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Evaluation of overall survival rate of different therapies in the treatment of T1–T3 prostate cancer: a network meta-analysis

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We performed this network meta-analysis (NMA) in order to compare the overall survival rate of six different therapies of T1–T3 prostate cancer (PC). The therapies include radiotherapy (RT), endocrine therapy (ET), Cryoablation (CRYO), radical prostatectomy (RP), RT+ET and RP+ET. Pubmed, Embase, Cochrane Library, Google Scholar, Web of Science and MEDLINE were searched to collect relevant literature from the inception of the study till February 2017. Cohort studies meeting the inclusion criteria were included in the study. A combination of direct and indirect evidence was performed to evaluate the odds ratio (OR) and draw surface under the cumulative ranking curves (SUCRA). Nine eligible cohort studies were included in this NMA, including 20,644 patients suffering from T1–T3 PC. The pairwise meta-analysis revealed that compared with the ET regimen, the RP and RP+ET regimens exhibited comparatively higher overall survival rates (OR=2.81, 95% CI=2.09~3.78; OR=3.15, 95% CI=1.80~5.50, respectively). The results of SUCRA values demonstrated that the RP + ET regimen occupied the first place (89.5%) in terms of overall survival rate, and the RP regimen came second (84.83%). Thus, the RP+ET regimen had better efficacy in the treatment of T1–T3 PC in combined-therapeutic regimens, and the RP regimen presented better efficacy in mono-therapeutic regimen. Our findings indicate that the RP+ET regimen had better efficacy on improving the overall survival rate of T1–T3 PC patients, and the RP regimen ranked second.

Key words: prostate cancer, therapies, overall survival rate, cohort studies, Bayesian network model, surface under the cumulative ranking curves (SUCRA)

Prostate cancer (PC), an adenocarcinoma, or glandular cancer, is the most common malignant cancer among males across the world [1]. According to an estimate, PC is the sixth leading cause of cancer death among men worldwide with approximately 258,000 deaths caused by PC in 2008 [2]. In addition, the number of deaths caused due to prostate cancer are roughly the same in developed and developing regions (136,000 and 122,000, respectively) [2]. The well-established risk factors for PC are complex, including diet, physical activity, age, race/ethnicity, and a family history of the disease, etc. [3–5]. PC can be divided into the following three stages: localized stage, regional stage and distant stage [6]. Based on the data between 1999 and 2005, approximately 80% of new PC cases were diagnosed at localized stages with a 5-year PC-specific survival rate approaching 100%, and about 12% of new PC cases were diagnosed at regional stages with a 5-year PC-specific survival rate approaching 100%, and about 4% of new PC cases were diagnosed at distant stages with a 5-year PC-specific survival rate approaching approximately 30% [6]. In our study, we included various PC treatments including radiotherapy (RT), endocrine therapy (ET), Cryoablation (CRYO), radical prostatectomy (RP), RT+ET and RP+ET.

Endocrine therapy (ET) plays an important role in the treatment of PC and external-beam radiotherapy (EBRT) is considered to be an effective treatment modality. However, a significant proportion of men suffer from relapse of the cancer [7]. Hall et al. reviewed more than 20,000 patients suffering from PC in the National Oncology Data Alliance, and observed survival improvements with dose-escalation of EBRT [8]. Furthermore, in 1997 it was unearthed that a combination of radiotherapy (RT) and long-term adjuvant ADT (anti-androgen therapy) was superior to individual radiotherapy in locally advanced prostate cancer [9, 10]. However, there is a lack of data comparing ADT, a kind of ET, with other therapy regimens. In 2012, Mottet et al. confirmed

that combined therapy strongly favored improved PFS (progression-free survival), loco-regional control, and metastasis-free survival, indicating that a combination of RT and long-term adjuvant ADT was superior to individual radiotherapy in the treatment of PC [11]. Cryoablation (CRYO), a definitive treatment for PC has undergone a resurgence of interest since the mid-1990s [12]. Studies on prostate CRYO have reported promising results with 5-year biochemical control rates ranging between 52% and 92% [13].

Although there is a plethora of studies comparing different therapies for T1–T3 PC, there is no comprehensive study comparing the overall survival rate of these aforementioned six treatments. Therefore, we aim to conduct a network meta-analysis (NMA) to compare the overall survival rate of RT, ET, CRYO, RP, RT+ET and RP+ET regimens in the treatment of T1–T3 PC. Simultaneously, we expect this study to be helpful for surgeons in the choice of treatment of T1–T3 PC.

Patients and methods

Search strategy. We retrieved PubMed, Embase, Cochrane library and other English language databases such as Google Scholar, Web of Science and MEDLINE to obtain all relevant literature. Relevant articles were also reviewed manually in case of the omission of any potentially relevant literature. The literature search was limited to the English language and ended in February 2017. The search terms included a combination of key words and free words as follows: prostate cancer, cancer prostate, prostate neoplasms, neoplasms prostate, prostate adenocarcinoma, adenocarcinoma of prostate; radiotherapy, RT; endocrine therapy, ET, endocrine treatment, hormone therapy, hormonotherapy; radical prostatectomy, RP, castration, orchiectomy; androgen deprivation therapy, ADT; estrogen, estradiol; maximal androgen blockage, MAB; luteinizing hormone releasing hormone-antagonist, LHRH-α, leuprorelin, goserelin, bicalutamide, diethylstilbestrol and cohort studies, etc.

Inclusion and exclusion criteria. The inclusion criteria were as follows: (1) study design: cohort study; (2) interventions: RT, ET, CRYO, RP, RT+ET and RP+ET; (3) study subjects: patients suffering from T1–T3 PC; (4) outcome: overall survival rate. The exclusion criteria were as follows: (1) patients who had undergone hormone therapy (including previous orchiectomy) or chemotherapy previously; (2) patients with a history of malignancy, excluding non-melanoma skin cancer; (3) studies with insufficient data integrity (e.g., non-paired studies); (4) repeated published literature; (5) conference reports, systematic reviews or summaries; (6) non-human studies and non-English studies.

Data extraction and quality assessment. Two authors (Si-Yang Chen and Yuan Du) independently carried out data extraction on the basis of a predefined form. Any disputes that appeared in the process of data extraction were resolved through discussion with multiple researchers. The risk of bias of included cohort studies was assessed by authors according to Newcastle-Ottawa Scale (NOS) [14]. This tool included the following 9 domains: representativeness of the exposed cohort (NOS01), selection of the non-exposed cohort (NOS02), ascertainment of exposure (NOS03), demonstration that outcome of interest was not present at the start of the study (NOS04), comparability of cohorts on the basis of the design or analysis (NOS05), assessment of outcome (NOS06), independent blind assessment (NOS07), was the follow-up long enough for outcomes to occur (NOS08), adequacy of follow-up of cohorts (NOS09). The total scores were 9 points, studies with more than 5 points were included in this study.

Statistical analysis. Firstly, traditional pairwise meta-analyses were performed in order to compare different treatment arms of studies directly. The pooled estimates of odds ratio (OR) and 95% confidence intervals (CI) were shown. Heterogeneity among these studies was tested using the Chi-square test and I-square test [15]. Secondly, R 3.2.1 statistical computing software was used to draw network diagrams. In the diagram, each node represents each intervention, the node size represents the sample size, and the line thickness between nodes represents the study number. Thirdly, we performed a Bayesian network meta-analysis to compare different diagnostic interventions with each other. Each analysis was based on non-informative priors for effective sizes and precision. Convergence and lack of auto correlation were checked and confirmed after four chains and a 20,000-simulation burn-in phase. Finally, direct probability statements were derived from an additional 50,000-simulation phase [16]. Fourthly, the surface under the cumulative ranking curve (SUCRA) was used in order to calculate the probability of each intervention being the most effective treatment method based on a Bayesian approach using probability values, and the larger the SUCRA value, the better the rank of the intervention [17, 18]. R (V.3.2.1) package gemtc (V.0.6) as well as Markov Chain Monte Carlo engine Open BUGS (V.3.4.0) were used in all computations in this study.

Results

Baseline characteristics of included studies. A total of 3,487 studies, which studied different therapies in the treatment of T1–T3 prostate cancer, were initially retrieved. After excluding duplicate studies (n=89), letters, reviews or meta-analyses (n=459), non-human studies (n=101) and non-English studies (n=322), 2516 full-text articles were included in the study. After full-text reviews, non-cohort studies (n=397), studies not associated to T1–T3 PC (n=1650), studies unrelated to therapeutic regimens (n=459) and studies lacking data integrity or lacking data (n=1) were ruled out. Finally, 9 cohort studies were eligible for this NMA [19–27] (Supplementary Figure 1). All included cohort studies were published between 2004 and 2016. Among the 9 cohort studies, 6 were performed in Caucasians, 2 in Asians, and 1 in mixed races. Moreover, all 9 studies were two-arm

Table 1. The baseline characteristics for included studies.

First author	Year	Ethnicity	Disease stage	Interventions		Dose and duration of drugs	Total	Sample size		Age(years)		Overall survival rate	
				T1	T2			T1	T2	T1	T2	T1	T2
McPartlin AJ	2016	Canada	T1–T2	RT	RT + ET (ADT)	bicalutamide 150 mg/d, 5 months	241	122	119	70.9 ±4.4	71.4 ±4.1	86.0%	82.0%
Amini A	2016	America	T1–T2	RT	RT + ET (ADT)	NR	14126	7568	6558	NR	NR	75.2%	73.4%
Koie T	2014	Japan	T1c–T3	RT + ET (LHRH agonist + ADT)	RP + ET (LHRH agonist + EMP)	leuprolide 11.25 mg/d or goserelin acetate 10.8 mg, EMP 280 mg/day, 6 months	156	78	78	73.5	71.0	92.1%	98.3%
Liu J	2013	America	T1–T2	ET (ADT)	RP	NR	3248	1624	1624	70.3	70.2	89.7%	96.1%
Tseng YD	2012	America	T1b–T2b	RT	RT+ET (LHRH agonist + ADT)	flutamide, 6 months	204	104	100	76 ±1.5	72 ±1.5	45.0%	68.5%
Jones CU	2011	Canada	T1–T2	RT	RT + ET (ADT)	flutamide 250 mg/d, goserelin 3.6 mg/d, leuprolide 7.5 mg/d, 4 months	1979	992	987	71 ±8.7	70 ±10.7	57.0%	62.0%
Donnelly BJ	2010	Canada	T2–T3	RT	cryoablation	–	244	122	122	68.6 ±5.1	69.4 ±6.1	88.5%	89.7%
Nguyen PL	2010	America	T1–T2	RT	RT + ET (LHRH agonist + ADT)	flutamide, 6 months	119	59	60	NR	NR	85.8%	90.9%
Homma Y	2004	Japan	T1b–T3	RT	RT + ET (LHRH agonist + ADT)	leuprorelin acetate 3.75 mg/month ± chlormadinone acetate 100 mg/d, 3 months	327	151	176	75.7 ±6.5	67.2 ±5.8	68.0%	87.0%

Notes: T = treatment; NR = not reported; PC = prostate cancer; RT = radiotherapy; ET = endocrine therapy; RP = radical prostatectomy; ADT = androgen-deprivation therapy; LHRH = luteinizing hormone-releasing hormone; EMP = estramustine phosphate.

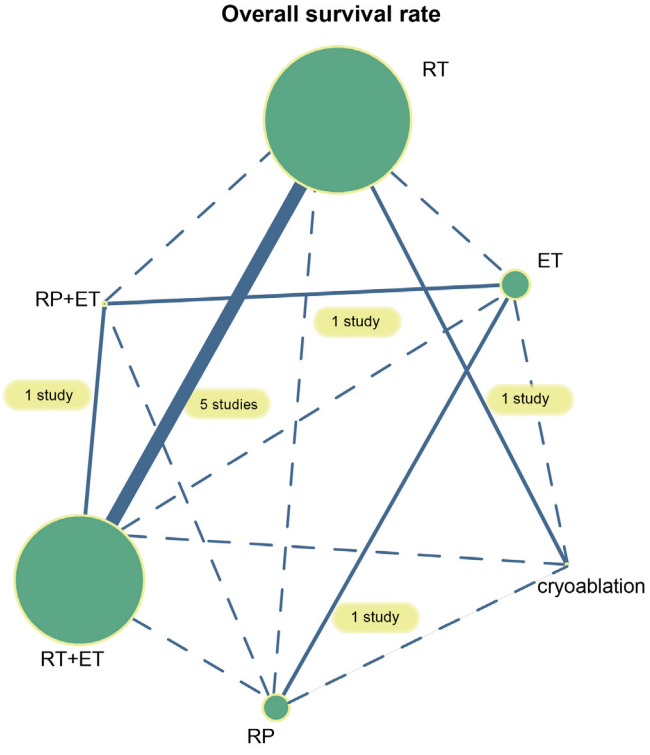

Figure 1. Network evidence diagram for different therapies in the treatment of T1–T3 PC. Note: RT = radiotherapy; ET = endocrine therapy; RP = radical prostatectomy.

trials. All patients were in T1–T3, and their ages were all about 70 years old, the baseline characteristics of included studies are displayed in Table 1. The NOS quality assessment of included studies is shown in Supplementary Figure 2. The included patients were aged between 60 and 85 years; and majority of the patients adopted RT in the treatment of T1–T3 PC (Figure 1).

Pairwise meta-analysis for overall survival rate of different therapies in the treatment of T1–T3 PC. We conducted a direct-paired comparison of RT, ET, CRYO, RP, RT+ET and RP+ET in the treatment of T1–T3 PC. The results reveal that RP and RP+ET therapy regimens fared better in overall survival rates compared to the ET regimen (OR=2.81, 95% CI=2.09~3.78; OR=3.15, 95% CI=1.80~5.50, respectively), whereas other therapies did not exhibit any significant differences in terms of overall survival rate (Table 2).

Main results of network meta-analysis. The results of this NMA revealed that RT, ET, CRYO, RP and RT+ET therapy regimens exhibited relatively lower overall survival rates compared to the RP+ET regimen (OR=0.09, 95% CI=0.00~1.13; OR=0.31, 95% CI=0.07~1.46; OR=0.10, 95% CI=0.00~1.87; OR=0.89, 95% CI=0.10~7.91; OR=0.11, 95% CI=0.00~1.31, respectively), which indicated that the efficacy of RP+ET may be relatively better in the treatment of T1–T3 PC compared to other therapies (Table 3; Figure 2).

SUCRA values of overall survival rates of treatments of T1–T3 PC. As shown in Figure 3, the SUCRA values demonstrate that the RP + ET therapy regimen exhibited the highest efficacy in the treatment of T1–T3 PC (89.5%) in terms of

Table 2. Estimated OR and 95% CI from pairwise meta-analysis in terms of overall survival rate.

Included studies	Comparisons	Efficacy events		Pairwise meta-analysis		
		Treatment 1	Treatment 2	OR (95% CI)	I^2	p_h-value
Overall survival rate						
5 study	E VS. A	5646/7824	6459/8845	1.20 (0.87~1.66)	82.5%	<0.001
1 study	F VS. E	77/78	72/78	6.42 (0.75~54.61)	NR	NR
1 study	D VS. B	1560/1624	1456/1624	**2.81 (2.09~3.78)**	NR	NR
1 study	C VS. A	109/122	108/122	1.13 (0.51~2.53)	NR	NR
1 study	F VS. B	153/176	103/151	**3.15 (1.80~5.50)**	NR	NR

Notes: OR = odd ratio; 95%CI = 95% confidence interval; A = radiotherapy (RT); B = endocrine therapy (ET); C = cryoablation; D = radical prostatectomy (RP); E = RT+ET; F = RP+ET.

Table 3. OR and 95% confidence intervals of six treatment modalities in term of overall survival rate.

	OR (95% confidence intervals)				
Overall survival rate					
A	3.47 (0.20, 170.68)	1.09 (0.21, 5.22)	10.22 (0.36, 683.76)	1.25 (0.64, 2.62)	11.35 (0.88, 424.98)
	B	0.30 (0.00, 8.04)	2.84 (0.63, 12.81)	0.36 (0.01, 6.14)	3.18 (0.68, 14.66)
		C	9.38 (0.26, 849.85)	1.15 (0.22, 7.08)	10.51 (0.53, 533.11)
			D	0.12 (0.00, 3.28)	1.13 (0.13, 9.72)
				E	8.88 (0.76, 302.41)
					F

Notes: Odds ratio and 95% confidence intervals below the treatments should be read from row to column while above the treatments should be read from column to row. OR = odds ratio; A = radiotherapy (RT); B = endocrine therapy (ET); C = cryoablation; D = radical prostatectomy (RP); E = RT+ET; F = RP+ET.

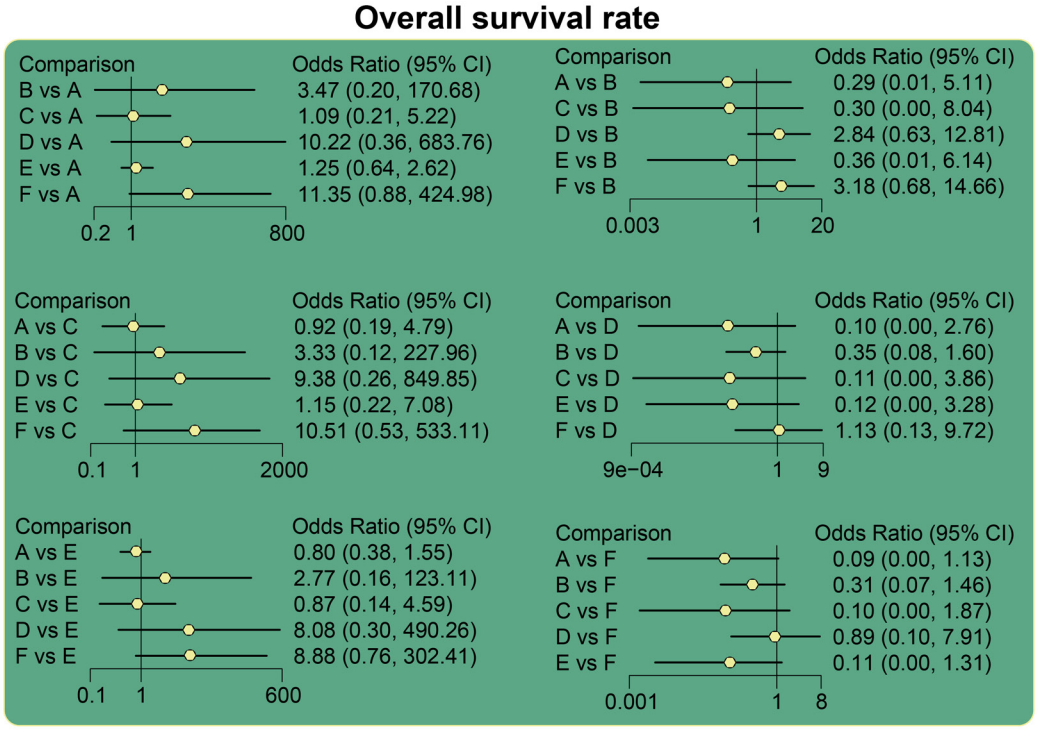

Figure 2. Relative forest plots for different therapies in the treatment of T1–T3 PC. Note: A= RT (radiotherapy); B= ET (endocrine therapy); C= cryo-ablation (CRYO); D= RP; E=RT+ET; F=RP+ET.

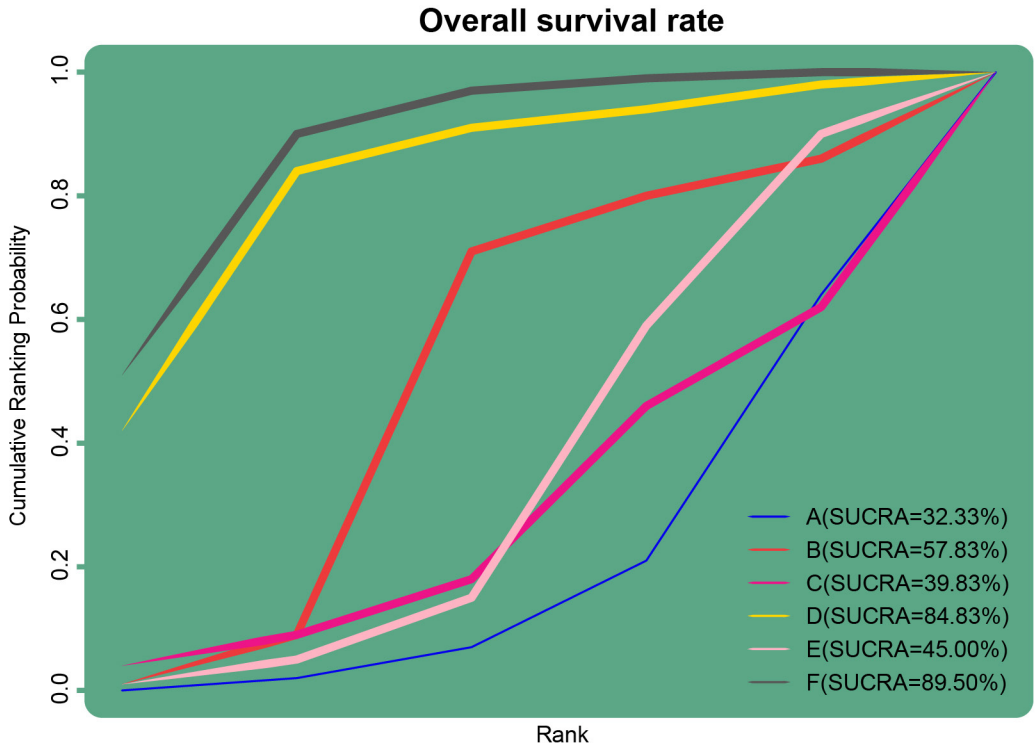

Figure 3. SUCRA values of different therapies in the treatment of T1–T3 PC. Note: (A= RT (radiotherapy); B= ET (endocrine therapy); C= cryoablation (CRYO); D= RP; E=RT+ET; F=RP+ET).

overall survival rate, whereas the RP regimen ranked second (84.83%). We conclude that the RP+ET therapy regimen exhibited better efficacy in combined-therapeutic regimens for the treatment of T1–T3 PC, whereas the RP therapy regimen exhibited better efficacy for the treatment of T1–T3 PC in mono-therapeutic regimens.

The patients included in the study belonged to Caucasian, Asian and mixed race ethnicities, which might have had a certain impact on the results. Therefore, to elude this bias, the ethnicity of the patients was taken in account for the calculation of the overall survival rate, and a meta-regression analysis was constructed. The interventions were reordered and a SUCRA value graph was plotted. The results revealed no significant differences before and after the meta-regression analysis, indicating that the ethnicity of patients did not affect the results of the present study (Figure 3).

Evaluation of publication bias. As seen in Figure 4, all dots are present in the funnel-shaped area, and symmetrical distribution is visible at both ends of the red line, indicating that no obvious publication bias exists in the present study.

Discussion

This study revealed that the RT+ET therapy regimen exhibits better efficacy in the treatment of T1–T3 PC, and the RP regimen may be the second choice for the treatment of T1–T3 PC. Multiple prospective randomized trials combining ADT and conventional dosage of EBRT for patients suffering from intermediate- and high-risk PC have demonstrated visible improvement in the rates of biochemical survival, disease-free survival, and overall survival (OS) [28–31]. Furthermore, several randomized trials performed in the conventional-dose era demonstrated the presence of a survival advantage with the addition of ADT to RT for patients suffering from intermediate-risk PC [24, 31, 32]. A previous study demonstrated that the usage of a combination of hormone therapy (HT) and EBRT resulted in reduction of the required lethal dose for prostate tumor, and clinical studies indicate this combined therapy increased the overall survival (OS) rate in patients [28]. Prostate specific antigen (PSA)-based cancer screening tests and increasing public awareness have increased the detection and diagnosis of localized and surgically curable cancer resulting in better prognosis [33]. However, disturbing frequency in radical prostatectomy (RP) specimens may portend an increased risk of eventual treatment failure and may not be curative [34]. The use of RP resulted in approximately a 90% survival rate in organ confined cancers [35], however, only a 57% disease-specific 10-year survival rate was observed after RP for locally advanced or T3 PC [36]. Therefore, this study focused on optimal endocrine therapy, individually or in association with RP, in order to improve the cure rates, delay symptomatic progression and to prolong the lives of patients suffering from PC.

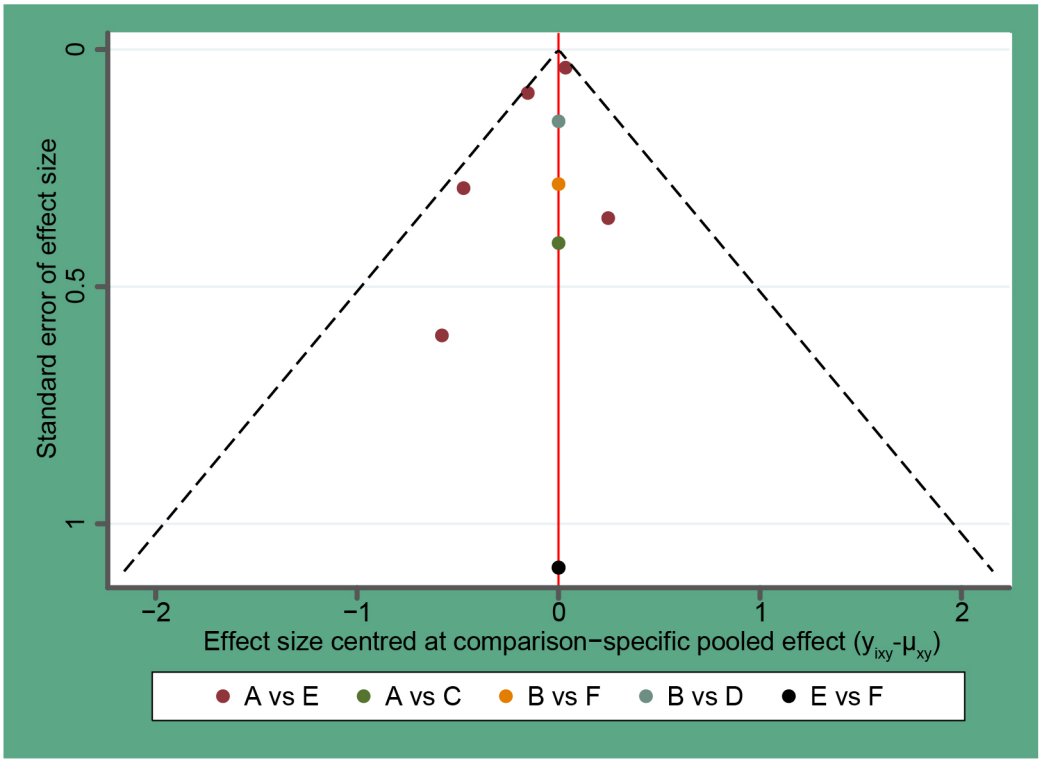

Figure 4. Evaluation of publication bias of different therapies in the treatment of T1–T3 PC. Note: A = RT (radiotherapy); B = ET (endocrine therapy); C = cryoablation (CRYO); D = RP; E = RT + ET; F = RP + ET.

The results of the pairwise meta-analysis reveal that RP and RP+ET regimens exhibit comparatively better efficacy compared to the ET regimen for the treatment of T1–T3 PC. The effects of the ET regimen were highly efficacious for localized and locally advanced PC and the benefit provided by prostatectomy may not be recognized readily in men receiving endocrine therapy [37, 38]. However, ET should be administered selectively as the therapy presents with various side-effects like hot flushes, male sexual dysfunction and osteoporosis [39–41]. Additionally, it has been reported that the usage of ET has significantly impaired the quality of life including physical functioning, fatigue and psychological distress in asymptomatic patients suffering from non-metastatic PC [42]. The SUCRA values also demonstrate that the RP+ET therapy regimen ranked the highest in terms of overall survival rate, and RP ranked second. The results of SUCRA values further confirm that the RP+ET regimen had better efficacy in the treatment of T1–T3 PC. Based on our results, we conclude that the RP+ET regimen exhibits better efficacy in the treatment of T1–T3 PC, and the RP regimen may be the second choice. We have comprehensively compared the efficacy of six therapies in the treatment of T1–T3 PC. The amount of included literature in the meta-analysis is relatively small and a sensitivity analysis could not be carried out. However, the included literature is of good quality, and there was no obvious publication bias. In addition, we performed a meta-regression analysis, which showed no change in the results. This further affirms the reliability of this study and provides valuable clinical significance. However, there was a difference in the number of participants in the pairwise comparison among interventions, and differences in the study of different comparisons, which may impact the results of the study. To tackle this problem, we constructed a comprehensive strategy in the early stage of literature screening and data statistics, and strictly followed the inclusion and exclusion criteria and employed the use of scientific statistical methods. In addition, we strictly controlled clinical heterogeneity, heterogeneity of methods and statistical heterogeneity. All of these strict guidelines and control methods solidify the results of this study. However, the dosage and duration of drugs used in the study could not be listed due to incomplete relevant data and non-compliant authors. Therefore, further research and analyses are required to find the right balance between the adverse effects of long-term ET on quality of life and the emotional and uncertain survival benefit of improving PSA values in individual patients.

Supplementary information is available in the online version of the paper.

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