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Testosterone Replacement Therapy in Men with Untreated or Treated Prostate Cancer: Do We Have Enough Evidences?

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Purpose: To investigate the oncologic safety of testosterone replacement therapy (TRT) in men with untreated or treated prostate cancer.

Materials and Methods: We systematically searched PubMed, Embase, and Cochrane library database from January 1941 to March 2019.

Results: In total, 36 articles met the eligibility criteria for this systematic review. They included a total of 2,459 TRT-treated patients, with a median of 20 patients per study (range: 1–1,142). Except for four studies, all were single-armed studies with poor quality scores (median MINOR, 9 of 24). Of the 36 studies, prostate cancer was managed through active surveillance (AS), in 5 studies; radical prostatectomy, in 11 studies; radiation therapy, in 5 studies; multiple intervention modalities, in 5 studies; and systemic therapy, in 9 studies. In comparison with TRT-treated and untreated patients, the pooled risk ratio (RR) was not significantly higher than one in comparisons of risk for disease progression (pooled RR, 0.83; 95% confidence interval, 0.57–1.21). The results of systematic review implied that TRT might be harmful in men with advanced disease (progression rate: 38.5%–100.0%), who undergo AS (15.4%–57.1%), and who successfully treated but having high-risk disease (0.0%–50.0%).

Conclusions: Compared to TRT-untreated patients, TRT-treated patients may not have increased risks for disease progression in prostate cancer. However, the quality of currently available evidence is extremely poor. TRT may be harmful in men with advanced disease burden, in those with untreated prostate cancer undergoing AS, and in those with successfully treated prostate cancer but having high-risk disease.

Keywords: Eunuchism; Hormone replacement therapy; Prognosis; Prostatic neoplasms; Safety; Testosterone

INTRODUCTION

Prostate-specific antigen (PSA) screening has resulted in a robust migration of the clinical stage in newly detected prostate cancers [1,2]. The American Cancer Society predicted 180,890 new prostate cancer cases in 2016, with 35%–40% of those being low risk [3]. This increasing detection of low-risk disease enables active surveillance as a viable treatment option for prostate cancer [4-6]. Moreover, owing to the increased life ex-

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pectancy caused by downward stage migration, an expanding population of patients successfully treated for prostate cancer strongly desire testosterone replacement therapy (TRT) for hypogonadal symptoms accompanied by decreased serum testosterone levels [7].

However, the effectiveness of TRT for men with untreated or treated prostate cancer is controversial. Per the demonstration of hormonal responsiveness in 1941 by Huggins and Hodges [8], the relationship between serum testosterone and prostatic health has been thought to be an "old dogma" in the form of "fuel for a fire." The United States Food and Drug Administration (FDA) stated, in all testosterone package inserts, that TRT is contraindicated in men with known or suspected prostate cancer, but it did not substantiate this contraindication [9]. The clinical guidelines by Endocrine Society recommend against treating hypogonadism in men with prostate cancer, citing lack of sufficient data to make a general recommendation in men previously treated for prostate cancer ('recommendation with low quality evidence') [10].

Meanwhile, the European Association of Urology stated that there is no conclusive evidence that TRT increases the risk of prostate cancer ('level of evidence=4'), and that men with prostate cancer can receive TRT with careful monitoring for prostate safety ('level of evidence=3') [11]. Similarly, the recent treatment guideline by the American Urologic Association stated that patients should be informed that there is inadequate evidence for TRT ('expert opinion'), but TRT can be considered in men who have undergone radical prostatectomy with favorable pathology (*e.g.*, negative margins, negative seminal vesicles, negative lymph nodes), without PSA recurrence [12].

The prescribing patterns of TRT in patients with treated [13] and untreated prostate cancer [14] are rapidly changing. In the Unites States, 94% of urologists prescribed TRT to patients who had been treated for prostate cancer previously [13]. Additionally, 65% of Canadian urologists stated that they would offer TRT to men who were on active surveillance for prostate cancer [14]. However, it remains unclear whether there are sufficient evidences for these beliefs. To our knowledge, no randomized studies have been reported regarding the safety of TRT in men with untreated or treated prostate cancer. There have been some review articles ('mainly by authors advocating TRT in prostate cancer') summarizing optimistic results from small-scale studies for TRT in patients with prostate cancer who have undergone active surveillance or other treatments [15-21]. However, the existing evidences have rarely been evaluated and synthesized in a systematic manner. Owing to the scarcity of reports in this regard, quality assessment and summation of these existing evidences ('if possible') to reach a reasonable conclusion are necessary. Therefore, we performed a systematic review and meta-analysis of published literature investigating the safety of TRT in men with untreated and treated prostate cancer.

MATERIALS AND METHODS

1. Search strategy for relevant studies

The entire process of this systematic review and meta-analysis followed the recent MOOSE and PRISMA recommendations [22,23]. We systematically searched online PubMed, Embase, and Cochrane library database from their respective inspections until March 2019. Our overall search strategies included terms for prostate cancer (prostatic neoplasm, prostate carcinoma, or prostate adenocarcinoma), treatments (watchful waiting, active surveillance, focal therapy, surgery, radiation therapy, androgen deprivation therapy, or chemotherapy), testosterone deficiency (hypogonadism or androgen deficiency), and hormone replacement therapy (testosterone replacement and testosterone supplementation). Detailed queries for the search strategy are presented in Appendix. Some studies were manually searched by referring the review articles or original research articles on similar subjects.

2. Selection criteria of eligible studies for meta-analysis

Original research articles or abstracts, articles in which the subjects were only patients with prostate cancer with or without treatment; those in which patients received TRT owing to symptomatic testosterone deficiency; those in which oncological outcome parameters were objectively described using standard investigation tools, such as biochemical recurrence or radiographic progression; those in which the sample size was provided; and double-armed studies (TRT-treated *vs.* TRT-untreated) in which the risks for progression in each group were presented separately for the estimation of risk ratio (RR) were included in this systematic review. In case of suspected duplication of patient

Table 1. Main characteristics of the eligible studies

Study	Year	Study design	No. of patient	No. of control	Mean initial PSA (ng/dL)	Tumor grade	Tumor stage	Risk group	Treatments for PCa	T preparation	Oncologic outcome parameter	Study quality assessment (0–24)[a]
Huggins [8]	1941	Case report	3	–	NA	NA	D2	NA	Ox	IM	PAP	7
Pearson [29]	1957	Case report	2	–	NA	NA	D2	NA	No, 1; Ox, 1	IM	PAP	5
Prout [30]	1967	Case series	26	–	NA	NA	C, 17; D, 9	NA	Ox	IM	PAP	8
Morales [31]	1971	Case report	2	–	NA	NA	D	NA	^{32}P	IM	PAP, Sx	5
Fowler [32]	1981	Case series	52	–	NA	NA	D	NA	No, 4; Ox ± E, 48	IM	PAP, imaging, Sx	8
Kaufman [7]	2004	Case series	7	–	5.2	Low, 6; Intermediate, 1	NA (localized)	Low, 6; Intermediate, 1	RP	Gel, 2; Patch, 3; IM, 2	PSA	7
Agarwal [33]	2005	Case series	10	–	7.0	Low, 2; Intermediate, 7; High, 1	NA (localized)	Low, 2; Intermediate, 7; High, 1	RP	Gel, 7; Patch, 1; IM, 1	PSA	8
Ferreira [34]	2006	Case series	5	–	51.6	Intermediate, 2; High, 3	NA (locally-advanced)	High, 5	Ox	IM	PSA	9
Sarosdy [35]	2007	Case series	31	–	5.3 (median)	Low, 22; Intermediate, 6; High, 3	cT1, 21; cT2a-b, 10	Low, 22; Intermediate, 6; High, 3	Brachytherapy	IM	PSA	13
Davila [36][b]	2008	Case series	20	–	RP, 6.05; EBRT, 3.5	Mean GS, 6.2 (RP) and 5.0 (EBRT)	NA (localized)	NA	RP, 14; EBRT, 6	Gel, 12; IM, 8	PSA	10
Mathew [37]	2008	Case report	1	–	80	Intermediate	pT3N1	High	ADT	Parenteral	PSA, imaging, Sx	6
Nabulsi [38][b]	2008	Case series	22	–	5.9	Low, 12; Intermediate, 7; High, 2	pT2, 20; pT3, 1	Low, 12; Intermediate, 7; High, 1	RP	Gel	PSA	11
Pushkar [39]	2008	Case series	16	–	3.5–9.1 (range)	Low, 13; Intermediate, 3	pT2N0	Low, 13; Intermediate, 3	RP	Gel, 13; Oral, 2; IM, 1	PSA	9
Khera [40]	2009	Case series	57	–	5.58	Low, 24; Intermediate, 26; High, 4	NA (localized)	Low, 24; Intermediate, 26; High, 4	RP	Gel	PSA	11
Morales [41]	2009	Case series	5	–	12.0	Low, 2; Intermediate, 1; High, 2	NA (localized)	Low, 1; Intermediate, 1; High, 3	EBRT	Gel, 2; Oral, 1; IM, 1	PSA	8
Morgentaler [42]	2009	Case report	1	–	8.5	Low	NA (localized)	Low	No	Gel	PSA	5
Morris [43]	2009	Phase I trial	12	–	91.0	Median GS, 8.0	M1, CRPC	High	ADT	Patch or Gel	PSA, imaging, Bx	14
Szmulewitz [44]	2009	Phase I trial	15	–	11.0	NA	M0/M1, CRPC	NA	ADT	Patch	PSA, imaging	14

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Table 1. Continued

Study	Year	Study design	No. of patient	No. of control	Mean initial PSA (ng/dL)	Tumor grade	Tumor stage	Risk group	Treatments for PCa	T preparation	Oncologic outcome parameter	Study quality assessment (0–24)[a]
Isbarn [45][b]	2010	Case series	69	–	NA	NA	NA (localized)	NA	RP	NA	PSA	5
Leibowitz [46]	2010	Case series	96	–	0.8–6,272 (range)	Low, 33; Intermediate, 41; High, 24; Unknown, 1	T1cN0, 42; T2N0, 32; T3N0, 3; TXN1, 11; M1, 8	NA	RP, 24; EBRT, 13; Brachytherapy, 1; ADT 59	Gel	PSA, imaging	11
Sathyamoorthy [47][b]	2010	Case series	130	–	NA	Mean GS, 6.7	NA (localized)	NA	RP	NA	PSA	9
Morales [48]	2011	Case series	7	–	5.7	Low, 6; High, 1	T1c, 6; T2, 1	Low, 6; High, 1	No	Gel, 1; Oral, 1; IM, 5	PSA	8
Morgentaler [49]	2011	Case series	13	–	5.1	Low, 12; Intermediate, 1	NA	Low, 12; Intermediate, 1	No	Gel, Oral, or IM	PSA, Bx	9
Matsushita [50][b]	2012	Case series	71	–	4.5 (median)	Median GS, 7.0	pT2, 60; pT3, 11	NA	RP	NA	PSA	10
Pastuszak [51]	2013	Case series	13	–	5.8 (median)	Low, 4; Intermediate, 7; High, 2	NA	Low, 4; Intermediate, 7; High, 2	EBRT, 10; Brachytherapy, 3	Gel, 12; SC, 1	PSA	9
Pastuszak [52]	2013	Case control	103	49	5.2 (median)	Low to intermediate, 92; High 11	≤pT2b, 8; pT2c, 37; ≥pT3, N1, or margin+, 24	Low to intermediate, 77; High 26	RP	NA	PSA	16
Balbontin [53]	2014	Case series	20	–	6.2	Low, 16; Intermediate, 3; High, 1	T1c, 15; T2a, 5	Low, 16; Intermediate, 3; High, 1	Brachytherapy	IM	PSA	9
Kaplan [54]	2014	Database	1,142	148,213	NA	Low, 92; Intermediate, 673; High, 377	T1, 482; T2, 560; T3, 33; T4, 66	NA	No, 151; RP, 212; RT, 588; ADT, 191	NA	Use of salvage ADT	11
Nakano [55]	2014	Case report	1	–	8.7	Low	T2aN0	Low	RP	IM	PSA	4
Wynia [56][b]	2014	Case control	57	54	NA	Low, 24; Intermediate, 33	pT2, 43; pT3, 11	NA	RP	NA	PSA	11
Berookhim [57]	2015	Case series	11	–	3.7	Low	T1c, 10; T2c, 1	Low	No	Oral±Gel	Bx, imaging	9
Kühn [58]	2015	Case series	32	–	7.7	Low, 20; Intermediate, 8; High, 4	≤pT2b, 19; pT2c, 4; ≥pT3, 3	Low; 20, Intermediate; 8, High, 4	RP, 26; RT, 4; HIFU; 2	Gel, 22; IM, 10	PSA	10
Pastuszak [59]	2015	Case series	98	–	NA	Low, 47; Intermediate, 28; High, 11; Unknown, 12	NA	Low, 47; Intermediate, 28; High, 11;	EBRT, 32; Brachytherapy, 46; EBRT + Brachytherapy, 20	Gel, IM, or SC	PSA	10

Table 1. Continued

Study	Year	Study design	No. of patient	No. of control	Mean initial PSA (ng/dL)	Tumor grade	Tumor stage	Risk group	Treatments for PCa	T preparation	Oncologic outcome parameter	Study quality assessment (0–24)[a]
Kacker [60]	2016	Case control	28	96	3.3	Low, 22; Intermediate, 6	NA	Low, 22; Intermediate, 6	No	Gel, 8; IM, 14; SC, 6	PSA, Bx	15
Ory [61]	2016	Case series	82	–	NA	Low, 32; Intermediate, 39; High, 11	NA	Low, 23; Intermediate, 30; High, 29	RP, 22; RT, 50; HIFU, 1; Cryotherapy, 1; No, 8	NA	PSA, Bx	10
Morgentaler [62][b]	2018	Case series	199	–	NA	NA	NA	NA	RP, 92; RT, 50; No, 57	NA	PSA, Bx	9

No.: number, PSA: prostate-specific antigen, PCa: prostate cancer, NA: not available, Ox: orchiectomy, IM: intramuscular injection, PAP: prostatic acid phosphatase, Sx: symptom, E: estrogen, RP: radical prostatectomy, EBRT: external beam radiation therapy, GS: Gleason score, ADT: androgen deprivation therapy, CRPC: castration-resistant prostate cancer, Bx: biopsy, SC: subcutaneous injection, RT: radiation therapy, HIFU: high intensity focused ultrasound.
[a]Evaluated using Methodological Index for Non-Randomized Studies (*MINORS*) [24]; [b]Only published in abstract forms.

data, the most recently published or the most informative single article was selected. If the study population underwent two or more treatment modalities, each datum was processed separately by the treatment type, or presented all at once when the separation was impossible. Owing to the scarcity of double-armed studies, all single-armed studies and case reports were included in the eligible studies. Studies that failed to satisfy the previously mentioned inclusion criteria, review articles or letters, laboratory studies, such as studies on *ex-vivo* or animal models, and studies with insufficient data to estimate the effects of TRT on oncological outcomes and its RR for progression were excluded.

To minimize bias, abstract screening and full text assessment for eligibility were independently performed by all three reviewers (MK, SSB, and SKH). All screened abstracts were classified into three categories: not eligible, unclear, and potentially eligible. The full texts of "potentially eligible" and "unclear" studies were obtained and assessed for eligibility. Any disagreements between the three reviewers were resolved by consensus.

3. Data extraction and quality assessments

The extracted data elements were 1) overall characteristics of the eligible studies: name of the first author, publication year, study design, population size (intervention and control group); 2) characteristics of the patients: mean PSA level at initial diagnosis, tumor grade, stage, and risk group; 3) treatment data: type of treatment for prostate cancer, type of TRT; and 4) outcome parameters: oncologic parameters for progression, median follow-up periods from initial diagnosis and commencement of TRT, and the number and risks for progression in each arm. The study quality was assessed independently by all three reviewers using the MINOR criteria (score range: 0–24) [24]. Any disagreement was resolved by discussion.

4. Statistical analysis

1) Primary analysis (narrative systematic review)

Existing evidences for TRT in men with untreated or treated prostate cancer were summarized (Table 1). The effects of TRT on prostate cancer progression were evaluated according to the treatment modality, as follows: active surveillance, radical prostatectomy, radiation therapy, multiple modalities, or systemic therapy

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Table 2. Effect of TRT on oncologic outcomes in men with untreated and treated prostate cancer

Study	Year	Median FU from diagnosis (mo)	Median FU from TRT (mo)	TRT-treated arm		TRT-untreated arm		RR of TRT	TRT effect on prognosis	Study quality assessment (0–24)[a]
				No. of patient	Progression (%)	No. of patient	Progression (%)			
Active surveillance										
Morgentaler [42]	2009	NA	24	1	0 (0.0%)	–	–	NA	Harmless	5
Morales [48]	2011	NA	33	7	4 (57.1%)	–	–	NA	Harmful	8
Morgentaler [49]	2011	NA	30	13	2 (15.4%)	–	–	NA	Harmful	9
Berookhim [57]	2015	NA	26 (mean)	1	0 (0.0%)	–	–	NA	Harmless	9
Kacker [60]	2016	38.9/42.7 (control)	38.9	28	3 (10.7%)	96	9 (9.4%)	1.14	Harmless	15
Ory [61]	2016	NA	27	8	0 (0.0%)	–	–	NA	Harmless	10
Morgentaler [62][c]	2018	NA	51 (mean)	57	2 (3.5%)	–	–	NA	Harmless	9
Total population				115		96				
Radical prostatectomy										
Kaufman [7]	2004	NA	16	7	0 (0.0%)	–	–	NA	Harmless	7
Agarwal [33]	2005	NA	19	10	0 (0.0%)	–	–	NA	Harmless	8
Davila [36][c]	2008	74 (mean)	12 (mean)	14	0 (0.0%)	–	–	NA	Harmless	10
Nabulsi [38][c]	2008	31	20	22	1 (4.5%)	–	–	NA	Harmless	11
Pushkar [39]	2008	NA	15 (mean)	16	0 (0.0%)	–	–	NA	Harmless	9
Khera [40]	2009	49 (mean)	13 (mean)	57	0 (0.0%)	–	–	NA	Harmless	11
Isbarn [45][c]	2010	43	19	69	0 (0.0%)	–	–	NA	Harmless	5
Sathyamoorthy [47][c]	2010	NA	8 (mean)	130	0 (0.0%)	–	–	NA	Harmless	9
Matsushita [50][c]	2012	37	19	71	1 (1.4%)	–	–	NA	Harmless	10
Pastuszak [52]	2013	27.5/16.5 (control)	15.2	103	4 (3.9%)	49	8 (16.3%)	0.24	Harmless	16
Nakano [55]	2014	69	33	1	0 (0.0%)	–	–	NA	Harmless	4
Wynia [56][c]	2014	NA	24	57	1 (1.8%)	54	8 (14.8%)	0.12	Harmless	11
Kühn [58]	2015	71	39.8	26	0 (0.0%)	–	–	NA	Harmless	10
Ory [61]	2016	NA	41	22	0 (0.0%)	–	–	NA	Harmless	10
Morgentaler [62][c]	2018	NA	52 (mean)	92	6 (6.5%)	–	–	NA	Harmless	9
Total population				697		103				

Table 2. Continued

Study	Year	Median FU from diagnosis (mo)	Median FU from TRT (mo)	TRT-treated arm		TRT-untreated arm		RR of TRT	TRT effect on prognosis	Study quality assessment (0–24)[a]
				No. of patient	Progression (%)	No. of patient	Progression (%)			
Radiation therapy										
Sarosdy [35]	2007	NA	60	31	1 (3.2%)	–	–	NA	Harmless	13
Davila [36][c]	2008	57 (mean)	9 (mean)	6	0 (0.0%)	–	–	NA	Harmless	10
Morales [41]	2009	NA	15	5	1 (20.0%)	–	–	NA	Harmful	8
Pastuszak [51]	2013	NA	29.7	13	1 (7.7%)	–	–	NA	Harmless	9
Balbontin [53]	2014	NA	31	20	0 (0.0%)	–	–	NA	Harmless	9
Kühn [58]	2015	71	39.8	4	0 (0.0%)	–	–	NA	Harmless	10
Pastuszak [59]	2015	NA	40.8	96	6 (6.3%)	–	–	NA	Harmless	10
Ory [61]	2016	NA	41	50	3 (6.0%)	–	–	NA	Harmless	10
Morgentaler [62][c]	2018	NA	47 (mean)	50	1 (2.0%)	–	–	NA	Harmless	9
Total population				275		0				
Multiple modalities										
Leibowitz [46]	2010	NA	15	96	41 (42.7%)	–	–	NA	Harmful	11
Kaplan [54]	2014	NA	12[b]	1,142	18 (1.6%)[b]	148,213	1,942 (1.3%)[b]	1.19	Harmless	11
Total population				1,238		148,213				
Advanced disease										
Huggins [8]	1941	NA	0.5	3	3 (100.0%)	–	–	NA	Harmful	7
Pearson [29]	1957	NA	0.5–1 (range)	2	0 (0.0%)	–	–	NA	Harmless	5
Prout [30]	1967	NA	0.1–11 (range)	26	10 (38.5%)	–	–	NA	Harmful	8
Morales [31]	1971	3–24	7–9	2	0 (0.0%)	–	–	NA	Harmless	5
Fowler [32]	1981	NA	1	52	45 (86.5%)	–	–	NA	Harmful	8
Ferreira [34]	2006	NA	25	5	3 (60.0%)	–	–	NA	Harmful	9
Mathew [37]	2008	180	27	1	1 (100.0%)	–	–	NA	Harmful	9
Morris [43]	2009	NA	2	12	6 (50.0%)	–	–	NA	Harmful	14
Szmulewitz [44]	2009	NA	2	15	12 (80.0%)	–	–	NA	Harmful	14
Total population				118		0				

TRT: testosterone replacement therapy, FU: follow-up, No.: number, RR: relative risks, NA: not available.
[a]Evaluated using Methodological Index for Non-Randomized Studies (*MINORS*) [24]; [b]Estimated from the expected events per 100-person years; [c]Only published in abstract forms.

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Table 3. Effect of TRT on oncologic outcomes in men with local definitive treatment according to risk groups

Study	Year	Median FU from diagnosis (mo)	Median FU from TRT (mo)	TRT-treated arm		TRT-untreated arm		RR of TRT	TRT effect on prognosis	Study quality assessment (0–24)[a]
				No. of patient	Progression (%)	No. of patient	Progression (%)			
Low-risk disease										
Kaufman [7]	2004	NA	17	6	0 (0.0%)	–	–	NA	Harmless	7
Agarwal [33]	2005	NA	19	2	0 (0.0%)	–	–	NA	Harmless	8
Sarosdy [35]	2007	NA	60	22	0 (0.0%)	–	–	NA	Harmless	13
Nabulsi [38][b]	2008	31	20	12	0 (0.0%)	–	–	NA	Harmless	11
Pushkar [39]	2008	NA	15 (mean)	13	0 (0.0%)	–	–	NA	Harmless	9
Khera [40]	2009	53.2 (mean)	17.2 (mean)	24	0 (0.0%)	–	–	NA	Harmless	11
Morales [41]	2009	NA	6	1	0 (0.0%)	–	–	NA	Harmless	8
Pastuszak [51]	2013	NA	29.7	4	0 (0.0%)	–	–	NA	Harmless	9
Pastuszak [52][c]	2013	27.5/16.5 (control)	15.2	77	0 (0.0%)	35	0 (0.0%)	1.0	Harmless	16
Balbontin [53]	2014	NA	31	16	0 (0.0%)	–	–	NA	Harmless	9
Nakano [55]	2014	69	33	1	0 (0.0%)	–	–	NA	Harmless	4
Wynia [56][b,c]	2014	NA	24	57	1 (1.8%)	54	8 (14.8%)	0.12	Harmless	11
Kühn [58]	2015	71	39.8	20	0 (0.0%)	–	–	NA	Harmless	10
Pastuszak [59]	2015	NA	40.8	47	0 (0.0%)	–	–	NA	Harmless	10
Ory [61]	2016	NA	41	13	0 (0.0%)	–	–	NA	Harmless	10
Total population				315		89				
Intermediate-risk disease										
Kaufman [7]	2004	NA	12	1	0 (0.0%)	–	–	NA	Harmless	7
Agarwal [33]	2005	NA	19	7	0 (0.0%)	–	–	NA	Harmless	8
Sarosdy [35]	2007	NA	60	6	0 (0.0%)	–	–	NA	Harmless	13
Nabulsi [38][b]	2008	31	20	7	0 (0.0%)	–	–	NA	Harmless	11
Pushkar [39]	2008	NA	15 (mean)	3	0 (0.0%)	–	–	NA	Harmless	9
Khera [40]	2009	44.8 (mean)	8.8 (mean)	26	0 (0.0%)	–	–	NA	Harmless	11
Morales [41]	2009	NA	7	1	0 (0.0%)	–	–	NA	Harmless	8
Pastuszak [51]	2013	NA	29.7	7	0 (0.0%)	–	–	NA	Harmless	9
Balbontin [53]	2014	NA	31	3	0 (0.0%)	–	–	NA	Harmless	9
Kühn [58]	2015	71	39.8	8	0 (0.0%)	–	–	NA	Harmless	10
Pastuszak [59]	2015	NA	40.8	28	2 (7.1%)	–	–	NA	Harmless	10
Ory [61]	2016	NA	41	29	1 (3.4%)	–	–	NA	Harmless	10
Total population				126		0				

Table 3. Continued

Study	Year	Median FU from diagnosis (mo)	Median FU from TRT (mo)	TRT-treated arm		TRT-untreated arm		RR of TRT	TRT effect on prognosis	Study quality assessment (0–24)[a]
				No. of patient	Progression (%)	No. of patient	Progression (%)			
High-risk disease										
Agarwal [33]	2005	NA	19	1	0 (0.0%)	–	–	NA	Harmless	8
Sarosdy [35]	2007	NA	60	3	1 (33.3%)	–	–	NA	Harmful	13
Nabulsi [38][b]	2008	31	20	1	1 (50.0%)	–	–	NA	Harmful	11
Khera [40]	2009	43 (mean)	8 (mean)	4	0 (0.0%)	–	–	NA	Harmless	11
Morales [41]	2009	NA	18	3	1 (33.3%)	–	–	NA	Harmful	8
Pastuszak [51]	2013	NA	29.7	2	1 (50.0%)	–	–	NA	Harmful	9
Pastuszak [52]	2013	27.5/16.5 (control)	15.2	26	4 (15.4%)	15	8 (53.3%)	0.29	Harmless	16
Balbontin [53]	2014	NA	31	1	0 (0.0%)	–	–	NA	Harmless	9
Kühn [58]	2015	71	39.8	4	0 (0.0%)	–	–	NA	Harmless	10
Pastuszak [59]	2015	NA	40.8	11	2 (18.2%)	–	–	NA	Harmful	10
Ory [61]	2016	NA	41	29	2 (6.9%)	–	–	NA	Harmless	10
Total population				85		15				
Miscellaneous										
Davila [36][b]	2008	57–74 (mean)	9–12 (mean)	20	0 (0.0%)	–	–	NA	Harmless	10
Isbarn [45][b]	2010	43	19	69	0 (0.0%)	–	–	NA	Harmless	5
Sathyamoorthy [47][b]	2010	NA	8 (mean)	130	0 (0.0%)	–	–	NA	Harmless	9
Morgentaler [62][b]	2018	NA	47–52 (mean)	142	7 (4.9%)	–	–	NA	Harmless	9
Total population				391		0				

TRT: testosterone replacement therapy, FU: follow-up, No.: number, RR: relative risks, NA: not available.
[a]Evaluated using Methodological Index for Non-Randomized Studies (*MINORS*) [24]; [b]Only published in abstract forms; [c]Low to intermediate risk group.

for advanced disease (Table 2). The effects of TRT on the prognosis of the patients in each study were assessed and the qualities of evidences were evaluated. In studies with local-intent modalities such as radical prostatectomy or radiation therapy, the effects of TRT on oncologic outcomes were assessed according to the risk groups (low, intermediate, and high; Table 3).

2) Secondary analysis (meta-analysis)

Using the double-armed studies, quantitative synthesis was performed to assess the risk of progression of prostate cancer in patients receiving TRT (Fig. 1). As a summarizing statistic for meta-analysis, the pooled RR was utilized. Owing to the relatively small number of selected studies, a fixed-effects model was adopted for meta-analysis. Weights between the studies were estimated using the Mantel–Haenszel method to obtain the summary with a pooled RR and its 95% confidence interval (CI) [25]. A pooled RR >1 indicated increased risks for disease progression in the study group (TRT-treated group) relative to the reference group (TRT-untreated group), and would be considered statistically significant if the 95% CI did not overlap the pooled MD value of one, with $p<0.05$. Inter-study heterogeneity was assessed using the Higgin's H-test (I^2 statistic) [26] and heterogeneity χ^2 test [27], and $p>0.05$ indicated the absence of significant heterogeneity. Possibilities of publication bias were assessed by drawing a funnel plot [28]. A non-commercialized software (RevMan version 5.3.5; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) was used for data synthesis.

5. Ethics statement

The present study protocol waived the requirement for approval by the institutional review board, because we reviewed and analyzed already published articles.

RESULTS

A methodological flow chart of the entire systematic review process is shown in Fig. 2. Our search strategy identified 208 articles (PubMed, 78 articles; Embase, 124 articles; Cochrane library database, 6 articles). Additionally, 29 articles were found by manual searching. After removal of duplicates, 205 abstracts were independently screened by three independent reviewers. After abstract screening, 125 articles were included for full text assessment. After careful review of the full articles, 89 articles were excluded for the following reasons: 37 were review articles, 12 were letters to the editor, 12 were out of scope, 15 covered the relevant subject but failed to satisfy the inclusion criteria in detailed methodology, 2 lacked eligibility data, and 11 studies were excluded owing to duplication of population. Eventually, 36 studies were selected for the narrative systematic review [7,8,29-62]. Among them, four studies had a double-armed design [52,54,56,60]; quantitative synthesis was performed using these studies to assess the risk of prostate cancer progression in patients receiving TRT.

1. Characteristics of included studies

The characteristics of the eligible studies are shown in Table 1. The 36 eligible studies included 2,459 TRT-treated patients, with a median number of 20 TRT-treated patients per study (range: 1–1,142). None of the selected studies were randomized prospective studies. Of the 36 included studies, two were single-armed prospective studies [43,44], four were double-armed retrospective studies [52,54,56,60], and the remaining studies had single-armed retrospective features (case

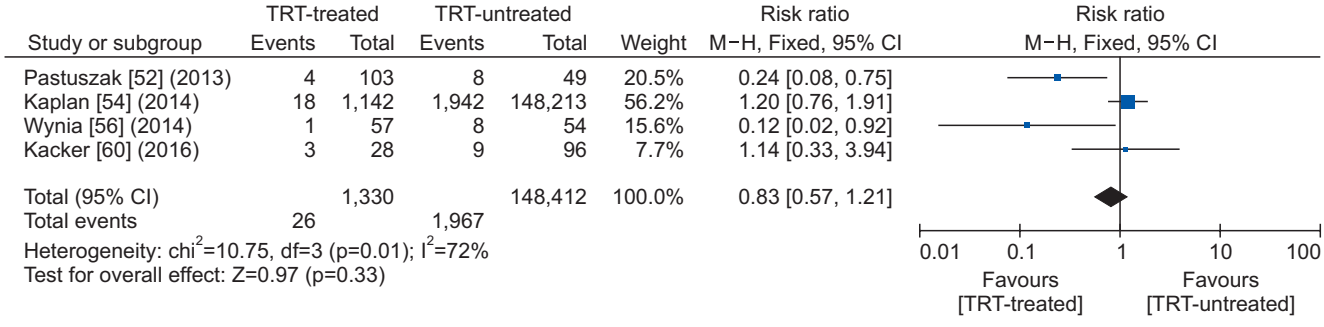

Fig. 1. A forest plot assessing the risk ratio for prostate cancer progression in patients with or without testosterone replacement therapy (TRT), using the fixed-effects model. M–H: Mantel–Haenszel, CI: confidence interval, df: degree of freedom.

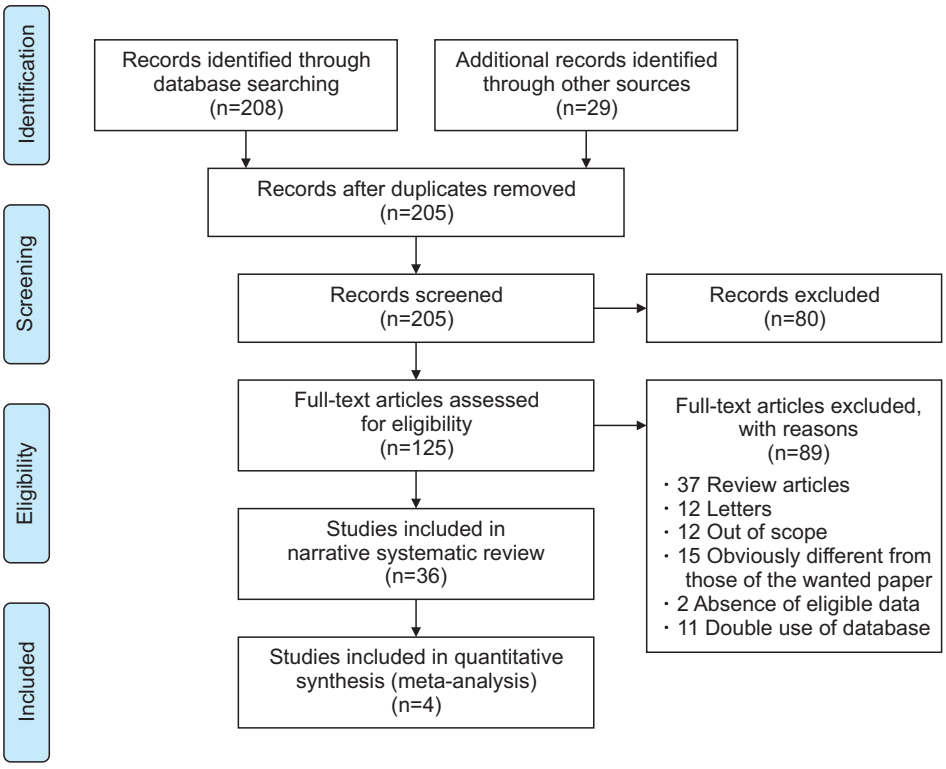

Fig. 2. Methodological flow chart of the systematic review.

series or case reports) [7,8,29-42,45-51,53,55,57-59,61,62]. Patients underwent active surveillance in 5 of the 36 studies [42,48,49,57,60], radical prostatectomy in 11 studies [7,33,38-40,45,47,50,52,55,56], radiation therapy in 5 studies [35,41,51,53,59], multiple intervention modalities in 6 studies [36,46,54,58,61,62], and systemic therapy in 9 studies [8,29-32,34,37,43,44], for the management of underlying prostate cancer. Except for some old studies conducted in the pre-PSA era [8,29-32], a database study [54], and a study with active surveillance [57], almost all studies utilized PSA as an oncologic outcome parameter [7,33-53,55,56,58-62]. As almost all included studies had single-armed retrospective feature, the quality scores measured by the MINOR criteria [24] were extremely low (median, 9 [range: 4–16]; Table 1). There was no significant correlation between population size and quality scores (p=0.330, by Pearson's correlation analysis).

2. Evidences for effects of testosterone replacement therapy in patients with active surveillance

Existing evidences for TRT in patients with active surveillance comprised 6 studies, which including a total of 115 TRT-treated patients, and 90 TRT-untreated controls (Table 2) [42,48,49,57,60-62]. Among the 6 included studies, only one was designed as a double-armed study [60], and all others were case reports or case series [42,48,49,57,61,62]. The median quality score of the six studies was as low as 9 (range: 5–15). Of the six studies, the results of two studies implied that TRT might have harmful effects on the prognosis of patients with active surveillance (progression rate: 15.4%–57.1% during 30–33 months of follow-up; Table 2) [48,49].

3. Evidences for effects of testosterone replacement therapy in patients with radical prostatectomy

Evidences for effects of TRT in patients with radical prostatectomy comprised 15 studies, which included a total of 697 TRT-treated patients and 103 TRT-untreated controls (Table 2) [7,33,36,38-40,45,47,50,52,55,56,58,61,62]. All the included 15 studies implied that TRT might be harmless in patients with radical prostatectomy (progression rate: 0.0%–6.5% during 8–52 months of follow-up; Table 2). However, all included studies were case reports or case series, except for two double-armed retrospective studies [52,56], with poor quality scores (median MINOR score, 10 [range: 4–16]; Table 2).

4. Evidences for effects of testosterone replacement therapy in patients with radiation therapy

Evidences for effects of TRT in patients with radiation therapy comprised 9 studies, which included a total of 275 TRT-treated patients (Table 2) [35,36,41,51,53,58,59,61,62]. As all included studies were case series, this study population had no TRT-untreated controls, and the median quality score was as low as 10 (range: 8–13). Of the nine studies, the results of one study implied that TRT might have harmful effects on the prognosis of patients with radiation therapy (progression rate: 20.0% during 15 months of follow-up; Table 2).

5. Evidences for effects of testosterone replacement therapy in patients with advanced disease

Evidences for TRT in patients with advanced disease comprised 9 studies, which included a total of 118 TRT-treated patients (Table 2) [8,29-32,34,37,43,44]. As all included studies were single-armed studies (Four case reports [8,29,31,37], three case series [30,32,34], and two phase I trials [43,44]), this study population had no TRT-untreated controls, and the median quality score was as low as 8 (range: 5–14). Of the nine studies, the results from seven studies implied that TRT might have harmful effects in the prognosis of patients with advanced disease (progression rate: 38.5%–100.0% during 0.1–27.0 months of follow-up; Table 2).

6. Other evidences for effects of testosterone replacement therapy in patients with prostate cancer

Data from two studies on the effects of TRT in patients with multiple modalities could not be processed separately according to the type of treatment modality (Table 2) [46,54], because one study failed to present the oncologic outcomes according to the treatment modality [46], and the other was a database study [54]. Underlying prostate cancers were managed with active surveillance, radical prostatectomy, radiation therapy, or systemic therapy in these two studies [46,54]. One case series implied that TRT might have harmful effects on the prognosis of patients with multiple treatment modalities (progression rate: 42.7% during 15 months of follow-up); however, another database study implied that TRT might be harmless in these populations (relative risk for progression, 1.19; p=0.114; Table 2) [54].

7. Effects of testosterone replacement therapy in patients with local definitive treatments, according to risk group

Effects of TRT in patients with local definitive treatments such as radical prostatectomy or radiation therapy were re-assessed according to the disease risk (Table 3). Evidences for effects of TRT in patients with low-risk disease undergoing local treatment comprised 15 studies, which included a total of 315 TRT-treated patients and 89 TRT-untreated controls (Table 3) [7,33,35,38-41,51-53,55,56,58,59,61]. All the included 15 studies implied that TRT might be harmless for low-risk patients (progression rate: 0.0%–1.8% during 6–60 months of follow-up; Table 3). With regard to patients with intermediate-risk disease, 12 single-armed studies with a total of 126 TRT-treated patients were selected (Table 3) [7,33,35,38-41,51,53,58,59,61]. The results implied that TRT might be harmless for intermediate-risk patients (progression rate: 0.0%–7.1% during 7–60 months of follow-up; Table 3). On the contrary, with regard to patients with high-risk disease, 11 studies with a total of 85 TRT-treated patients and 15 TRT-untreated controls were selected (Table 3) [33,35,38,40,41,51-53,58,59,61]. Of the 11 studies, the results from 5 studies implied that TRT might be harmful for patients with high-risk disease (progression rate: 18.2%–50.0% during 18–60 months of follow-up; Table 3). However, as previously mentioned, most of the included studies were single armed, with low quality scores (low-risk, 10; intermediate-risk, 9.5; high-risk, 10).

8. Effects of testosterone replacement therapy in patients with prostate cancer: results of a meta-analysis

Of the 36 included studies, four studies were double armed [52,54,56,60]. Underlying prostate cancers were managed with active surveillance in one study [60], radical prostatectomy, in two studies [52,56]; and multiple modalities, in one study [54] (Table 1). Fig. 1 summarizes the result of comparisons between the TRT-treated and TRT-untreated patients. In comparison with TRT-treated and untreated patients, the pooled RR was not significantly higher than one in comparisons of risk for disease progression (pooled RR, 0.83; 95% CI, 0.57–1.21; studies, 4). This implies that compared to TRT-untreated patients, TRT-treated patients

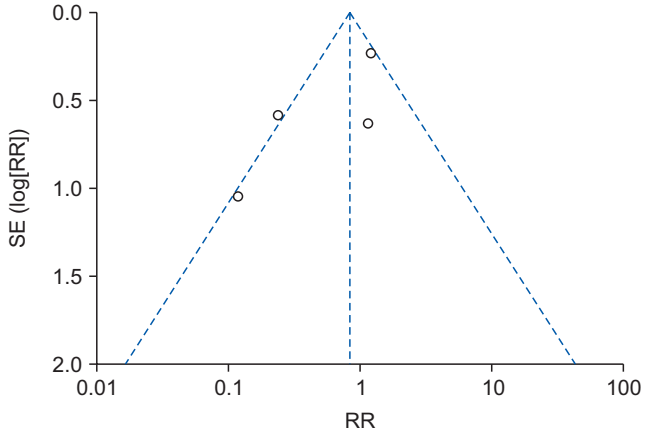

Fig. 3. A funnel graph of the assessment of potential publication bias in studies assessing the risk ratio (RR) for prostate cancer progression in patients with or without testosterone replacement therapy. SE: standard error.

do not have increased risks for disease progression. Despite our attempt to limit inter-study heterogeneity through strict inclusion and exclusion criteria, the heterogeneity between overall treatment outcomes still remained (heterogeneity χ^2 test, p=0.01; I^2=72%; Fig. 1). However, there was no clear evidence of asymmetry in the funnel plot analysis (Fig. 3). Therefore, it can be concluded that there was no clear evidence of publication bias.

DISCUSSION

1. Testosterone replacement therapy and prostate cancer

Although no randomized controlled trials have been performed to assess TRT and the risk of prostate cancer, evidence to date fails to suggest an increased risk. Calof et al [63] conducted a meta-analysis of 19 placebo-controlled TRT trials and found no significant increase in prostate cancer. A systematic review of 11 placebo-controlled studies by Shabsigh et al [64] showed that men with prostate cancer who received TRT had neither increased risk of prostate cancer nor greater Gleason grade. At a physiologic level, the idea that TRT will not induce development of prostate cancer can be explained by the "saturation model" [65]. As per this theory, while a certain level of testosterone is required to stimulate prostatic growth, higher serum levels do not promote intra-prostatic cancerous growth because of androgen receptor (AR) saturation. This saturation model has been supported by a study that showed that the AR has a maximal binding level for androgen, which occurs at around 60–90 ng/dL [66], and the study demonstrated maintaining a stable intra-prostatic testosterone level irrespective of the levels of circulating testosterone by exogenous testosterone [67].

However, the safety of TRT in patients predisposed to prostate cancer could be a completely different concern. In 1941, Huggins and Hodges [8] already reported that exogenous testosterone stimulates prostate cancer cells, and therefore, leads to disease progression. Similarly, the study by Fowler and Whitmore [32] demonstrated that administration of exogenous testosterone to 52 men with metastatic prostate cancer has been associated with 87% of unfavorable responses. In contrast, men successfully treated for prostate cancer may not have had any residual cancer cells to be stimulated by androgens. In light of evidence that TRT may not be as harmful to men successfully treated for prostate cancer as once believed, several investigators have reported the use of TRT in men after curative treatment for prostate cancer from the mid-2000s [7,33,35].

2. Existing evidences for testosterone replacement therapy in prostate cancer

Our search strategy found 36 eligible studies as existing evidences for TRT in men with untreated and treated prostate cancer (Fig. 2, Table 1). Except for four studies [52,54,56,60], almost studies were single-armed case reports or series with small sample sizes (median number of TRT-treated patients, 20). Therefore, the quality scores measured by the MINOR criteria were also extremely low (median, 9; Table 1). Existing evidences of TRT in men after curative treatment (radical prostatectomy or radiation therapy) for prostate cancer demonstrated relatively good safety outcomes (Table 2). All studies of TRT in patients with radical prostatectomy (studies, 15; TRT-treated, 697 patients; TRT-untreated, 103 patients) implied that TRT might be harmless in patients treated with radical prostatectomy (progression rate: 0.0%–6.5%). Except for one study (progression rate: 20.0%) [41], all studies of TRT in patients with radiation therapy (studies, 8; TRT-treated, 270 patients; TRT-untreated, 0 patient) also demonstrated relatively good safety outcomes (progression rate: 0.0%–7.7%). However, it should be noted that currently available studies are underpowered and their duration is too short to detect any effects attributable to TRT (Table 2).

Using results from four double-armed studies, data synthesis was performed (Fig. 1). The results of our meta-analysis demonstrated that compared to TRT-untreated patients, TRT-treated patients do not have increased risks for disease progression (pooled RR, 0.83; 95% CI, 0.57–1.21; Fig. 1). Although our included studies showed no clear evidence of publication bias (Fig. 3), owing to the following limitations of our data, one should be careful when interpreting the results. First, the included studies were heterogeneous. Underlying prostate cancers were managed with active surveillance in one study [60], radical prostatectomy in two studies [52,56], and multiple modalities in one study (Table 1) [54]. Second, the sample size of one database study (TRT-treated, 1,142 patients; TRT-untreated, 148,213 patients) [54] was larger than those of the other three studies [52,56,60]. Therefore, the results of our meta-analysis are likely to converge to the results of a large-scale study (weight, 56.2%; Fig. 1).

These findings suggest that we do not yet have sufficient evidences for TRT in men with prostate cancer. Therefore, prospective studies are warranted to establish clear evidences for TRT in men with untreated or treated prostate cancer. Currently, an FDA-approved, randomized controlled trial in hypogonadal men is ongoing to investigate the effect of TRT initiated 3 months after radical prostatectomy (Baylor College of Medicine, ClinicalTrials.gov identifier NCT00848497) [68]. The results of these studies are expected to be an important evidence for TRT in men with prostate cancer.

3. Clinical implications of the current study

Despite the current study being a small-scale single-arm study with low quality, currently available evidences for TRT in men with prostate cancer suggest the following clinical implications. Firstly, TRT might be harmful in men with advanced disease. In our systematic review, seven of the nine studies demonstrated poor progression rates (38.5%–100.0%) following TRT (Table 2). This suggests that exogenous androgens may activate the remaining cancer cells.

Secondly, in men with prostate cancer who undergo active surveillance without definite treatment, caution should be exercised when performing TRT. Despite relatively small-scale underpowered studies (median number of TRT-treated patients, 8), considerable number of studies (2 of 6 studies) have reported high progression rates (15.4%–57.1%) in men with active surveillance after TRT (Table 2). These results suggest that untreated and remaining prostate cancer cells are likely to be activated and exacerbated by exogenous androgens even if the tumor is at an early stage, with low aggressiveness.

Lastly, even in men in whom prostate cancer has been successfully treated with curative modalities (radical prostatectomy or radiation therapy), attention should be paid to the use of TRT in high-risk disease. While all studies on TRT in men with low-risk (studies, 15; TRT-treated, 315 patients; TRT-untreated, 89 patients) and intermediate-risk disease (studies, 12; TRT-treated, 126 patients; TRT-untreated, 0 patient) implied that TRT might be harmless (progression rate: 0.0%–1.8% and 0.0%–7.1%), 5 of 11 studies on TRT in men with high-risk disease (TRT-treated, 85 patients; TRT-untreated, 15 patients) revealed relatively high progression rates (18.2%–50.0%; Table 3). Even after successful curative treatments (radical prostatectomy or radiation therapy), men with high-risk disease can harbor micrometastases, which cannot be detected by imaging. In these cases, the remaining cancer cells might be affected by exogenous androgens. In summary, TRT may be harmful in men with advanced disease burden, in men with untreated prostate cancer undergoing active surveillance, and in men who have been successfully treated for prostate cancer but had high-risk disease. However, prospective studies are warranted to confirm these hypotheses.

4. Limitations of the current study

However, our study has some limitations. First, as previously mentioned, none of the studies included in the current systematic review specified a randomized controlled study design. Therefore, it is difficult to draw any conformational conclusions even after the rigorous reviews. Nevertheless, the present study, which quantitatively assessed the currently available evidences for TRT in men with prostate cancer, is of relatively limited significance. Our result could provide some relevant implications for inadequate TRT candidates in men with prostate cancer. The results of our study can also provide some clues to design further prospective studies. Moreover, owing to the unavailability of sufficient number of studies for data synthesis (4 studies), sensitivity analysis could not be performed. More evidence is required to clarify those

points. Lastly, in our current meta-analysis, there was tremendous heterogeneity for the included studies (heterogeneity χ^2 test, p=0.01; I^2=72%; Fig. 1). Heterogeneity can be caused by numerous factors, such as inclusion criteria, type of treatment, sample size, follow-up period, oncologic outcome parameters, and adjustment for other co-factors. It is also very difficult to explain the inter-study heterogeneity owing to the variability in clinical characteristics across patients within studies. To reduce the heterogeneity-related bias, we adopted the fixed-effects model for data synthesis, which is known to draw more conservative results, and is fit for relatively small number of studies [69]. Despite the limitations, this is the first study to quantitatively analyze the existing evidence for TRT in men with untreated and treated prostate cancer. As a result, some clues about inappropriate patient populations for TRT could be found.

CONCLUSIONS

Even after the rigorous review, the quality of the currently available evidence was extremely poor. The results of our meta-analysis implied that compared to TRT-untreated patients, TRT-treated patients do not have increased risks for disease progression in prostate cancer. Our systematic review also implied that TRT may be harmful in men with advanced disease burden, in those with untreated prostate cancer undergoing active surveillance, and in those successfully treated for prostate cancer but having high-risk disease. Prospective studies are warranted to confirm these implications.

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Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: MK, SKH. Data curation: MK, SSB. Formal analysis: MK, SSB. Methodology: MK, SSB. Supervision: SKH. Writing – original draft: MK. Writing – review & editing: SKH.

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Appendix. Detailed query settings for search strategy

Search	Query
#1	Search "Prostatic Neoplasms"[MeSH]
#2	Search prostat* cancer
#3	Search prostat* carcinoma
#4	Search prostat* adenocarcinoma
#5	Search (#1 or #2 or #3 or #4)
#6	Search "Hormone Replacement Therapy"[MeSH]
#7	Search testosterone replacement
#8	Search testosterone therapy
#9	Search testosterone supplementation
#10	Search androgen replacement
#11	Search androgen therapy
#12	Search androgen supplementation
#13	Search (#6 or #7 or #8 or #9 or #10 or #11 or #12)
#14	Search (#5 and #13)
#15	Search "Hypogonadism"[MeSH]
#16	Search testosterone deficiency
#17	Search androgen deficiency
#18	Search (#15 or #16 or #17)
#19	Search (#14 and #18)
#20	Search "Watchful Waiting"[MeSH]
#21	Search surveillance
#22	Search "High-Intensity Focused Ultrasound Ablation"[MeSH]
#23	Search HIFU
#24	Search "Cryotherapy"[MeSH]
#25	Search cryo*
#26	Search focal therapy
#27	Search focal treatment
#28	Search "Prostatectomy"[MeSH]
#29	Search prostatectomy
#30	Search "Radiotherapy"[MeSH]
#31	Search radiation
#32	Search "Brachytherapy"[MeSH]
#33	Search brachy*
#34	Search "Drug Therapy"[MeSH]
#35	Search chemo*
#36	Search androgen deprivation
#37	Search hormone*
#38	Search (#20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37)
#39	Search (#19 and #38)

Presented as query form of PubMed.
Core logics of search queries were not different in other database searches.