Running Title: 5-ARIs Could Prevent the Clinical agnd Pathological Progression of PCa

5α-Reductase Inhibitors Could Prevent the Clinical and Pathological Progression of Prostate Cancer : A Meta-analysis

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Abstracts:

Purpose**:**To explore the efficacy of 5-ARIs in PCa

Methods: Searching through the major medical databases such as PubMed, Science Citation Index, EMBASE, Medline, Web of Science, Cochrane Library for all published studies in English until 2018. The following search terms were used: “Finasteride”, “dutasteride”, “5α reductase inhibitors”, “5-ARIs”, “prostate cancer”, “prostate neoplasm” and the additional related studies were manually searched. Newcasle-Ottawa Scale (NOS) assessed the qualities of studies, and the outcome measures were observed by RR or OR with 95% CIs.

Results: we conducted 9 eligible studies for analyses from 2011 to 2017. We found that 5-ARIs group may have fewer progression (OR =0.48 95%CI: 0.37-0.61; P<.00001, I^2=4%, P=.39) and lower pathological progression (OR=0.46; 95%CI: 0.29-0.73; P=.001, I^2=0% P=.45) ,compared with control groups. However, the OS did not show significant difference between two groups (OR=1.10; 95%CI:0.90-1.35; P=.35,I_2=93% P<.00001).

Conclusion: The use of 5-ARIs could prevent progression in Pca patients both in clinical and pathological.

1. **Introduction:**

Inhibitors of 5a-reductase(5-ARIs), such as finasteride and dutasteride, are widely used in medical treatment of benign prostatic hyperplasia (BPH)(1), and these drugs inhibit the conversion of testosterone to dihydrotestosterone(DHT) to reduce the prostate size and alleviate the lower urinary obstruction(2).And blocking DHT could lead to a lower level of androgen, which is involved in the development of prostate cancer, thus we may wonder that 5-ARIs may have an effect on the prostate cancer or not. The Prostate Cancer Prevention Trial (PCPT)(3), a large, phase III and double blind, placebo-control trial, included 18800 men and compared finasteride with placebo, and the result supported that finasteride may decrease the risk of new prostate cancer though changes in intraprostatic androgen. The data was impressing, however, some other studies(4) also pointed out that there are no strong evidences that showed the benefit of the finasteride and analogous 5-ARIs after the end-of-study follow-up. Therefor, researches have a conflict about the efficacy of 5-ARIs in prostate cancer, and we did this meta-analysis to quantify the effect of 5-ARI on PC patients.

2. Methods:

Search Strategy

We searched Pubmed, Embase and the Cochrane Library(until May 6, 2018). In addition, we searched potentially relevant trials from the references of selected studies by hand. The search strategy was followed by using all possible combinations of the medical subject headings(MeSH) or non-MeSH terms: “Finasteride”, “dutasteride”, “5α reductase inhibiors”, “5-ARIs”, “prostate cancer”, “prostate neoplasm” and the additional related studies were manually searched. Each search strategy met each database.(Figure 1)

Selection Criteria

Studies that were published in English were selected if they met the following criteria: (1) All patients should be diagnosed prostate cancer(PCa) in pathology. (2) All patients’ clinical and pathological parameters were covered (3) All studies should be controlled trials which compared 5-ARIs with placebo (4) The observations should report at least one of our outcomes: progression of cancer and overall survival(OS). (5) The same trial that were reported by different articles should be excluded. (6) Case report , letters , systematic reviews, comments and animals trial should be excluded.

Data extraction

Two reviewers independently assessed all eligible publications, and disagreements were resolved by discussion with a third reviewer. Data from all full-text studies that accorded with selection criteria were independently extracted by each reviewer using a standardized extraction form. All the data extracted from the studies included details on first author name, publication year, country, study design,study period, number of patients, duration of follow-up, events(table 1).

Outcome Measures

The primary outcome measures were progression of cancer, defined as the number of the patients who got disease progressing including clinical and pathological

progression. Secondary outcome measures in this meta-analysis were overall-survival(OS), defined as the time from observation to death during the research.

Statistical Analysis

Differences were expressed as RR with 95% CIs for primary outcome and OR for secondary outcome. The RR below 1 meant an advantage of 5-ARIs better than the placebo such as none or analogy . I^2 statistic were used to quantify the Heterogeneity across trials, which is a standardized measure of inconsistency and chi-square(Cochrane Q statistic) test.If I^2 statistics <50% and as a *p* value >0.05 for chi-square test, it indicted to have low level of heterogeneity. A fix-effects model was used to pool estimates in low level of heterogeneity.A random-effects model was used to pool estimates in high level of heterogeneity .Patient characteristics and other confounding factors in all the studies didn't have significant heterogeneity. Meanwhile, Subgroup analyses were planned to assess the effect of different progression of tumor. A P value <.05 was affirmed as statistically significant.

Quality Assessment

The methodological quality of each controlled trials was evaluated by using the Newcasle-Ottawa Scale (NOS) (5) which was recommended for assessing the qualities of studies and a study with >= 7 awarded stars was considered as a high-quality study. (Table 1)

4.Results:

After removing 122 duplicates, 209 potential studies were identified though reviewing abstracts and articles, 42 studies were excluded due to no combination therapy, incomplete outcome data, no comparison group, or not in English. The final set of eligible studies included 9 studies(6-14), published from 2011 to 2017. The selection strategy was shown in Fig.1. The characteristics of 9 included studies were summarized in Table 1. A total of 19764 patients were included in this meta-analysis. 1319 patients were treated with 5-ARIs.

Effect of interventions on primary outcome measure

Progression was the primary outcome measure in this meta-analysis. Using a random-effects model, progression , including clinical and pathological

progression were extracted from studies directly;The pooled OR was 0.48(95%CI: 0.37-0.61; P<.00001, Fig 2). This represented significantly fewer progression in patients treated with 5-ARIs ,and there were no heterogeneity(I_2=4%, P=0.39, Fig 2).

Furthermore, the subgroup analyses were undergoing and shown in Fig 3 . the pathological progression was also decreased in 5-ARIs groups (OR=0.46; 95%CI: 0.29-0.73; P=.001, heterogeneity P=0.45,I_2=0% ,Fig 3.), thus patients with Pca gained more benefit from 5-ARIs.

The second outcome, Overall survival(OS) did not show significant difference between two groups (OR=1.10; 95%CI, 0.90-1.35; P=0.35, heterogeneity p<0.00001,I_2=93% ,Fig4.).

The funnel plots showed there were no significant publication bias.

5.Discussion:

We present this meta-analysis to assess the effect of 5-ARIs in treatment with PCa, and the results showed a inspiring outcome that 5-ARIs may prevent the progression of PCa.In our study, it indicated a fewer progression in 5-ARIs groups (5-ARIs vs Placebo OR=0.48 95%CI:0.37-0.61; p<0.00001).Furthermore, the subgroup analysis was also undertook and we identified a positive effect of 5-ARIs in pathological progression (5-ARIs vs Placebo OR=0.46; 95%CI, 0.29-0.73; p=0.001, heterogeneity p=0.45,I_2=0%). Moreover, the results were coincident with recent researches, and increasing evidence suggested that there may be a close affinity betweent PCa and 5-ARIs. In a large, randomized and placebo-controlled trial, the Prostate Cancer Prevention Trail(PCPT), a total of 18882 patients were assigned to finasteride or placebo for PCa with 7 years follow-up, and the study showed that the finasteride could reduce the risk of prostate cancer by 25%(15). Meanwhile, Fritz Schroder.et(11) also conducted a randomized, placebo-controlled Avodart after radical therapy for prostate cancer study (ARTS), which included 294 subjects with dutasteride treatment over 2 years and they draw a conclusion that dutasteride could delay the progression of Pca , even in patients with biochemical failure after radical therapy for clinically localized disease. In fact, the drugs, such as finasteride, dutasteride and other 5-ARIs, inhibited testosterone to DHT, which played an important role in PCa mechanism. The progression of PCa could perform in the clinical or pathological way. The clinical progression may behave as a tumor metastasis, a higher level of PSA, biochemical progression after therapies. And studies demonstrated that PCa was some androgen-relative tumor, thus impeding the original substrate of translation to androgen should prevent the progression of PCa in somehow. Besides, the pathological progression can be defined as increased grade, increased number of scores to more than three, or any core involvement over 50%. Noticeably, the trial[13] reported that those taking a 5-ARIs could bring an approximate 50% reduction in the rate of pathological progression.However, many conflicts(16) also pointed out that the finasteride contributed to the increase in high-grade cancers. Long-term 5-ARIs treatment had been proposed to alter the histologic appearance of prostate cancer tissue,which would falsely lead to High Gleason grades in a low-grade tumor(6), but larger prostate are more likely to undergrad

at initial diagnostic biopsy, thus patients who took 5-ARIs might theoretically likely to detect higher grade with subsequent biopsies(17)and it might not be ascribed the higher Gleason Score in a low-grade tumor to a pathologic progression. Eventually, as the aspect of amount of observation(13), 5-ARIs appeared to diminish the progression of PCa patients.

Counting for the overall survivals, our study found there were no significant difference between 5-ARIs and placebo (OR=1.10; 95%CI, 0.90-1.35; p=0.35). A recent Finnish Prostate Cancer Screening trail(18) similarly implicated the 5-ARIs users didn't have impact on the survivals(HR=1.51, P=0.8 >0.05). Meanwhile, a larger study(19), which included over 3 million patients from Denmark, reported that 5-ARIs were associated with an increase risk of PCa-specific mortality(HR=2.1, 95%CI: 1.97-2.30). However, even more studies should be needed to definitely prove this in the future.

To our knowledge, this is the first meta-anlysis to systemically asses the efficiency of 5-ARIs in progression of the Pca patients. The present meta-analysis carries few limitations that must be taken into account. The main limitation is that our meta-analysis contain few randomized data, most the studies included were observational. Although the heterogeneity of studies were not obvious, all the patients in different groups were not possible to match for age, BMI, preoperative therapy, and various bias may affect the primary outcome. All these factors may have contributed to a higher heterogeneity between studies. Because of these limitations, a lager and randomized control trials were needed to confirm these results.

5. Conclusion

The use of 5-ARIs could prevent progression in Pca patients both in clinical and pathological.

6.Compliance with Ethical Standards:

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Conflict of interest : None of the authors have a conflict of interest to declare.

Ethical approval: This article does not contain any studies with human or animals performed by any of the authors

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Table 1： Quality of studies

Reference	Country	Center	Design	Period	Sample		Age		Follow-up	Event	Quality
					5-ARI	Placebo	5-ARI	Placebo	(years)		
Aners Kjellman 2013	Denmark	M	T	1989-2001	199	2806	73.9±8.3	73.6±8.5	3	1,2	*********
Antonio Finalli 2011	Canada	S	T	1995-2010	70	218	65.6±6.4	63.8±7.8	4	3,4	*******
Ashley E.Ross 2011	USA	M	T	1994-2010	47	540	66	65	4	3,4	******
Charles Dai 2017	Egypt	S	T	2002-2015	70	301	66±7	64±7	3	1,3	*******
Fritz Schroder 2013	USA	S	R	N	147	146	69.7	68.6	2	3	******

Laurent Azoulay 2015	Canada	M	T	1999-2009	574	13318	76.2±8.2	71.9±9.2	5	3,5	********
Neil E Fleshner 2012	Canada	S	R	2006-2007	147	155	N	N	3	3,4	*****
Rodolfo Monotironi 2013	Italy	S	R	N	41	42	64±4	63±7	2	3,4	******
Teemu J.Murtola 2013	Finland	S	T	1995-2009	24	901	N	N	4	1,3,4	*****

Center: M: multiple centers, S: single center ;Event: 1:Overall survival,2:Prostate-cancer specific surviva, 3:Progression, 4:Pathologic progression, 5:All cause mortality;T:Retropective, R:Rondomized;N: not mentioned

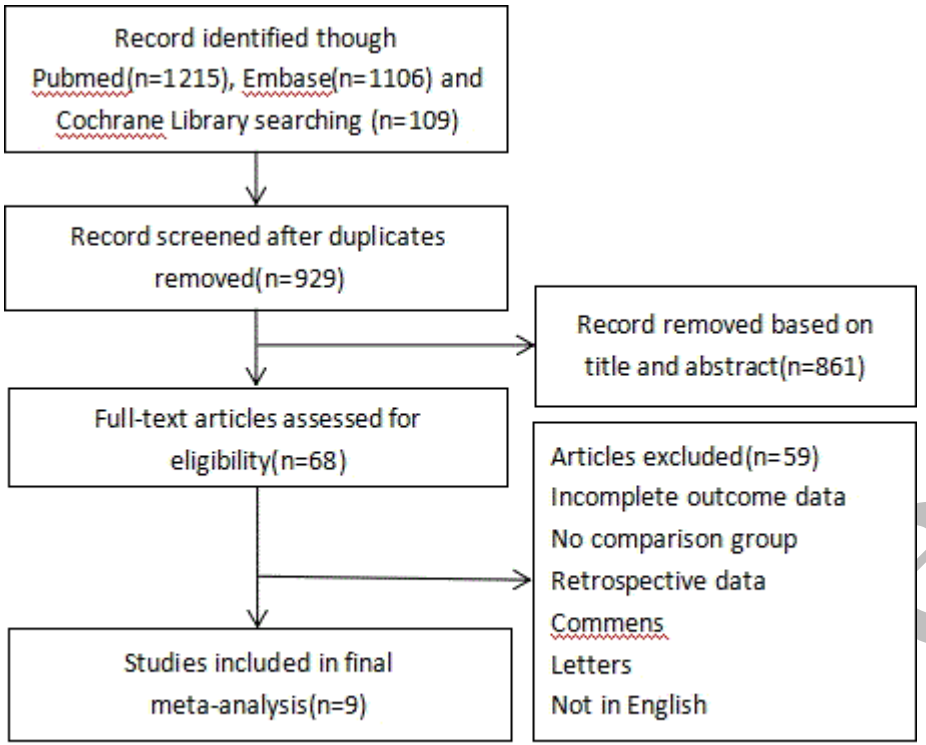
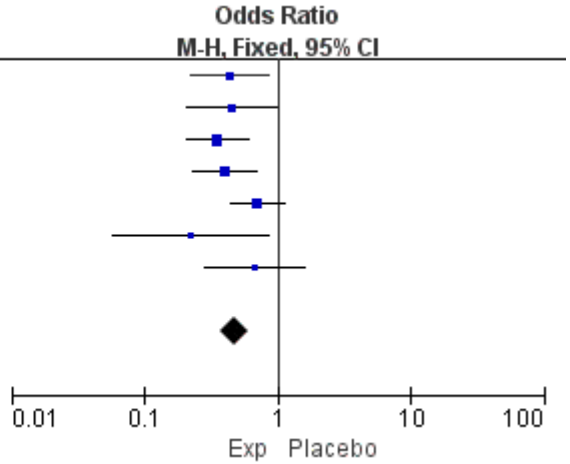


Fig.1 Selecting flowchart for included studies in the meta-analysis

Study or Subgroup	Experimental Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Antonio Finalli 2011	14	70	47	129	13.2%	0.44 [0.22, 0.87]
Ashley E.Ross 2011	8	47	169	540	11.2%	0.45 [0.21, 0.98]
Charles Dai 2017	25	70	184	301	22.3%	0.35 [0.21, 0.61]
Fritz Schroder 2013	25	146	49	144	20.5%	0.40 [0.23, 0.70]
Neil E Fleshner 2012	54	147	70	155	21.6%	0.71 [0.44, 1.12]
Rodolfo Monotironi 2013	8	20	15	20	4.5%	0.22 [0.06, 0.86]
Teemu J.Murtola 2013	8	24	383	901	6.6%	0.68 [0.29, 1.60]
Total (95% CI)		**524**		**2190**	**100.0%**	**0.48 [0.37, 0.61]**
Total events	142		917			

Heterogeneity: $Chi^2 = 6.28$, $df = 6$ ($P = 0.39$); $I^2 = 4\%$

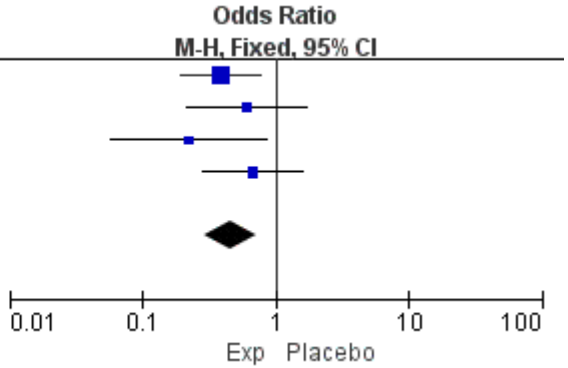
Test for overall effect: $Z = 6.03$ ($P < 0.00001$)



Study or Subgroup	Exp Events	Exp Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Antonio Finalli 2011	13	70	48	129	45.6%	0.38 [0.19, 0.78]
Ashley E.Ross 2011	4	47	72	540	17.5%	0.60 [0.21, 1.74]
Rodolfo Monotironi 2013	8	20	15	20	14.9%	0.22 [0.06, 0.86]
Teemu J.Murtola 2013	8	24	383	901	22.0%	0.68 [0.29, 1.60]
Total (95% CI)		**161**		**1590**	**100.0%**	**0.46 [0.29, 0.73]**
Total events	33		518			

Heterogeneity: Chi² = 2.40, df = 3 (P = 0.49); I² = 0%

Test for overall effect: Z = 3.30 (P = 0.0010)



Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Aners Kjellman 2013	111	199	1628	2804	54.1%	0.91 [0.68, 1.22]
Charles Dai 2017	24	70	73	301	10.3%	1.63 [0.93, 2.85]
Laurent Azoulay 2015	61	133	4797	13318	29.1%	1.50 [1.07, 2.12]
Teemu J.Murtola 2013	18	24	888	901	6.5%	0.04 [0.02, 0.13]
Total (95% CI)		**426**		**17324**	**100.0%**	**1.10 [0.90, 1.35]**
Total events	214		7386			

Heterogeneity: Chi² = 41.28, df = 3 (P < 0.00001); I² = 93%

Test for overall effect: Z = 0.93 (P = 0.35)