitive impairment that the reaction time was improved but visual and verbal memory were temporally impaired.

However, other prospective studies did not show a significant association between ADT and cognitive dysfunction. In 159 non-metastatic PC patients with ADT and 82 healthy controls, no consistent evidence of ADT affecting cognitive function was found at 12 months [48] and 36-month [49] of ADT [50]. Morote et al [51] showed in 308 patients that 6-month use of an luteinizing hormone releasing hormone (LHRH) agonist did not affect performance in five neuropsychological measures.

8. Intermittent androgen deprivation therapy and dementia risk

Various articles showed their results of adverse events from the use of ADT in PC patients and the incidence of adverse effects correlates sighnificantly with the duration of ADT use [2,3,12,13,47]. Nead et al [47] stratified the duration of ADT use to show significantly increasing risk of developing dementia after at least 12 months of ADT use (HR=2.36). Many efforts have been made to minimize the adverse effects of ADT depending upon duration of ADT use and the intermittent ADT method was introduced ins tead of continuous use of ADT to restore the hypogonadal state

of testosterone to normal [1,52], in which the GnRH agonist was started and stopped cyclically. Hershman et al [53] performed a large cohort study using Unites States Medicaire Claams data to analyze the favorable effect of intermittent ADT on multiple adverse events. A total of 1,134 eligible Unites States-based patients with metastatic PC was enrolled under the hypothesis that the intermittent ADT would reduce long-term health-related events including cognitive dysfunction compared to continuous ADT. However, they failed to show its favorable effect and concluded no apparent reduction of cognitive function in older patients with metastatic PC.

9. Meta-analyses of androgen deprivation therapy

Several meta-analyses have analyzed the relationship between ADT and cognitive dysfunction including the dementia risk with retrospective data. McGinty et al [54] showed that in seven neuropsychological tests, 193 patients with ADT had worse performance only in visuomotor tasks than controls or their own baseline during a 3–6 months follow-up. The other six cognitive domains did not show any differences between the ADT group and controls. Another meta-analysis study [29] showed that ADT in both localized and advanced PC conferred a 41% higher risk of depression. Nead et al's meta-analysis [55] including 50,541 patients showed a 47% increased risk of dementia in PC patients with ADT. However, another meta-analysis showed an inconclusive association between overall cognitive impairment and ADT in a retrospective cohort study. The risk of overall cognitive impairment after ADT including senile dementia and AD was non-significantly increased (HR=1.28, 95% CI=0.93–1.76, p=0.13) [55].

10. Limitations of the previous studies

The aforementioned studies showed similar or different results from each other about the significant or non-significant association between ADT and cognitive dysfunction diseases such as dementia. The conflicting outcomes about the effects of ADT on mental health have been largely influenced by inherent limitations such as different baseline cohorts, study designs, methodologies, ADT characteristics including agent type, duration, and strategies, and follow-up duration. The complexity of cognitive function which is affected by various factors such as baseline intelligence quotient (IQ) and intra- and interpersonal cognitive function is another major limitation resulting in difficulties launching a longitudinal prospective cohort study. Future studies should be designed to consider late-onset hypogonadism and androgen deficiency increase before ADT and during ADT because late-onset hypogonadism and andropause happen with an approximated incidence of 2.1%–12.8% in middle-aged males with several symptoms, such as low libido, osteoporosis, and low physical performance [56]. The castration level <20 ng/dL might not be achieved under ADT, and decreased levels of testosterone and reaching the castration level were important because they directly correlate with the dementia incidence [33]. Lastly, smoking status and metabolic profiles were also important factors for dementia that should be evaluated in future studies [57].

CONCLUSIONS

ADT has become a major therapeutic intervention for diverse staged PC in recently changed PC guidelines resulting in increasing numbers of long-term ADT patients. The adverse effects of ADT on mental health including cognitive dysfunction have recently been focused on to define their potential association, especially in 40- to 65-year-old PC patients. Work in *in vitro* and *in vivo* models and humans suggests that androgens may affect cognitive function in various brain areas. However, present studies using common neuropsychological tests showed contradictory results on the effects of ADT. Some of the representative studies showed no significant relations between ADT with cognitive dysfunction.

However, due to the complexity of brain function and intra-/interpersonal variations of cognitive function, no randomized clinical trials with ADT exist to address the question of an increased risk by ADT for dementia development depending on ADT duration and agents in PC management. Better tools are urgently needed to assess the cognitive impact of ADT prospectively and to optimize the care of future PC patients. It is also important to discuss preventive measures for minimizing the adverse effects of ADT on cognitive function because various novel highly potent anti-androgens, such as apalutamide, darolutamide, and enzalutamide have been introduced in combination with LHRH agonists for early non-metastatic PC.

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Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: SHK. Data curation: JYJ, HHL, SP. Writing – original draft: SHK, HHL. Writing – review & editing: JYJ, HHL, SP, SHK.

REFERENCES

1. Meng MV, Grossfeld GD, Sadetsky N, Mehta SS, Lubeck DP, Carroll PR. Contemporary patterns of androgen deprivation therapy use for newly diagnosed prostate cancer. Urology 2002;60(3 Suppl 1):7-11; discussion 11-2.
2. Bolla M, de Reijke TM, Van Tienhoven G, Van den Bergh AC, Oddens J, Poortmans PM, et al.; EORTC Radiation Oncology Group and Genito-Urinary Tract Cancer Group. Duration of androgen suppression in the treatment of prostate cancer. N Engl J Med 2009;360:2516-27.
3. Keating NL, O'Malley A, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. J Natl Cancer Inst 2012;104:1518-23.
4. Kluger J, Roy A, Chao HH. Androgen deprivation therapy and cognitive function in prostate cancer. Curr Oncol Rep 2020;22:24.
5. Leranth C, Petnehazy O, MacLusky NJ. Gonadal hormones affect spine synaptic density in the CA1 hippocampal subfield of male rats. J Neurosci 2003;23:1588-92.
6. Westlye LT, Kaufmann T, Alnæs D, Hullstein IR, Bjørnebekk A. Brain connectivity aberrations in anabolic-androgenic steroid users. Neuroimage Clin 2016;13:62-9.
7. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR; Baltimore Longitudinal Study of Aging. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 2001;86:724-31.
8. Zarrouf FA, Artz S, Griffith J, Sirbu C, Kommor M. Testosterone and depression: systematic review and meta-analysis. J Psychiatr Pract 2009;15:289-305.
9. Härkönen K, Huhtaniemi I, Mäkinen J, Hübler D, Irjala K, Koskenvuo M, et al. The polymorphic androgen receptor gene CAG repeat, pituitary-testicular function and andropausal symptoms in ageing men. Int J Androl 2003;26:187-94.
10. Cherrier MM, Matsumoto AM, Amory JK, Ahmed S, Bremner W, Peskind ER, et al. The role of aromatization in testosterone supplementation: effects on cognition in older men. Neurology 2005;64:290-6.
11. Foland-Ross LC, Ross JL, Reiss AL. Androgen treatment effects on hippocampus structure in boys with Klinefelter syndrome. Psychoneuroendocrinology 2019;100:223-8.
12. Higano CS. Side effects of androgen deprivation therapy: monitoring and minimizing toxicity. Urology 2003;61(2 Suppl 1):32-8.
13. Gilbert SM, Kuo YF, Shahinian VB. Prevalent and incident use of androgen deprivation therapy among men with prostate cancer in the United States. Urol Oncol 2011;29:647-53.
14. Moffat SD, Zonderman AB, Metter EJ, Kawas C, Blackman MR, Harman SM, et al. Free testosterone and risk for Alzheimer disease in older men. Neurology 2004;62:188-93.
15. Hsu B, Cumming RG, Waite LM, Blyth FM, Naganathan V, Le Couteur DG, et al. Longitudinal relationships between reproductive hormones and cognitive decline in older men: the Concord Health and Ageing in Men Project. J Clin Endocrinol Metab 2015;100:2223-30.
16. Maki PM, Sundermann E. Hormone therapy and cognitive function. Hum Reprod Update 2009;15:667-81.
17. Cherrier MM, Matsumoto AM, Amory JK, Johnson M, Craft S, Peskind ER, et al. Characterization of verbal and spatial memory changes from moderate to supraphysiological increases in serum testosterone in healthy older men. Psychoneuroendocrinology 2007;32:72-9.
18. Izard JP, Siemens DR. Androgen deprivation therapy and mental health: impact on depression and cognition. Eur Urol Focus 2020. doi: 10.1016/j.euf.2019.11.010 [Epub].
19. Kenny AM, Fabregas G, Song C, Biskup B, Bellantonio S. Effects of testosterone on behavior, depression, and cognitive function in older men with mild cognitive loss. J Gerontol A Biol Sci Med Sci 2004;59:75-8.
20. Dinh KT, Reznor G, Muralidhar V, Mahal BA, Nezolosky MD, Choueiri TK, et al. Association of androgen deprivation therapy with depression in localized prostate cancer. J Clin Oncol 2016;34:1905-12.
21. Cherrier MM, Rose AL, Higano C. The effects of combined androgen blockade on cognitive function during the first cycle of intermittent androgen suppression in patients with prostate cancer. J Urol 2003;170:1808-11.
22. Cherrier MM, Borghesani PR, Shelton AL, Higano CS. Changes in neuronal activation patterns in response to

androgen deprivation therapy: a pilot study. BMC Cancer 2010;10:1.

23. Cherrier MM, Cross DJ, Higano CS, Minoshima S. Changes in cerebral metabolic activity in men undergoing androgen deprivation therapy for non-metastatic prostate cancer. Prostate Cancer Prostatic Dis 2018;21:394-402.
24. Chao HH, Hu S, Ide JS, Uchio E, Zhang S, Rose M, et al. Effects of androgen deprivation on cerebral morphometry in prostate cancer patients--an exploratory study. PLoS One 2013;8:e72032.
25. Hogervorst E, Bandelow S, Combrinck M, Smith AD. Low free testosterone is an independent risk factor for Alzheimer's disease. Exp Gerontol 2004;39:1633-9.
26. Muller M, Schupf N, Manly JJ, Mayeux R, Luchsinger JA. Sex hormone binding globulin and incident Alzheimer's disease in elderly men and women. Neurobiol Aging 2010;31:1758-65.
27. Cherrier MM, Asthana S, Plymate S, Baker L, Matsumoto AM, Peskind E, et al. Testosterone supplementation improves spatial and verbal memory in healthy older men. Neurology 2001;57:80-8.
28. Nead KT, Gaskin G, Chester C, Swisher-McClure S, Dudley JT, Leeper NJ, et al. Androgen deprivation therapy and future Alzheimer's disease risk. J Clin Oncol 2016;34:566-71.
29. Nead KT, Sinha S, Yang DD, Nguyen PL. Association of androgen deprivation therapy and depression in the treatment of prostate cancer: a systematic review and meta-analysis. Urol Oncol 2017;35:664.e1-9.
30. Jayadevappa R, Chhatre S, Malkowicz SB, Parikh RB, Guzzo T, Wein AJ. Association between androgen deprivation therapy use and diagnosis of dementia in men with prostate cancer. JAMA Netw Open 2019;2:e196562.
31. Tully KH, Nguyen DD, Herzog P, Jin G, Noldus J, Nguyen PL, et al. Risk of dementia and depression in young and middle-aged men presenting with nonmetastatic prostate cancer treated with androgen deprivation therapy. Eur Urol Oncol 2019. doi: 10.1016/j.euo.2019.08.003 [Epub].
32. Khosrow-Khavar F, Rej S, Yin H, Aprikian A, Azoulay L. Androgen deprivation therapy and the risk of dementia in patients with prostate cancer. J Clin Oncol 2017;35:201-7.
33. Eckstein N, Haas B. Clinical pharmacology and regulatory consequences of GnRH analogues in prostate cancer. Eur J Clin Pharmacol 2014;70:791-8.
34. Baik SH, Kury FSP, McDonald CJ. Risk of Alzheimer's disease among senior medicare beneficiaries treated with androgen deprivation therapy for prostate cancer. J Clin Oncol 2017;35:3401-9.
35. Lehrer S, Rheinstein PH, Rosenzweig KE. No relationship of anti-androgens to Alzheimer's disease or cognitive disorder in the MedWatch database. J Alzheimers Dis Rep 2018;2:123-7.
36. Chung SD, Lin HC, Tsai MC, Kao LT, Huang CY, Chen KC. Androgen deprivation therapy did not increase the risk of Alzheimer's and Parkinson's disease in patients with prostate cancer. Andrology 2016;4:481-5.
37. Kao LT, Lin HC, Chung SD, Huang CY. No increased risk of dementia in patients receiving androgen deprivation therapy for prostate cancer: a 5-year follow-up study. Asian J Androl 2017;19:414-7.
38. McHugh DJ, Root JC, Nelson CJ, Morris MJ. Androgen-deprivation therapy, dementia, and cognitive dysfunction in men with prostate cancer: How much smoke and how much fire? Cancer 2018;124:1326-34.
39. Treanor CJ, Li J, Donnelly M. Cognitive impairment among prostate cancer patients: an overview of reviews. Eur J Cancer Care (Engl) 2017. doi: 10.1111/ecc.12642.
40. Green HJ, Pakenham KI, Headley BC, Yaxley J, Nicol DL, Mactaggart PN, et al. Altered cognitive function in men treated for prostate cancer with luteinizing hormone-releasing hormone analogues and cyproterone acetate: a randomized controlled trial. BJU Int 2002;90:427-32.
41. Salminen EK, Portin RI, Koskinen A, Helenius H, Nurmi M. Associations between serum testosterone fall and cognitive function in prostate cancer patients. Clin Cancer Res 2004;10:7575-82.
42. Jenkins VA, Bloomfield DJ, Shilling VM, Edginton TL. Does neoadjuvant hormone therapy for early prostate cancer affect cognition? Results from a pilot study. BJU Int 2005;96:48-53.
43. Almeida OP, Waterreus A, Spry N, Flicker L, Martins RN. One year follow-up study of the association between chemical castration, sex hormones, beta-amyloid, memory and depression in men. Psychoneuroendocrinology 2004;29:1071-81.
44. Gunlusoy B, Ceylan Y, Koskderelioglu A, Gedizlioglu M, Degirmenci T, Ortan P, et al. Cognitive effects of androgen deprivation therapy in men with advanced prostate cancer. Urology 2017;103:167-72.
45. Gonzalez BD, Jim HS, Booth-Jones M, Small BJ, Sutton SK, Lin HY, et al. Course and predictors of cognitive function in patients with prostate cancer receiving androgen-deprivation therapy: a controlled comparison. J Clin Oncol 2015;33:2021-7.
46. Yang J, Zhong F, Qiu J, Cheng H, Wang K. Dissociation of event-based prospective memory and time-based prospective memory in patients with prostate cancer receiving androgen-deprivation therapy: a neuropsychological study. Eur J Cancer Care (Engl) 2015;24:198-204.

47. Nead KT, Gaskin G, Chester C, Swisher-McClure S, Leeper NJ, Shah NH. Association between androgen deprivation therapy and risk of dementia. JAMA Oncol 2017;3:49-55.
48. Wu LM, Amidi A, Tanenbaum ML, Winkel G, Gordon WA, Hall SJ, et al. Computerized cognitive training in prostate cancer patients on androgen deprivation therapy: a pilot study. Support Care Cancer 2018;26:1917-26.
49. Alibhai SM, Breunis H, Timilshina N, Marzouk S, Stewart D, Tannock I, et al. Impact of androgen-deprivation therapy on cognitive function in men with nonmetastatic prostate cancer. J Clin Oncol 2010;28:5030-7.
50. Alibhai SM, Timilshina N, Duff-Canning S, Breunis H, Tannock IF, Naglie G, et al. Effects of long-term androgen deprivation therapy on cognitive function over 36 months in men with prostate cancer. Cancer 2017;123:237-44.
51. Morote J, Tabernero ÁJ, Álvarez Ossorio JL, Ciria JP, Domínguez-Escrig JL, Vázquez F, et al.; ANAMEM Investigator Group. Cognitive function in patients with prostate cancer receiving luteinizing hormone-releasing hormone analogues: a prospective, observational, multicenter study. Int J Radiat Oncol Biol Phys 2017;98:590-4.
52. Hussain M, Tangen CM, Berry DL, Higano CS, Crawford ED, Liu G, et al. Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med 2013;368:1314-25.
53. Hershman DL, Unger JM, Wright JD, Ramsey S, Till C, Tangen CM, et al. Adverse health events following intermittent and continuous androgen deprivation in patients with metastatic prostate cancer. JAMA Oncol 2016;2:453-61.
54. McGinty HL, Phillips KM, Jim HS, Cessna JM, Asvat Y, Cases MG, et al. Cognitive functioning in men receiving androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. Support Care Cancer 2014;22:2271-80.
55. Nead KT, Sinha S, Nguyen PL. Androgen deprivation therapy for prostate cancer and dementia risk: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis 2017;20:259-64.
56. Sun M, Cole AP, Hanna N, Mucci LA, Berry DL, Basaria S, et al. Cognitive impairment in men with prostate cancer treated with androgen deprivation therapy: a systematic review and meta-analysis. J Urol 2018;199:1417-25.
57. Hall SA, Esche GR, Araujo AB, Travison TG, Clark RV, Williams RE, et al. Correlates of low testosterone and symptomatic androgen deficiency in a population-based sample. J Clin Endocrinol Metab 2008;93:3870-7.