Cognitive and Psychological Impacts of Different Treatment Options for Prostate Cancer: A Critical Analysis

Konstantina G. Yiannopoulou, Aikaterini I. Anastasiou, Konstantinos Kontoangelos, Charalambos Papageorgiou, Ioannis P. Anastasiou

Department of Neurology, "Henry Dunant" Hospital Center; Medical School of Athens, National and Kapodistrian University of Athens; 1st Department of Psychiatry, Medical School, National & Kapodistrian University of Athens, Eginition Hospital; 1st Urology Department, Laiko Hospital, National and Kapodistrian University of Athens, Athens, Greece

Abstract

Objectives: Psychological morbidity as well as cognitive impairment are increasingly reported in prostate cancer (PCa) patients. However, despite growing numbers of PCa survivors and the well estimated negative impact of cognitive decline and emotional distress on survivors' quality of life, no study has assessed the whole range of cognitive and psychological sequelae as a response to treatment options for PCa. The objective of the present review was to systematically characterize the types and estimate the prevalence of the cognitive impairment and emotional burdens that were found in PCa survivors secondary to different treatment options. Methods: Systematic, general reviews, meta-analysis, and overviews of review studies in English, that were published in PubMed during the last 10 years until August 2019 and that reported psychological distress, anxiety, depression, cognitive decline, or dementia among individuals with PCa exposed to a particular treatment option were analyzed. Results: A total of 21 articles were reviewed. Some of the studies described one or more cognitive or psychological consequences of only one therapeutic strategy while others compared the psychological impacts among different strategies. Most of these studies suggested that either radical prostatectomy or active surveillance and radiotherapy were well-tolerated treatments in terms of psychological modifications. However, many of these patients may require additional emotional support. There is also increasing evidence that androgen deprivation therapy may be associated with depression, while controversy surrounding the association between cognitive dysfunction, dementia, and androgen deprivation therapy remains ambivalent. Conclusion: Emotional distress and cognitive decline may accompany every PCa treatment option to different degrees. Accurate information on the short- and long-term effect of treatments on cognitive and psychological aspects should be provided to patients during treatment decision-making. There is also a need to develop well-targeted psychological and neurological interventions that could help those experiencing ongoing post-treatment difficulties.

Introduction

Prostate cancer (PCa) is the most common non-skin cancer in males over 70 years of age in Europe. It is one of the major health concerns in developed countries. The incidence is highest in Northwestern Europe (> 200 per...
100,000 men), while global rates have shown a continuous increasing tendency in the last 20 years. This fact is probably secondary to a progressive aging population and to the ongoing use of the prostate-specific antigen test and subsequent biopsy that contribute to a significant increase in the diagnosis of PCa [1].

Given the longevity associated with the PCAs (over 70% of patients with PCAs can expect to live for 10 years or more from the time of diagnosis), the management of survivorship issues within this population assumes paramount importance. Such issues revolve around the effective maintenance of the quality of life (QoL) throughout post-treatment survivorship. Specific psychological and cognitive concerns associated with the painful cancer journey should be better addressed [2, 3].

Both PCAs diagnosis and treatment options for PCAs have a negative impact on psychological and mental well-being, and are associated with a decreased QoL [3]. Over recent decades, numerous studies of PCAs have demonstrated a significant association between specific treatment methods and the incidence of complications [4].

The most common psychological symptoms experienced by PCAs patients are anxiety and depression [4]. Furthermore, recent studies indicated that the high fear of cancer recurrence (FCR) is an understudied topic in PCAs survivors [5].

There is also increasing controversy surrounding the association between cognitive dysfunction and certain PCAs treatment options [6].

Even patients diagnosed with the milder form of the disease, localized PCAs, have to choose among the available treatment options while every one of them has its own efficacy rate as well as its own set of complications, side effects and financial costs. They usually have to undergo either multiple surgical approaches to prostatectomy, or various forms of external-beam and interstitial radiation. There is also the option of a growing list of energy ablative technologies and the option of expectant management, which is separated into watchful waiting (WW) and active surveillance (AS) [7, 8]. Androgen deprivation therapy (ADT) has been an essential treatment option initially restricted to more advanced stages of the disease, and recently extended to earlier stages [7, 8]. Accurate information on the short- and long-term effects of treatments on cognitive and psychological aspects should be provided to patients during treatment decision-making.

The aim of the present review was to systematically characterize the types and estimate the prevalence of the cognitive impairment and emotional burdens that are found in PCAs survivors secondary to different treatment options.

**Materials and Methods**

PubMed was queried in August, 2019. Eligible studies were systematic, general reviews, meta-analysis, and overviews of review studies in English that were published during the last 10 years and that reported psychological distress, anxiety, depression, cognitive decline, or dementia among individuals with PCAs exposed to a particular treatment option. The following search terms were used: “prostate cancer”, “active surveillance”, “radical prostatectomy”, “radiotherapy”, “hormonal therapy”, “androgen deprivation therapy”, “anxiety”, “distress”, “depression”, “cognitive impairment”, and “dementia”.

Some studies analyzed one or more cognitive and psychological consequences of only one therapeutic strategy while others compared the cognitive and psychological impacts among different strategies. Overall, 21 review articles were examined. There were 6 studies analyzed the psychological consequences of AS, 13 studies reported the cognitive and psychological consequences of ADT, and 2 additional review studies compared the cognitive and psychological impacts among different treatment strategies.

**Results**

**Cognitive and Psychological Burdens Following Expectant Management (WW and AS)**

AS is the most conservative management approach, conducted for those patients with “low-risk” or “favorable-risk” disease, which is supposed to avoid long-term adverse effects on the patient’s QoL. It is characterized by a routine protocol of close monitoring with digital rectal examination, periodic prostate biopsy, and serial prostate-specific antigen testing [9].

However, there are concerns that this method may potentially harm patients’ well-being through living with the knowledge of untreated PCAs [10]. On the contrary, this option may be under-used, because of fears of psychological adverse events in those accepting AS [11].

The first systematic review about psychological impacts of AS by van den Bergh et al. [12] analyzed scarce observations derived from non-randomized studies with a limited follow-up after diagnosis. Nevertheless, it concluded that AS does not cause much anxiety or distress in the short term in men who follow this strategy.

The men who were on AS according to the systematic review by Bellardita et al. [10] usually reported good levels of well-being and did not appear to suffer major negative psychological impacts. The research findings
suggested little presence of anxiety and depression and high overall QoL related to their disease. However, the authors underlined that there are few long-term studies, so more well-designed research is needed to make definitive recommendations.

In accordance to the previous study, the systematic review by Carter et al. [11] supported that patients can be informed that AS involves no greater threat to their psychological well-being as part of the informed consent process, and clinicians need not limit access to AS based on a prejudice of adverse sequelae on overall psychological well-being.

An additional recent systematic review by Dickey et al. [13] reassured that the majority of articles indicated low levels of anxiety and depression among men undergoing AS. At the same time, this review highlighted that the results of clinical trials indicated that additional research is needed to determine the exact psychological impact among men undergoing AS on a longitudinal basis.

On the contrary, another review study by Kazer et al. [14] highlighted the psychological burden of living with PCa in AS due to high levels of anxiety and uncertainty secondary to this method and suggested that effective clinician education and counseling, as well as referral of the patients for adjuvant support services must be integrated in clinical practice. In support of the previous point of view, a more recent review by Ruane-McAteer et al. [15] suggested that many quantitative studies may not provide a precise estimation of the psychological burden of AS due to methodological concerns. Further studies of combined high quality methods are necessary to provide clarity on the psychological impact of AS. Consequently, they warn that clinicians should be aware that despite conclusions of previous reviews, patients may require additional emotional support.

Additionally, a qualitative systematic review about WW or AS as therapeutic options for PCa and other chronic clinical entities by Rittenmeyer et al. [16] concluded that the whole process of making the decision to choose WW is complex. A total of 16 studies, critically assessed by 2 independent reviewers and deemed to be of high quality, were included in the final review. The review suggested that patients experience a plethora of emotions that often lead to uncertainty and anxiety. An empathic, reassuring relationship with the healthcare practitioner eases the burden of this treatment option and is highly recommended, as well as more future studies of high quality.

Overall, 4 systematic reviews supported that AS is not a threat for the psychological well-being of PCa patients [10–13] while 2 reviews warned practitioners of the possibility of increased psychological distress in their patients despite findings of many other reviews [14, 15]. Furthermore, a more general qualitative systematic review about WW or AS in different chronic diseases including PCa concluded that patients following this process experience high levels of distress [16]. All of the studies recommended further longitudinal studies of high-quality methodology (table 1).

**Table 1.** Reviews on the cognitive and psychological burdens of AS

| Study                        | Design                        | Results                                                                 |
|------------------------------|-------------------------------|-------------------------------------------------------------------------|
| van den Bergh et al. [12], 2012 | non-randomized studies        | no significant anxiety or distress prevalence                           |
| Bellardita et al. [10], 2015  | six cross-sectional studies and 4 cohorts | no significant anxiety or distress prevalence                           |
| Carter et al. [11], 2015      | review of 34 articles: 24 observational, 8 RCTs, and 2 interventional studies | no significant anxiety or distress prevalence                           |
| Dickey et al. [13], 2019      | review of 11 articles: 8 quantitative non-RCT studies, 1 with mixed methods, 1 quantitative cross-sectional questionnaire survey, and 1 systematic review | no significant anxiety or distress prevalence                           |
| Kazer et al. [14], 2013       | review of 14 non-randomized studies | underestimated anxiety and uncertainty prevalence in the literature          |
| Ruane-McAteer et al. [15], 2017 | review of 23 articles: 20 quantitative and 3 qualitative | no significant anxiety or distress prevalence in the literature; however, caution because of the low quality of the research |
| Rittenmeyer et al. [16], 2016  | review of 16 selected studies  | no clear prevalence of uncertainty and anxiety                           |

RCT = Randomized controlled trial.
Cognitive and Psychological Burdens Following ADT

Depression in ADT Patients There is increasing evidence that ADT may be associated with depression according to review articles by Casey et al. [17], Donovan et al. [18], Rhee et al. [19], and a systematic review and meta-analysis by Nead et al. [20]. It was further reported by Cherrier et al. [21] that when ADT patients are estimated by a diagnostic depression instrument, approximately 12.8% meet clinical criteria for depression. Also, certain depressive symptoms (poor appetite, disrupted sleep, worry, intrusive thoughts, and low mood) can also adversely impact intact cognitive functioning [20].

Anxiety and other Mood Changes in ADT Patients Cherrier et al. [21] also reported that men undergoing ADT often present a broad symptomatology of mood changes beyond depression. This can include fatigue, moodiness, irritability, tension, anxiety, and apathy.

Cognitive Impairment in ADT Patients There is also increasing controversy surrounding the association between cognitive dysfunction and the receipt of ADT, with some evidence suggesting an increased risk of dementia.

According to an overview of reviews by Treanor et al. [22] about cognitive impairment among PCa patients on ADT, prevalence rates varied between 10 and 69%. Cognitive domains impaired by ADT included: verbal memory, visuospatial ability, and executive functions. It was highlighted by the authors that there is a need to agree on a definition of cognitive impairment in the clinical epidemiology of cancer and to standardize the selection of measures in order to aid accurate assessment and fair comparisons across studies regarding the prevalence of cognitive impairment among PCa patients.

Another review by Mundell et al. [23] reported a similar impact of ADT on the same cognitive domains and recommended routine assessment of cognitive function in these men. Two previous systematic reviews by McGinty et al. [24] and Jamadar et al. [25] supported that PCa patients who received ADT performed significantly worse specifically on visual-motor tasks compared to non-cancer control groups.

On the contrary, a systematic review and meta-analysis by Sun et al. [26] concluded that analysis between overall cognitive impairment and use of ADT defined according to International Cognition and Cancer Task Force criteria in a pooled analysis were inconclusive. This study supported that in retrospective cohort studies the risk of overall cognitive impairment after ADT was not significant and suggested that better prospective longitudinal studies need to be designed for the assessment of this end point.

Other reviews (McHugh et al. [6] and Wu et al. [27]) were somewhere between suggesting cognitive impairment may or may not occur in PCa patients in ADT. However, because of methodological shortcomings and heterogeneity of clinical studies, conclusions regarding the effects of hormone therapy on cognitive functions remain ambivalent. They also supported the need of larger scale neuropsychological studies that also evaluate the impact of impairments on activities of daily living. Furthermore, it was recommended [6] that recent studies do not form a body of work that can independently support a conclusion or change in practice.

The most recent review about ADT impact on cognition by Cherrier et al. [21] highlighted the uncertainty and controversy in different studies and the factors that may contribute to variations in findings. These factors include the specific method of ADT treatment (continuous vs. intermittent), methods of achieving androgen deprivation (orchiectomy vs. gonadotropin-releasing hormone agonists or other therapeutic options), the timing of cognitive assessment (only on ADT vs. comparing pre-ADT baseline to treatment), the presence of concomitant treatments (e.g., radiation), and use of control groups (healthy controls vs. men with PCa not on ADT). Nonetheless, it concluded that well-designed prospective longitudinal studies completed to date suggested that ADT can adversely impact cognition for some men and future research should address the factors that can make these men more susceptible to cognitive decline from ADT.

Dementia in ADT Patients Even more ambivalent is the controversy in the literature about the increased risk of dementia among PCa patients under ADT.

The first systematic review and meta-analysis on ADT for PCa and dementia risk by Nead et al. [28] included 9 studies and concluded that the currently available combined evidence suggested that ADT in the treatment of PCa may be associated with an increased dementia risk. It was recommended that the potential for neurocognitive deficits secondary to ADT should be discussed with patients and prospectively evaluated.

According to the next general review study on the topic by McHugh et al. [6] propelling the public concerns about an association between ADT use and dementia was a recent single institution, retrospective study undertaken at Stanford University [28], that revealed a 4.4% absolute increased dementia risk in ADT users (3.5% in non-users vs. 7.9% in users). In addition to being a retrospective, single institution study, this study was not adequately powered to analyze the dementia risk by type of ADT, nor could the disease state for ADT use be characterized.
The same general review [6] also presented three recent population-based studies (one from the UK and two from Taiwan) [29–31] where the use of ADT was not associated with an increased risk of dementia.

The recommendation of this review study [6] to physicians was that until prospective, randomized controlled studies with close and long periodic follow-ups are completed, they might discuss the possible association of ADT and cognitive impairment prior to the initiation of ADT with their patients. Once ADT is started, these patients can be routinely assessed during follow-up for mild cognitive changes; with early specialist referral should cognitive impairment emerge.

Although the last review about ADT and dementia by Cherrier et al. [21] underlined that ADT was shown to disrupt and reduce brain metabolism in brain regions that overlap with regions of metabolic disruption in Alzheimer’s disease (AD) as measured by positron emission tomography concluded that the results of studies examining the onset of AD and/or dementia suggest that this connection exists for some but not all men undergoing ADT.

Overall, there is increasing evidence that ADT may be associated with depression in a high prevalence of approximately 12.8% while other emotional distress indicators such as anxiety and irritability can be present [20].

On the contrary, controversy surrounding the association between cognitive dysfunction, dementia, and ADT remains contradictory. Most of the review studies concluded that recent clinical studies did not form a body of work that can independently support a conclusion or change in practice. In support of this ambivalence, the two most recent retrospective cohort clinical studies provided opposite conclusions. The study by Jayadevappa et al. [33] assessed 62,330 men who received ADT within 2 years of PCa diagnosis, and 91,759 men with PCa who did not receive ADT. They concluded that ADT was associated with subsequent diagnosis of dementia or AD over a follow-up period of at least 10 years. On the contrary, Robinson et al. [34] studied 18,758 PCa patients in ADT, 7,209 PCa patients in WW, and 121,018 matched controls and concluded that their study did not support previous observations of an increased risk of AD for men on ADT. They observed only a small upward tendency in risk of non-AD dementia.

The only slight difference for physicians might be to discuss the possible – though not certain – association of

| Study                     | Design                                                                 | Results                                                                 |
|---------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|
| Casey et al. [17], 2012   | review of 9 studies on neuropsychological symptoms: 4 quantitative non-RCTs, 3 reviews, and 1 cohort study | significant prevalence of dementia and cognitive decline               |
| Donovan et al. [18], 2015 | review of 12 studies on neuropsychological symptoms: 8 quantitative non-RCTs, 3 reviews, and 1 cohort study | significant prevalence of dementia and cognitive decline               |
| Rhee et al. [19], 2015    | review of 4 studies on neuropsychological symptoms: 1 quantitative non-RCTs, 1 review, and 2 RCTs | significant prevalence of dementia and cognitive decline               |
| Cherrier et al. [21], 2020| review of 47 studies on neuropsychological symptoms: 32 quantitative non-RCTs, 7 reviews, 2 RCTs, 3 cohort studies, and 1 qualitative study | significant prevalence of depression, equivocal prevalence of dementia and cognitive decline |
| Treanor et al. [22], 2017 | review of 28 studies                                                                 | significant prevalence (10–69%) of cognitive decline                |
| Mundell et al. [23], 2017 | review of 11 longitudinal studies                                                                 | significant prevalence of decline in multiple cognitive domains in many studies |
| McGinty et al. [24], 2014 | review of 14 longitudinal comparative studies with objective neuropsychological data | significant cognitive deficits only in visuomotor tasks               |
| Sun et al. [26], 2018     | review of 26 studies: 2 prospective and 4 retrospective studies were analyzed | no significant prevalence of cognitive decline                       |
| Jamadar et al. [25], 2012 | review of 11 studies: 1 RCT, 1 observational study, and 9 non-RCT quantitative studies | significant cognitive deficits only in spatial memory, and perhaps verbal memory |
| Wu et al. [27], 2017      | review of 6 studies: 4 review studies and 2 RCTs                                                                 | possible cognitive deficits                                          |
| McHugh et al. [6], 2018   | review of 7 studies for cognitive impairment (1 RCT and 6 non-RCTs) and 4 observational studies for dementia | possible cognitive deficits                                          |
| Nead et al. [20], 2017    | review of 9 comparative studies                                                                 | possible increased dementia risk                                     |

RCT = Randomized controlled trial.
ADT and cognitive impairment prior to the initiation of ADT with their patients, and to assess them for memory and functional deficits, with early specialist referral if cognitive impairment emerges (table 2).

**Cognitive and Psychological Burdens Following Radiotherapy or Radical Prostatectomy (RP)**

There are no review studies about cognitive or psychological sequelae exclusively following radiotherapy or RP.

**Cognitive and Psychological Burdens following AS, RP, Radiotherapy, or ADT**

There were 2 review studies that compared some psychological consequences of particular therapeutic options for PCa.

The review article by Klaassen et al. [35] analyzed the current literature and addressed the relationship among different profiles of PCa patients, depression, and suicidal ideation. It concluded that PCa patients at increased risk for suicide are men with distant disease and especially survivors more than 15 years after diagnosis. Additionally, patients that received ADT are 23% more likely to develop depression compared to those without ADT. The study warned that the outcome of these high-risk patients might be tragic. Hence, it should be optimized by screening for depression and suicidal ideation and timely psychiatric referral.

Overall, 18 studies were included and critically evaluated by a recent critical analysis (Maggi et al. [36]) on the psychological impact of different primary treatments for PCa.

Four of these studies were particularly focused on AS. Three of them (Anderson et al. [37], van den Bergh et al. [38], and Wilcox et al. [39]) concluded that AS was associated with favorable levels of anxiety and depression. On the contrary, one study (Watts et al. [40]) showed that AS patients experienced higher rates of anxiety and depression (23 and 12%, respectively) than those expected in the general population.

Ten of the selected studies analyzed RP cases. All showed 5% of cases or less with moderate or severe anxiety or depression after surgery with stable results during follow-up [41–51]. Five studies analyzed radiotherapy cases [46–50].

Most showed post-radiotherapy stable percentages of anxiety in 12–14% of the cases. Lower and stable results (7% of cases) were found for depression.

Three studies compared the three different treatments (AS, RP, and radiotherapy). Venderbos et al. [50] concluded that AS in the long-term does not cause anxiety when compared to radiotherapy and RP. However, the percentages of highly anxious cases were not dramatically different in all 3 groups (AS 8%, radiotherapy 12%, and RP 13%). In the post-treatment follow-up, anxiety was similarly distributed among the 3 treatments (13–16% of cases) while depression showed a lower percentage (5–7%) according to Donovan et al. [18]. Sciarra et al. [52] showed that cases with RP and AS maintained low and stable percentages of anxiety and depression. On the contrary, cases with radiotherapy showed a significant increase in the percentage of suspicious anxiety (57%) and depression (58%) at a 1-month interval. At a 12-month interval, no cases with RP showed anxiety and depression, whereas 5.3% of cases with AS reported a suspicious depression, and 5.9 and 3.9% with radiotherapy showed a suspicious or definite anxiety and depression, respectively. In conclusion, all of the selected treatment options (AS, RP, and radiotherapy) were well tolerated in terms of definite anxiety and depression during the post-treatment follow-up.

### Table 3. Reviews of cognitive and psychological burdens on different therapeutic options in PCa patients

| Study                          | Design                                                                 | Results                                                                                                                                 |
|-------------------------------|------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Klaassen et al. [35], 2018    | review of 15 studies for depression and suicidal ideation in PCa patients after AS, RP, and radiotherapy, ADT treatment: 5 cohort and 10 non-RTCs | ADT patients: 23% more likely to develop depression compared to those without ADT; high risk group for suicidal ideation |
| Maggi et al. [36], 2019       | review of 18 studies for anxiety and depression in PCa patients after AS, RP, and radiotherapy, treatment: 2 multi-center randomized studies, 8 multi-center but non-randomized studies, and 8 single-center study controls; 10 studies comparatively considered the different treatments for PCa and 8 studies analyzed only one treatment | AS, RP, and radiotherapy are tolerated in terms of definite anxiety and depression |

RCT = Randomized controlled trial.
To sum up, these 2 multiple review studies further supported the high prevalence of depression in ADT patients and they added the suspicion of suicidal ideation in this particular group of patients, especially for those who were diagnosed with PCa for more than 15 years.

Anxiety in AS still remains a vague issue that seems mild and well tolerated but needs alertness from the physicians and further research. Anxiety or depression after RP shows a 5% prevalence that seems stable during follow-up.

Post-radiotherapy percentages of anxiety remained stable in 12–14% of the cases. Lower and stable results (7% of cases) were found for depression in this patient population.

In conclusion, all of the primary treatments for PCa (AS, RP, and radiotherapy) were well tolerated in terms of definite anxiety and depression during the post-treatment follow-up (table 3).

**Discussion**

Despite growing numbers of PCa survivors, there is little research regarding factors that contribute to psychological adjustment and cognitive stability in PCa patients, while different mental and emotional consequences of every treatment option are hypothesized to play a role in men’s neurological and psychological health [4, 39]. This lack of evidence makes it very difficult for physicians working with PCa patients to interpret psychological data in clinical practice. Patients and clinicians might wish to know how cognitive and psychological aspects may be differently influenced by treatment choice. Information on the short- and long-term effects of treatments on cognitive and psychological aspects should be provided to patients during treatment decision-making.

Furthermore, knowledge of the presence of the psychological burden and/or cognitive decline in PCa patients is important because research to generate models of causality, prognosis, and treatment effects depend on the accurate determination of prevalence and also the need to develop well-targeted psychological and neurological interventions that could help those experiencing ongoing post-treatment difficulties.

It is obvious that the vaguest area in PCa treatment options’ sequelae is the risk of cognitive decline following ADT. It was highlighted by previous authors that there is a need to agree on a definition and a standardized assessment of cognitive impairment among PCa patients [21]. It is also well recognized that better prospective studies need to be designed for the assessment of this end point [25].

We also suggest that selected elements of the current guidance provided by the US Food and Drug Administration for clinical trials in AD [53] and of the new research framework proposed by the National Institute on Aging and the Alzheimer’s Association [54], could be integrated in prospective randomized clinical trials for the prevalence of mild cognitive impairment, AD, or other forms of dementia in PCa patients following ADT. In addition to basic neuropsychological assessment and brain magnetic resonance imaging for every PCa patient before ADT, APOE4 genotyping could help to detect asymptomatic subjects at risk of developing AD [55].

**Key Points**

- Either RP or AS and radiotherapy are well-tolerated treatments in terms of psychological modifications. However, clinicians should be aware that despite findings of previous reviews, patients may require additional emotional support. An empathic, reassuring relationship with the healthcare practitioner eases the burden of any possible psychological distress and is highly recommended.
- There is increasing evidence that ADT may be associated with mild or major depression while controversy surrounding the association between cognitive dysfunction, dementia, and ADT remains ambivalent.
- Recent studies on cognitive or psychological consequences of ADT do not form a body of work that can independently support a conclusion or change in practice for ADT patients. Nevertheless, physicians might discuss the possible – though not certain – association of ADT and depression or cognitive impairment prior to the initiation of ADT with their patients, and to assess them for temporal neuropsychological changes, with early specialist referral if mood changes or cognitive impairment emerge.
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