

Review Article

Oncological safety of testosterone replacement therapy in prostate cancer survivors after definitive local therapy: A systematic literature review and meta-analysis

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Abstract

Aim: To evaluate the association between testosterone replacement therapy (TRT) in prostate cancer (CaP) patients who underwent definitive local therapy with curative intent with biochemical recurrence (BCR). **Materials and methods:** A literature search using PubMed, Scopus, Web of Science, and Cochrane Library was conducted on November 2018 to identify relevant studies according to the Preferred Reporting Items for Systematic Review and Meta Analysis guidelines. The pooled BCR rate in CaP men treated with TRT after definitive local therapy with curative intent was calculated using a random effects model. **Results:** Twenty-one studies were eligible. The overall pooled BCR rate was 0.01 (95%CI 0.00–0.02) suggesting a lack of association between TRT and BCR; there was no heterogeneity among included studies ($I^2 = 24.34\%$, $P = 0.15$). In subgroup analyses, pooled BCR rates were 0.00 (95%CI 0.00–0.02) in patients treated with radical prostatectomy and 0.02 (95%CI 0.00–0.04) in patients treated with external beam radiation therapy, brachytherapy, cryotherapy, or high intensity focused ultrasound; there was no heterogeneity in the subgroup analyses ($I^2 = 19.88\%$, $P = 0.18$). **Conclusions:** In this systematic review and meta-analysis, we did not observe higher rate of BCR after TRT for nonmetastatic CaP patients after definitive local therapy. Based on these data, others and we have outlined a phase I/II trial assessing the safety and benefits of TRT in select men with secondary symptomatic hypogonadism who have no active disease after definitive local CaP therapy with curative intent. © 2019 Elsevier Inc. All rights reserved.

Keywords: Prostate cancer; Testosterone Replacement therapy; Testosterone deficiency; Radical prostatectomy; Radiation therapy

1. Introduction

Prostate cancer (CaP) is an androgen-dependent tumor and the main treatment for the metastatic CaP is androgen

deprivation therapy (ADT) [1]. The average age at time of CaP diagnosis is 68 years, with approximately 20% to 30% of men in this age group estimated to suffer from secondary hypogonadism [2,3]. Testosterone replacement therapy (TRT) in symptomatic men with low testosterone due to secondary hypogonadism has shown to improve sexual function,

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mood symptoms, anthropometric parameters, and quality of life [4,5]. The treatment of secondary hypogonadal men with a history of CaP using testosterone supplements remains controversial because of its inherent oncologic risks [6]. Some studies have suggested, however, that TRT is oncologically safe in select patients harboring localized CaP [7–11]. Conclusions from these studies are limited by their rather small sample sizes, short-term follow-up, and heterogeneity in applied therapeutic modalities.

To better elucidate the potential oncological risks and safety of TRT in patients with symptomatic secondary hypogonadism who are considered cured after local therapy for nonmetastatic CaP, we performed a systematic review and meta-analysis. We hypothesized that TRT after CaP definitive therapy such as radical prostatectomy (RP) and radiation therapy (RT) with curative intent does not increase the risk of biochemical recurrence (BCR).

2. Materials and methods

2.1. Search strategy

A full electronic literature search using PubMed, Scopus, Web of Science, and Cochrane Library was conducted by 2 independent authors on November 2018 to find relevant studies for this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Review and Meta Analysis guidelines [12]. The search terms used were (“testosterone replacement therapy” OR “testosterone” OR “hormone replacement therapy”) AND (“prostate cancer” OR “radical prostatectomy” OR “radiation therapy” OR “brachytherapy” OR “cryotherapy” OR “HIFU” OR “definitive therapy”). The protocol for this systematic review was registered in PROSPERO (Prospective Register of Systematic Reviews, CRD42019121335) and is available in full on the University of York website.

2.2. Inclusion criteria

The following criteria were considered to select eligible studies: prospective or retrospective studies including full text or meeting abstracts regarding TRT for the management of testosterone deficiency among patients who underwent definitive therapy for nonmetastatic CaP with BCR as endpoint. Definitive therapeutic modalities included RP, external beam RT (EBRT), brachytherapy (BT), cryotherapy (CT) or high-intensity focused ultrasound (HIFU). We excluded studies in other than English language, case reports, review articles, replies, expert opinions or comment letters and studies that investigated TRT in patients with metastatic and/or untreated CaP or patients on active surveillance. Studies with heterogeneous patients population (e.g., active surveillance and RP) were included if it was possible to selectively extract the data of patients who received definitive therapy. In case of studies including the same

patient group, we chose the study with more up to date and complete data (e.g., full-text article in comparison with meeting abstract).

2.3. Data extraction

Data were extracted on first author, year of publication, total number of patients, country of study, CaP therapeutic modality, study design, BCR definition, BCR rate, patients' age, CaP risk stratification, time to initiate TRT after definitive therapy, TRT duration, serum testosterone level before and after TRT, serum prostate-specific antigen (PSA) level before and after TRT, follow-up duration, TRT efficacy on sexual function, and type of testosterone product. BCR was the primary outcome.

2.4. Statistical analyses (and risk of bias assessment)

The random effects model with exact confidence intervals was used. Many articles reported a zero rate of BCR, therefore a Freeman-Tukey double arcsine transformation was used to allow inclusion of studies with zero cases of BCR. Metaprop tool in Stata 14 (Stata-Corp., College Station, TX) was employed. In this meta-analysis, we did not consider the exact value of post-treatment serum PSA to compare 2 groups. But we divided patients into 2 groups (positive and negative BCR) according to the used BCR definition based on the type of therapeutic modality. Heterogeneity among the results of the studies was evaluated by I^2 criteria. An $I^2 > 50\%$ with $P < 0.05$ implied that heterogeneity existed. The Begg's test was used for publication bias assessment. We used validated institute of health economics quality appraisal checklist to assess the quality of the study [13].

3. Results

3.1. Literature search process

A total of 13,099 studies were found after an initial search; 9,747 records remained after exclusion of duplicates (Fig. 1). After exclusion of nonrelevant studies, review articles, case reports, comments, expert opinions, replies, and studies in other than English language, 26 studies remained. Finally, 21 studies (11 full-text articles and 10 meeting abstracts) were included for qualitative and quantitative evidence synthesis.

3.2. Characteristics of the included studies

Tables 1 and 2 summarize the studies' characteristics and patients' clinical data, respectively. Three studies were designed prospectively [8,14,15], and 18 studies were retrospective in design [7,9–11,16–29]. All studies were published between 2004 and 2018. In total, 1,084 patients with a history of TRT after definitive local therapy for

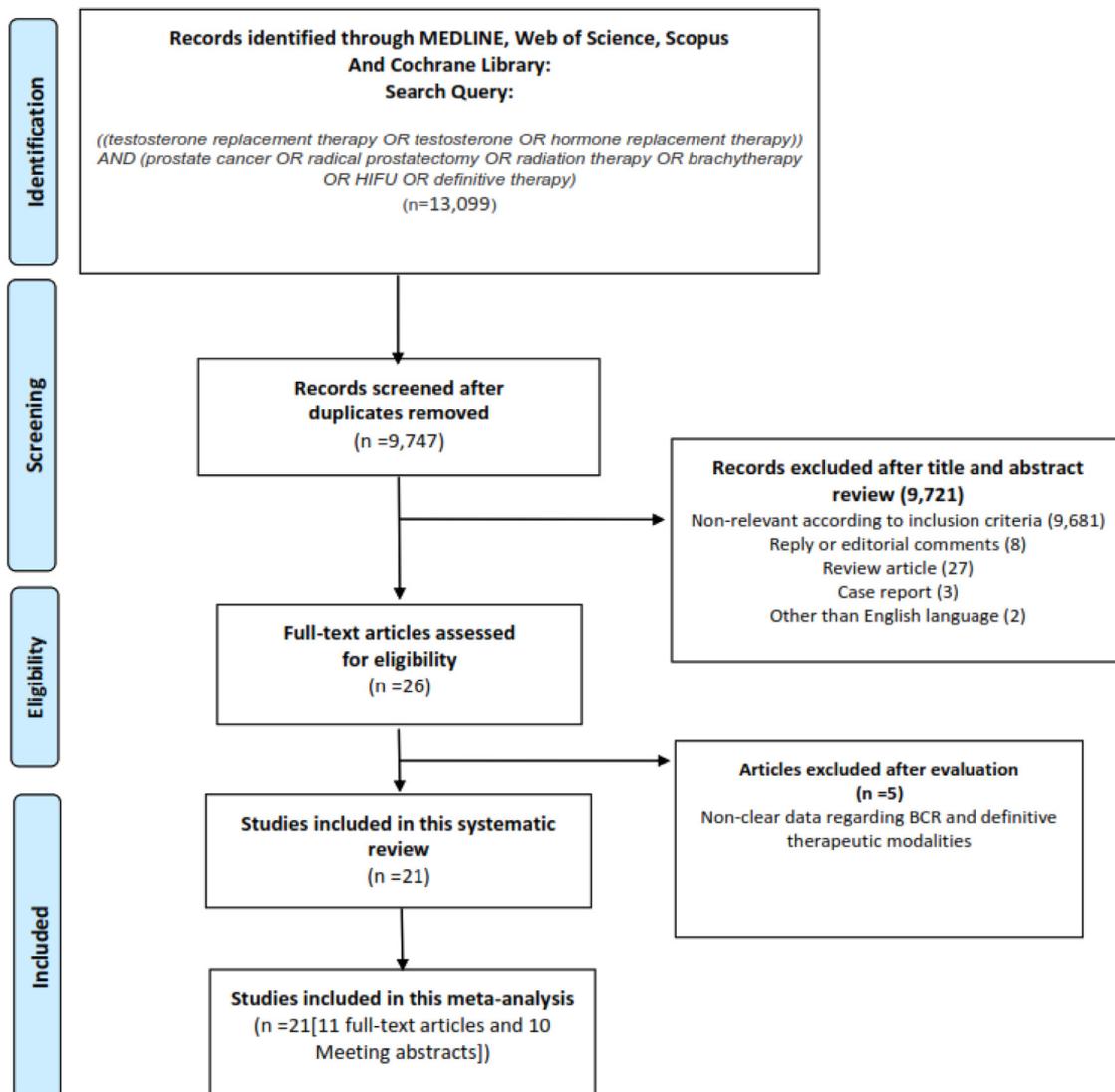


Fig. 1. PRISMA flow chart for article selection process to analyze the safety of testosterone replacement therapy after definitive local therapy for patients with nonmetastatic prostate cancer.

nonmetastatic CaP were included: 733 patients underwent RP and 351 underwent other therapeutic modalities such as EBRT, BT, CT, or HIFU. From 18 studies with available data, 15 came from North America, 2 from Germany, and 1 from Chile.

Five studies included patients who had been treated with both RP and other therapeutic modalities prior to TRT. Ten studies included RP only patients and 6 included patients treated with other therapeutic modalities.

Sixteen studies reported the patients' Gleason score (GS) with information available in 328 cases: GS ≤ 6 , 7 and ≥ 8 were each found in 175 (53%), 124 (38%), and 29 (9%) patients, respectively. Ten of 13 studies that reported GS, included also high-risk CaP cases with a GS ≥ 8 . Fourteen studies reported the time between definitive local therapy for CaP and start of TRT ranging from 1 month to 17.2 years. Nine studies reported

the duration of TRT after CaP treatment with an upper limit of TRT duration of 102 months. Ten of 21 studies reported on serum testosterone levels after TRT; all reported a statistically significant increase in serum testosterone levels after TRT.

TRT efficacy was evaluated in 6 studies [7,8,14,18,25,28]. Four studies used validated questionnaires and 2 studies relied on subjective reporting. The Expanded Prostate Cancer Index Composite (EPIC), Sexual Health Inventory for Men (SHIM), and Androgen Deficiency in the Aging Male questionnaires were each used in 4 studies. Agarwal et al. found significant improvement among 10 TRT treated patients after RP using the EPIC questionnaire (EPIC questionnaire score mean \pm SD: 38 ± 5 to 49 ± 3 [$P = 0.00005$]) [7]. Balbontin et al. used SHIM questionnaire to assess erectile function before and after TRT. The authors demonstrated significant improvement from a mean baseline SHIM score of 17.8 to

Table 1
Summary of studies' characteristics for testosterone replacement therapy in prostate cancer patients with a history of definitive local treatment.

Author	Year	Region	N ^a	Study type	Full text/meeting abstract	BCR definition	IHE QA score (0–18)
Kaufman et al. ⁹	2004	USA	7	Retrospective	Full text	PSA \geq 0.1 ng/ml	9
Agarwal et al. ⁷	2005	USA	10	Retrospective	Full text	PSA \geq 0.1 ng/ml	8
Sarosdy et al. ²⁰	2007	USA	31	Retrospective	Full text	NA ^c	10
Khera et al. ²⁵	2007	USA	21	Retrospective	Meeting abstract	NA	8
Morales et al. ¹⁴	2008	Canada	5	Prospective	Full text	NA ^b	9
Davila et al. ²¹	2008	NA	20	Retrospective	Meeting abstract	NA	7
Nabulsi et al. ¹⁵	2008	NA	22	Prospective	Meeting abstract	NA	9
Khera et al. ¹⁰	2009	USA	57	Retrospective	Full text	PSA \geq 0.1 ng/ml	10
Isbarn et al. ²²	2010	Germany	69	Retrospective	Meeting abstract	NA	6
Sathyamoorthy et al. ²⁷	2010	USA	133	Retrospective	Meeting abstract	NA	7
Matsushita et al. ²⁴	2012	USA	61	Retrospective	Meeting abstract	NA	8
Pastuszak et al. ¹⁸	2013	USA	13	Retrospective	Full text	NA [†]	11
Pastuszak et al. ¹⁹	2013	USA	103	Retrospective	Full text	PSA \geq 0.2 ng/ml	11
Balbontin et al. ⁸	2014	Chile	20	Prospective	Full text	'nadir +2 ng/mL' PSA threshold (Phoenix definition)	11
Wynia et al. ²⁸	2014	USA	57	Retrospective	Meeting abstract	NA	8
Kacker et al. ²³	2014	NA	93	Retrospective	Meeting abstract	RP: PSA > 0.2 ng/ml, RT: Phoenix definition	5
Berookhim et al. ²⁹	2015	USA	13	Retrospective	Meeting abstract	Phoenix criteria	8
Kuhn et al. ¹¹	2015	Germany	32	Retrospective	Full text	PSA > 0.2 ng/ml, confirmed at least twice after RP. A rise in the PSA level of >2 ng/ml over the nadir at least twice after RT.	8
Pastuszak et al. ¹⁷	2015	USA	98	Retrospective	Full text	(1) PSA greater than absolute nadir plus 2 ng/ml, (2) PSA greater than current nadir plus 3 ng/ml, (3) two consecutive increases in PSA of \geq 0.5ng/ml	11
Ory et al. ¹⁶	2016	Canada	74	Retrospective	Full text	RP: postop PSA > 0.2ug/l/ RT: Phoenix definition	9
Morgentaler et al. ²⁶	2018	USA	145	Retrospective	Meeting abstract	PSA \geq 0.3 ng/ml after RP. Phoenix definition for EBRT or BT	5

BT = brachytherapy; BCR = biochemical recurrence; EBRT = external beam radiation therapy; IHE QA = institute of health economics quality appraisal; NA = not available; PSA = prostate specific antigen; RP = radical prostatectomy; RT = radiation therapy.

^a In studies with control group, "N" presents the patients that underwent TRT.

^b The 0% of BCR rate is presented according to the Phoenix definition.

^c Reported 0% of BCR rate based on "1 mg/dl" cut point for PSA.

Table 2

Results of testosterone replacement therapy in hypogonadal men treated with definitive local prostate cancer therapeutic modalities.

Author	CaP therapeutic Modality (n)	Age, year (range or SD)	BCR cases ^a	Gleason score (n)	Time to initiate TRT after CaP treatment, months (range)	Duration of TRT, months (range)	Testosterone, ng/dl before/after TRT (range)	PSA, ng/ml before TRT/after TRT (range)	Mean/Median Follow-up, months (range)
Kaufman et al. ⁹	RP (7)	Mean: 62.2 (50–70)	0	6(6), 7(1)	NA	NA	Mean: 97.2 (19-269)/434.3 (214–740)	<0.1/ <0.1	Range: 12–144 after RP
Agarwal et al. ⁷	RP (10)	Mean: 64 (59–69)	0	6(2), 7(7), 8(1)	More than 12	Median: 19	Mean: 197/591	<0.1/<0.1	Median: 19 after TRT initiation
Sarosdy et al. ²⁰	BT(20), BT + EBRT(11) [BT ± EBRT + ADT (14)]	Median: 65 (51–79)	0	5(3), 6(19), 7(6), 8 or 9(3)	Median: 24 (6–54)	Median: 54 (6–102)	Median: 188 (30–255)/498(365–1373)	Median: 5.3(0.4–74)/ <1	Median: 60 (18–108) after BT
Khera et al. ²⁵	RP (21)	Mean: 63.1 (51–80)	0	Mean GS: 6.4	Mean: 54.4 (1–181)	NA	Mean: 275/440	Mean: 0.005/ 0.005	Mean: 12 (1–60) after TRT initiation
Morales et al. ¹⁴	EBRT (5)	Mean: 65 (52–75)	0	6(2), 7(1), 8(2)	NA	14.5 (6–27)	Mean: 50 (32–265)/507.2 (244.9–933.7)	Mean: 0.3 (0.1–0.97)/0.47 (0.1–1.08)	Mean: 14.6 (6–27) after TRT initiation
Davila et al. ²¹	RP(14), EBRT(6)	Mean: 69 in RP group,66 in RT group	0	Mean GS: 6.2 in RP cases and 5 in RT cases	NA	NA	Mean: 291 for RP and 279 for EBRT/ 630 for RP and 834 for EBRT	Mean: 0.1for RP,0.15 for EBRT/ 0.1 for RP, 0.1 for EBRT	Mean: 12 for RP, 9 for EBRT
Nabulsi et al. ¹⁵	RP (22)	Mean: 61(±9)	1	≤6 (58%), 7(32%)	Median: 11 (2.5–118)	Mean:24 Median: 20 (14–30)	Mean: 228/427	NA/ NA	Median: 20 (14–30) after TRT initiation
Khera et al. ¹⁰	RP (57)	Mean: 64 (53–83)	0	≤6 (24), 7 (26) ≥8 (4) Missing data (3)	Mean: 36 (1–136)	NA	Mean: 255/459	<0.1/ <0.1	Mean: 13 (1–99) after TRT initiation
Isbarn et al. ²²	RP (69)	Median: 56	0	NA	Median: 24	≥6	Median: 2.9/NA	Mean: <0.1/ <0.1	Median: 19 (6–72)
Sathyamoorthy et al. ²⁷	RP (133)	Mean: 64.9	0	NA	NA	NA	Mean: 262/418	Mean: 0.003/ 0.01	≥363 days
Matsushita et al. ²⁴	RP (61)	Mean: 62 (±8)	1	Median GS:7	Mean: 26	NA	Mean: 239/691	UD/ NA	Mean: 25 after TRT initiation
Pastuszak et al. ¹⁸	EBRT(10), BT(3), EBRT + ADT (4)	Median: 68.0 (62.0–77.0)	0	6(4), 7(7), 8(2)	Median: 13.5 (2.6–170.9)	Median: 29.7 (2.3–67.3)	Median: 178.0 (88.0–263.5)/667.5 (472.8–772.5)	Median: 0.30 (0.06–0.95)/ 0.66 (0.16–1.35)	Median: 29.7 (2.3–67.3) after TRT initiation
Pastuszak et al. ¹⁹	RP (103 hypogonadal cases)	Median: 61.0 (55.0 –67.0)	4 (in TRT group)	NA	Mean: 12.3 (7.8–16.8)	NA	Median: 261.0 (213.0–302.0)/NA	Median: 0.004 (0.002–0.007)/ NA	Median: 27.5 (6.2–189.3)
Balbontin et al. ⁸	BT (20)	Mean: 63.5 (49–74)	0	≤6(16), 7(3), 8(1)	Mean: 14 (3–36)	≥ 12	Mean: 313 (106–592)/ 587 (330–985)	Mean: 0.7 (0.58 –8.21)/ 0.1	Median: 31 (12–48) after TRT initiation

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Table 2 (Continued)

Author	CaP therapeutic Modality (n)	Age, year (range or SD)	BCR cases ^a	Gleason score (n)	Time to initiate TRT after CaP treatment, months (range)	Duration of TRT, months (range)	Testosterone, ng/dl before/after TRT (range)	PSA, ng/ml before TRT/after TRT (range)	Mean/Median Follow-up, months (range)
Wynia et al. ²⁸	RP (57)	NA	1	TRT group: 6(24), 7(33) control group: 6(20), 7(34)	NA	NA	Mean: 265/550	Mean: 0.005/NA	Median: 24
Kacker et al. ²³	AS(33), RP(53), EBRT or BT (40)	Mean: 64(±9)	RP (0), EBRT or BT (2)	NA	NA	NA	NA	NA/ NA	Mean: 31.2 for AS/ 30 for RP/ 26.7 for RT, EBRT or BT
Berookhim et al. ²⁹	EBRT(7), BT(3), EBRT + BT(3)	Mean: 63	0	6(8), 7(4), 9(1)	Mean: 92.4 (14.4–206.4)	NA	Mean: 211 (22–462)/591 (353–1056)	Mean: 0.2 (0.05–1.5)/ 0.4 (0.05–1.7)	Mean:20 (1–70)
Kuhn et al. ¹¹	RP(26), EBRT(1), BT(3), HIFU(2)	Mean: 65.6 (51–80)	0	≤6 (20), 7 (8) ≥8 (4)	Median: 40.3 (3–108)	Mean: 31.2 (2–108)	Median: 70.8 (0.1–319)/ NA	Median: 0.17 (0–4.37)/ RP:0.01 (0–0.11), RT:0.23 (0–1.1)	Mean: 39.8 (12–108)
Pastuszak et al. ¹⁷	EBRT(16), BT (25), EBRT + ADT (16), BT + ADT(21), BT + EBRT(7), BT + EBRT + ADT(13)	Median: 70 (63.0–74.3)	6 (2 BT, 1 EBRT, 1EBRT +ADT, 2BT +ADT)	5(3), 6(44), 7(28), 8(7), 9(4), missing data (12)	Median: 28.6 (13.8–40.4)	NA	Median: 209.0 (152–263)/ 420.0 (231–711)	Median: 0.08 (0.00 –0.33)/ 0.09 (0.00–0.60)	Median: 40.8 (1.5–147.4)
Ory et al. ¹²	RP(22), EBRT (37), BT(13), AS(8) HIFU(1), CT(1)	Median: 75.5 (70–82)	3 case in RT group	6(32), 7(39), 8(7), 9(4)	Median: RP:15 RT:45 AS:NA HIFU:4 CT:17	Median: RP:48 RT:36 AS:33 HIFU:4 CT:9	Median: 182 (131-222)/ 380 (221–599)	Median: RP: UD, RT:0.125, AS:3.9, HIFU:0.26, CT:1.1/RP: UD RT:0.18, AS:5.2, HIFU:1.2, CT:3.2	Median: 41 (22–57)
Morgentaler et al. ²²	RP(92), EBRT or BT (50), HIFU(3),AS(57)	Mean: 68 (41–88)	RP(6), EBRT or BT(1), HIFU(2)	NA	NA	NA	NA/ NA	NA/ NA	Mean: 47

ADT = androgen deprivation therapy; AS = active surveillance; BCR = biochemical recurrence; BT = brachytherapy; CaP = prostate cancer; CT = cryotherapy; EBRT = external beam radiation therapy; GS = Gleason score; HIFU = high-intensity focused ultrasound; NA = not available; PSA = prostate specific antigen; RP = radical prostatectomy; RT = radiation therapy; TRT = testosterone replacement therapy; UD = undetectable.

^aThe number presents BCR in patients that underwent TRT and definitive therapy.

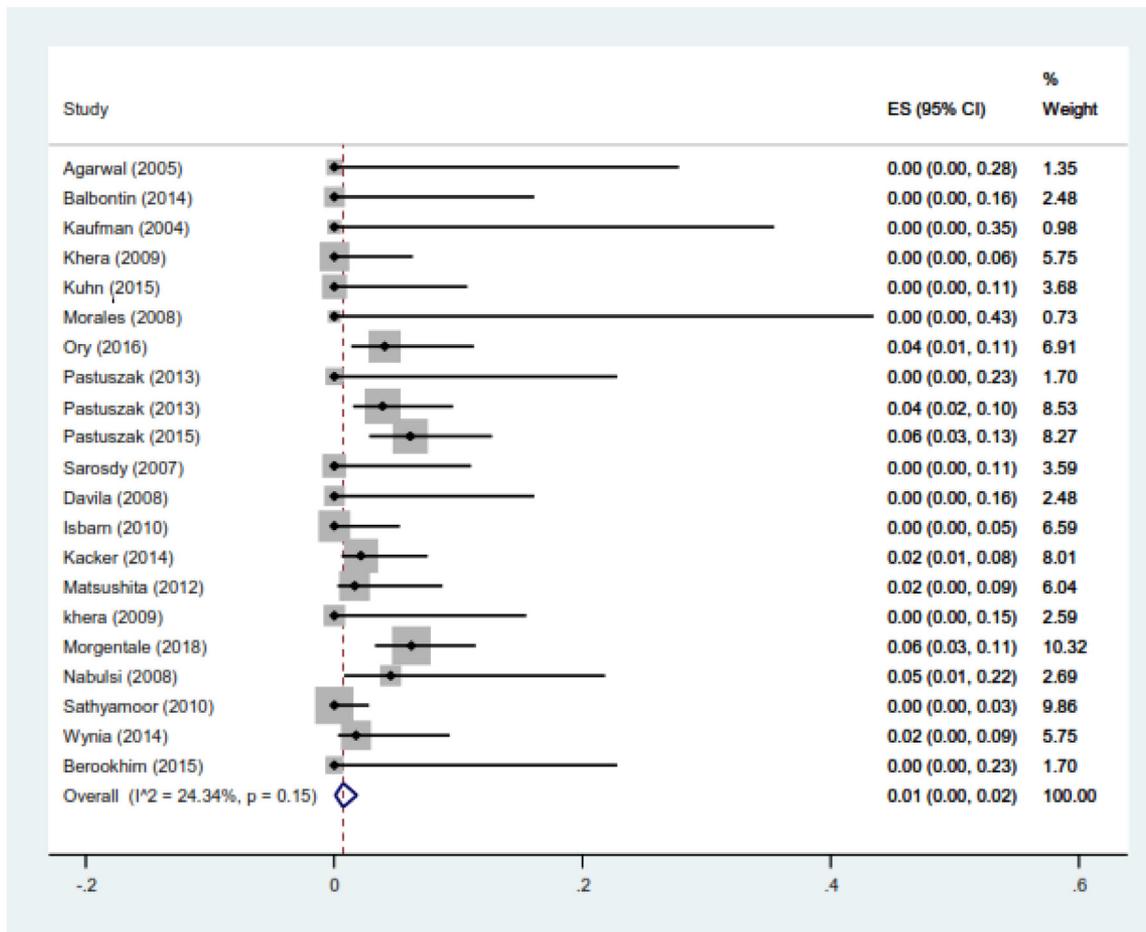


Fig. 2. Forest plot showing the rate of biochemical recurrence after testosterone replacement therapy in prostate cancer patients with a history of definitive local therapy.

22.1 after TRT ($P = 0.002$) [8]. Khera et al. reported that one of 11 patients who could be contacted by telephone had a good response after TRT as suggested by a decrease in his Androgen Deficiency in the Aging Male Score (4.6 ± 2.2 to 0.9 ± 1.1 , $P < 0.01$) [25]. Finally, a 87.5% improvement in libido was reported by Wynia et al. based on the SHIM questionnaire [28]. The average serum testosterone level post TRT in studies that used valid questionnaires was 542 ng/ml. The other 2 studies indicated significant subjective improvement in hypogonadal symptoms after TRT.

We extracted data from the 10 studies that reported on the type of testosterone product used. The main testosterone products were topical (gel) or transdermal products for 178 patients, intramuscular injection for 45 patients, and oral products for 7 patients.

The definition of BCR varied among studies. Eleven studies reported their definition of BCR: 3 articles considered a serum PSA cut point of “ ≥ 0.1 ng/ml,” 4 studies of “ ≥ 0.2 ng/ml” and 1 study of “ ≥ 0.3 ng/ml.” The Phoenix definition (nadir + 2 ng/ml) was the most frequently used BCR definition in RT treated patients.

3.3. Meta-analysis

All patients

Twenty-one studies were included in the meta-analysis. The chi-square and I^2 test did not show any significant heterogeneity in all analyses. Begg’s test indicated no publication bias ($P = 0.67$).

The forest plot presents the analysis of BCR in CaP patients who underwent TRT after cancer treatment (Fig. 2). The overall pooled BCR rate 0.01 (95%CI 0.00–0.02), implying no association between TRT and BCR. There was no heterogeneity among included studies ($I^2 = 24.34\%$, $P = 0.15$). The weights are often relates closely to sample size. Greater weights are given to the results from studies that provide a larger number of patients. Greater weights increase the power of meta-analysis and are likely to be closer to the “true effect.”

Subgroup meta-analysis

Subgroup meta-analysis was performed to compare the difference between RP and all nonsurgical therapeutic

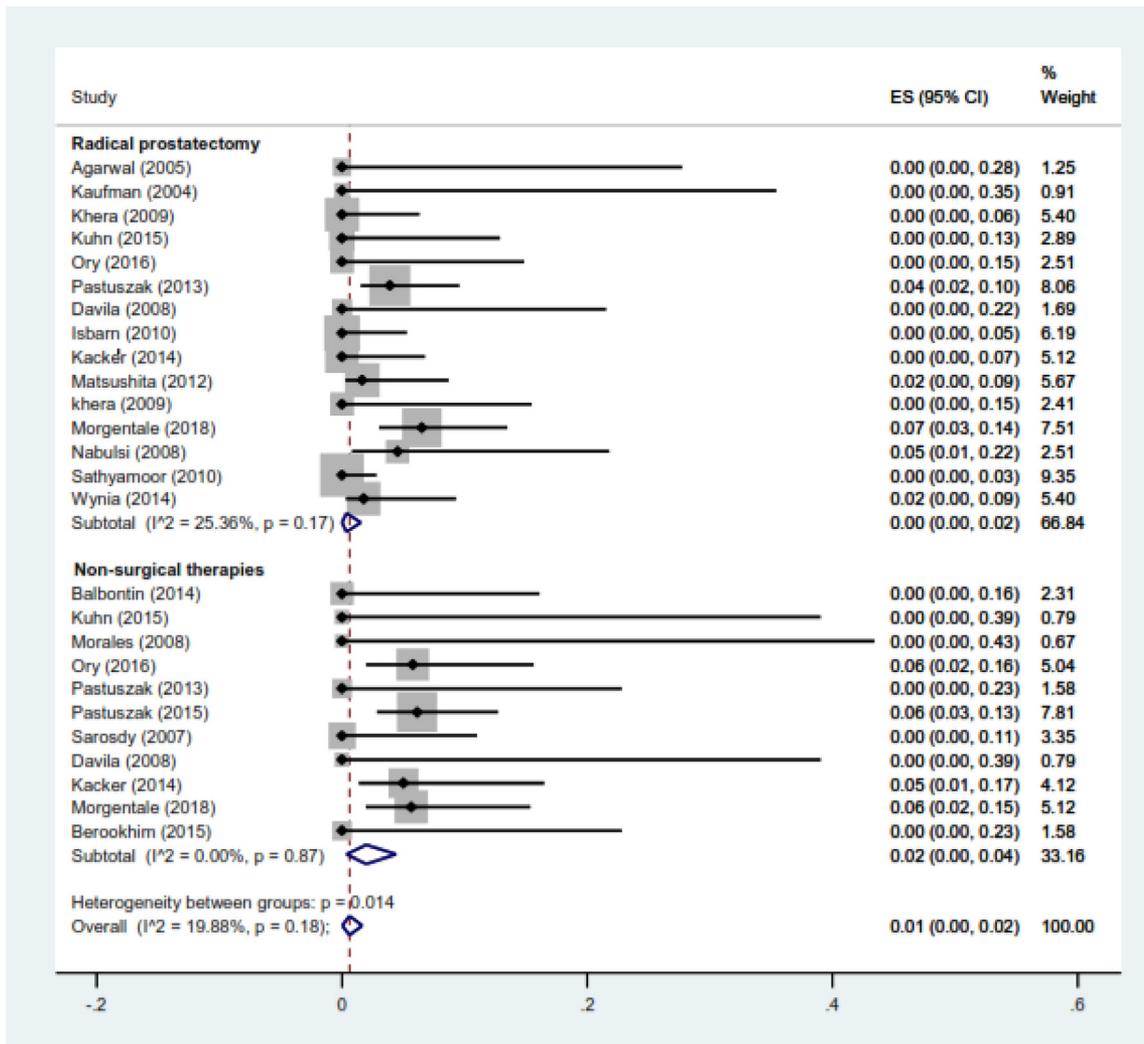


Fig. 3. Forest plot subgroup analyses showing the rate of biochemical recurrence after testosterone replacement therapy in radical prostatectomy and nonsurgical therapeutic modalities.

modalities including EBRT, BT, CT, or HIFU in terms of the effect of TRT on BCR (Fig. 3). Fifteen studies reported BCR rate in patients treated with RP and 11 studies reported in those with nonsurgical therapeutic modalities. The BCR rates were 0.00 (95%CI 0.00–0.02) in the RP group and 0.02 (95%CI 0.00–0.04) in the nonsurgical therapeutic modalities group. There was no heterogeneity in these analyses ($I^2 = 19.88\%$, $P = 0.18$). Studies with larger sample size have a greater weight in meta-analysis.

4. Discussion

We assessed the oncological safety of TRT in patients with a history of definitive local therapy for localized CaP. The overall BCR rate was low with no significant association between TRT and BCR. In subgroup analyses, patients who had undergone RP experienced lower BCR rates than

those who had undergone a primary nonsurgical therapies such as EBRT, CT, HIFU, and BT.

The overall BCR rates in patients who received TRT after definitive treatment was lower than the reported rates in literature after primary definitive treatment alone [30]. This observation may be explained by several facts. First, although we did not find significant heterogeneity among included studies, these studies actually varied widely in term of design, methods, interventions, and follow-up duration. In fact, the follow-up duration after TRT was relatively short to capture this protracted end point. Second, our analysis included highly selected patients who were eligible for TRT therapies. Therefore, they were inherently at lower risk of BCR. Then, the receipt of adjuvant therapies such as ADT might have underestimated the true BCR rates masking any potential positive association, if any. We identified only 3 studies that included concomitant or adjuvant ADT cohorts with an overall proportion of 6.3%. However,

such case-mix cannot be accurately addressed by the currently available data [17,18,20].

We observed a lower pooled BCR rate after TRT in patients who were treated with RP in comparison with those treated with nonsurgical therapies with curative intent. Such discrepancy can be explained, briefly, by the inherent differences in patient populations in term of disease characteristics such tumor stage and grade, time of TRT, and, importantly, the definition of BCR. The latter was not standardized among included studies, and as such, might introduce residual bias especially in patients who received radiotherapy as a primary treatment. This would err on the side of higher BCR rates in patients with nonsurgical therapies.

The efficacy of TRT was confirmed objectively in 4 studies that utilized validated questionnaires [7,8,25,28]. The improvement in hypogonadal symptoms matched the statistically significant increment in the average serum testosterone level after TRT. Notably, only 1 patient out of 108 experienced BCR post-TRT. The average serum testosterone level in these studies was 542 ng/dl. However, the safe post TRT serum testosterone level remains to be elucidated since these studies were not designed to define cut-off points or to direct treatment decision.

This study is not without limitations. The majority of included studies in this systemic review were retrospective in design with a lack of high quality prospective randomized trials. While only 2 studies evaluated TRT safety using a control groups [19,28], 1 study compared it to nonhypogonadal men with history of RP [19]. Such a nonmatched control group, along with lack of control groups in the other studies precluded drawing robust conclusion about the safety of TRT. Moreover, the heterogeneity of BCR definition was not only in RT groups but also in the RP cohorts. Several studies adopted different cut-off points to define BCR after RP. The impact of specific TRT product (gel, transdermal, intramuscular, and oral) could not be assessed based on the data presented in the currently available studies. Until further investigations evaluate this aspect, it is recommended to start with short acting preparations where physicians can halt TRT upon the occurrence of undesirable effect [31]. Despite limited ability to generalize these findings for all CaP survivors, highly selected hypogonadal CaP patients who treated with curative intent such as low-risk patients with low preoperative serum PSA, low surgical GS, and organ-confined disease might benefit from TRT without affecting BCR rate. Finally, a few studies addressed the efficacy of TRT as an end point using validated questionnaires. Indeed, this is an essential outcome that has been overlooked in the majority of reports and play a key role in patient counselling and decision making in CaP survivors.

5. Conclusions

We found that TRT after definitive CaP therapy seems oncologically safe and does not increase the BCR rate.

However, due to lack of prospective randomized trials, all patients should be informed regarding the possible adverse effects such as cancer progression. We suggest to perform phase I/II trials with the minimum follow-up of 1 year to assess the oncological safety of TRT in secondary hypogonadal men with a history of CaP. Until such studies reporting, we cannot declare the safety of TRT in secondary hypogonadal men after definitive therapy of CaP with conclusive evidence.

Conflict of interest

No conflict of interest disclosures from any authors.

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