

Nayak et al. Do androgen-directed therapies improve outcomes in prostate cancer patients undergoing radical prostatectomy? A systematic review and meta-analysis

APPENDIX

Literature search strategy

Database: Embase Classic+Embase <1947 to 2019 September 17>, Ovid MEDLINE(R) ALL <1946 to September 16, 2019>, EBM Reviews - Cochrane Central Register of Controlled Trials <August 2019>

Search Strategy:

-
- 1 exp Prostatic Neoplasms/ (364380)
 - 2 (prostat* adj2 (cancer or neoplasm* or carcinoma* or adenocarcinoma* or malignan* or tumor* or tumour*)).tw. (331824)
 - 3 (prostat* and (cancer or neoplasm* or carcinoma* or adenocarcinoma* or malignan* or tumor* or tumour*)).kw. (67045)
 - 4 or/1-3 (424917)
 - 5 (prostat* adj3 resect*).tw. (16245)
 - 6 prostat* resect*.kw. or turp.tw,kw. (9528)
 - 7 exp Prostatectomy/ or prostatectom*.tw,kw. (109777)
 - 8 or/5-7 (119455)
 - 9 4 and 8 (74454)
 - 10 prostatectom*.ti. (42818)
 - 11 9 or 10 (89496)
 - 12 exp Androgen Antagonists/ (80935)
 - 13 exp Antineoplastic Agents, Hormonal/ (751582)
 - 14 exp Gonadotropin-Releasing Hormone/ (71531)
 - 15 (Buserelin or Goserelin or Leuprolide ior Nafarelin or Triptorelin or Pamoate).tw,kw. (10321)
 - 16 (antiandrogen* or anti androgen* or androgen receptor antagonist* or ADT or androgen suppression or androgen deprivation or hormone therapy or chemical castration).tw,kw. (82906)
 - 17 ((gonadotrophin releasing hormon* or gonadotrphin releasing hormone or gonadotrphin releasing hormone) adj3 (antagonist* or analogue* or agonist*)).tw. (3430)
 - 18 (Cyproterone or bicalutamide or Estrogen* or oestrogen* or Leuprolide or Lupron or flutamide or niftolid or zoladex or eulexin or casodex or nilutamide or nilandrone or diethylstilbestrol or Gonadorelin or megastrol or Finasteride or Proscar or Avodart or Dutasteride or Degarelix acetate or Firmagon or Abiraterone acetate or Zytiga or Enzalutamide or Xtandi or grha).tw,kw. (435522)
 - 19 DIETHYLSTILBESTROL/ (26646)
 - 20 exp estrogens/ or exp progestins/ (585977)
 - 21 castration/ or orchietomy/ (77832)
 - 22 (Orchietom* or Orchidectom*).tw,kw. (22088)
 - 23 or/12-22 (1540546)
 - 24 11 and 23 (12519)
 - 25 randomized controlled trial.pt. (967031)
 - 26 controlled clinical trial.pt. (184335)

Nayak et al. Do androgen-directed therapies improve outcomes in prostate cancer patients undergoing radical prostatectomy? A systematic review and meta-analysis

- 27 random*.tw. (3413640)
- 28 placebo.ab. (749094)
- 29 clinical trials as topic.sh. (221606)
- 30 trial.ti. (781351)
- 31 cohort studies/ or prospective studies/ or retrospective studies/ (2615784)
- 32 (cohort* or prospective* or retrospective*).tw,kw. (4438347)
- 33 Follow-Up Studies/ (1723062)
- 34 follow up.tw,kw. (2563525)
- 35 or/25-34 (10259725)
- 36 24 and 35 (7043)
- 37 case reports.pt. (2046692)
- 38 36 not 37 (6993)
- 39 38 use medall (2053)
- 40 ("20180615" or "20180616" or "20180617" or "20180618" or "20180619" or 2018062* or 2018063* or 201807* or 201808* or 201809* or 20181* or 2019*).dt. (1618067)
- 41 39 and 40 (158)
- 42 exp *prostate tumor/ (154603)
- 43 (prostat* adj2 (cancer or neoplasm* or carcinoma* or adenocarcinoma* or malignan* or tumor* or tumour*)).tw. (331824)
- 44 42 or 43 (351460)
- 45 exp *prostatectomy/ (46602)
- 46 prostatectom*.tw. (81698)
- 47 ((prostat* adj3 resect*) or turp).tw. (18983)
- 48 45 or 46 or 47 (102565)
- 49 44 and 48 (56052)
- 50 prostatectom*.ti. (42818)
- 51 49 or 50 (75880)
- 52 exp *antiandrogen/ or *androgen deprivation therapy/ (25671)
- 53 exp *"antineoplastic hormone agonists and antagonists"/ (177913)
- 54 *gonadorelin/ (37994)
- 55 (Buserelin or Goserelin or Leuprolide ior Nafarelin or Triptorelin or Pamoate).tw. (10195)
- 56 (antiandrogen* or anti androgen* or androgen receptor antagonist* or ADT or androgen suppression or androgen deprivation or hormone therapy or chemical castration).tw. (80700)
- 57 ((gonadotrophin releasing hormon* or gonadotrphin releasing hormone or gonadotrphin releasing hormone) adj3 (antagonist* or analogue* or agonist*)).tw. (3430)
- 58 (Cyproterone or bicalutamide or Estrogen* or oestrogen* or Leuprolide or Lupron or flutamide or niftolid or zoladex or eulexin or casodex or nilutamide or nilandrone or diethylstilbestrol or Gonadorelin or megastrol or Finasteride or Proscar or Avodart or Dutasteride or Degarelix acetate or Firmagon or Abiraterone acetate or Zytiga or Enzalutamide or Xtandi).tw. (422271)
- 59 *diethylstilbestrol/ (14734)
- 60 exp *estrogen/ or exp *gestagen/ (302518)
- 61 *orchietomy/ or (Orchietom* or Orchidectom*).tw. (28085)
- 62 or/52-61 (821203)
- 63 51 and 62 (8011)

Nayak et al. Do androgen-directed therapies improve outcomes in prostate cancer patients undergoing radical prostatectomy? A systematic review and meta-analysis

- 64 random*.tw. or placebo*.mp. or double-blind*.tw. (3895488)
- 65 cohort analysis/ (756050)
- 66 (cohort* or retrospective* or prospective*).tw. (4422312)
- 67 longitudinal study/ (258047)
- 68 prospective study/ or retrospective study/ (2616065)
- 69 *follow up/ (43333)
- 70 follow up.tw. (2547297)
- 71 or/64-70 (9695290)
- 72 63 and 71 (5118)
- 73 72 use emczd (3182)
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- 75 73 and 74 (405)
- 76 conference*.pt,ab,so. (4543313)
- 77 75 and 76 (222)
- 78 75 not 77 (183)
- 79 exp Prostatic Neoplasms/ (364380)
- 80 (prostat* adj2 (cancer or neoplasm* or carcinoma* or adenocarcinoma* or malignan* or tumor* or tumour*)).tw. (331824)
- 81 (prostat* and (cancer or neoplasm* or carcinoma* or adenocarcinoma* or malignan* or tumor* or tumour*)).kw. (67045)
- 82 or/79-81 (424917)
- 83 (prostat* adj3 resect*).tw. (16245)
- 84 prostat* resect*.kw. or turp.tw,kw. (9528)
- 85 exp Prostatectomy/ or prostatectom*.tw,kw. (109777)
- 86 or/83-85 (119455)
- 87 82 and 86 (74454)
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- 90 exp Androgen Antagonists/ (80935)
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- 93 (Buserelin or Goserelin or Leuprolide ior Nafarelin or Triptorelin or Pamoate).tw,kw. (10321)
- 94 (antiandrogen* or anti androgen* or androgen receptor antagonist* or ADT or androgen suppression or androgen deprivation or hormone therapy or chemical castration).tw,kw. (82906)
- 95 ((gonadotrophin releasing hormon* or gonadotrphin releasing hormone or gonadotrphin releasing hormone) adj3 (antagonist* or analogue* or agonist*)).tw. (3430)
- 96 (Cyproterone or bicalutamide or Estrogen* or oestrogen* or Leuprolide or Lupron or flutamide or niftolid or zoladex or eulexin or casodex or nilutamide or nilandrone or diethylstilbestrol or Gonadorelin or megastrol or Finasteride or Proscar or Avodart or Dutasteride or Degarelix acetate or Firmagon or Abiraterone acetate or Zytiga or Enzalutamide or Xtandi or grha).tw,kw. (435522)
- 97 DIETHYLSTILBESTROL/ (26646)
- 98 exp estrogens/ or exp progestins/ (585977)

Nayak et al. Do androgen-directed therapies improve outcomes in prostate cancer patients undergoing radical prostatectomy? A systematic review and meta-analysis

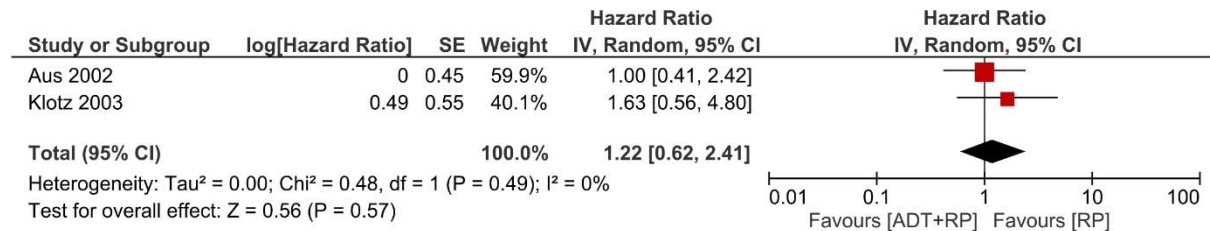
- 99 castration/ or orchiectomy/ (77832)
- 100 (Orchiectom* or Orchidectom*).tw,kw. (22088)
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- 102 89 and 101 (12519)
- 103 conference abstract.pt. (3582555)
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- 105 "Journal: Conference Abstract".pt. (138427)
- 106 103 or 104 or 105 (3721000)
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- 109 limit 108 to yr="2018 -Current" (26)
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- 112 limit 111 to yr="2018 -Current" (55)
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- 116 114 use emczd (57) Embase**
- 117 114 use cctr (48) Cochrane**
- 118 77 or 109 (248)

Conference Abstracts

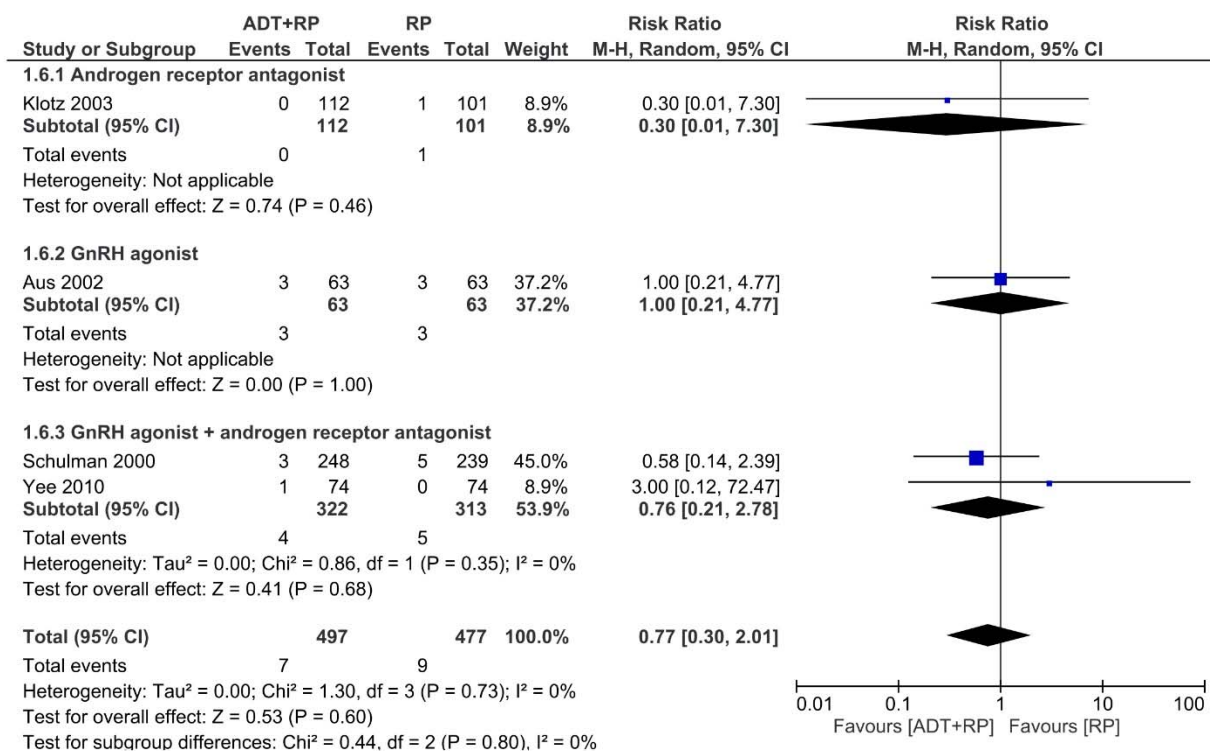
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- 120 119 use emczd (219) Medline**
- 121 119 use cctr (20) Embase**

Nayak et al. Do androgen-directed therapies improve outcomes in prostate cancer patients undergoing radical prostatectomy? A systematic review and meta-analysis

Supplementary Fig. 1. Forest plot of hazard ratios of overall survival for neoadjuvant androgen-directed therapy (ADT) with prostatectomy (RP) vs. RP alone. CI: confidence interval.

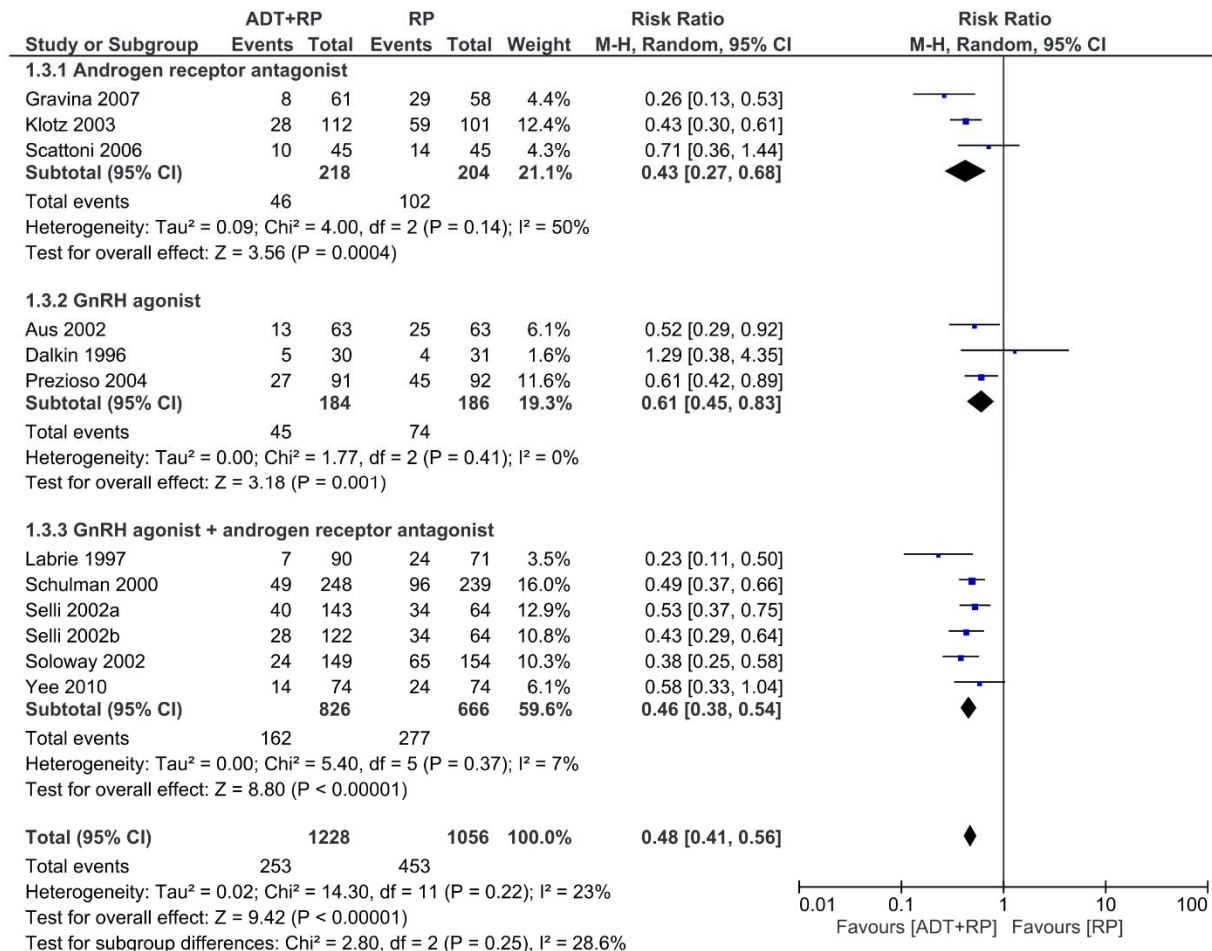


Supplementary Fig. 2. Forest plot of prostate cancer death for neoadjuvant androgen deprivation therapy (ADT) with prostatectomy (RP) vs. RP alone. CI: confidence interval.



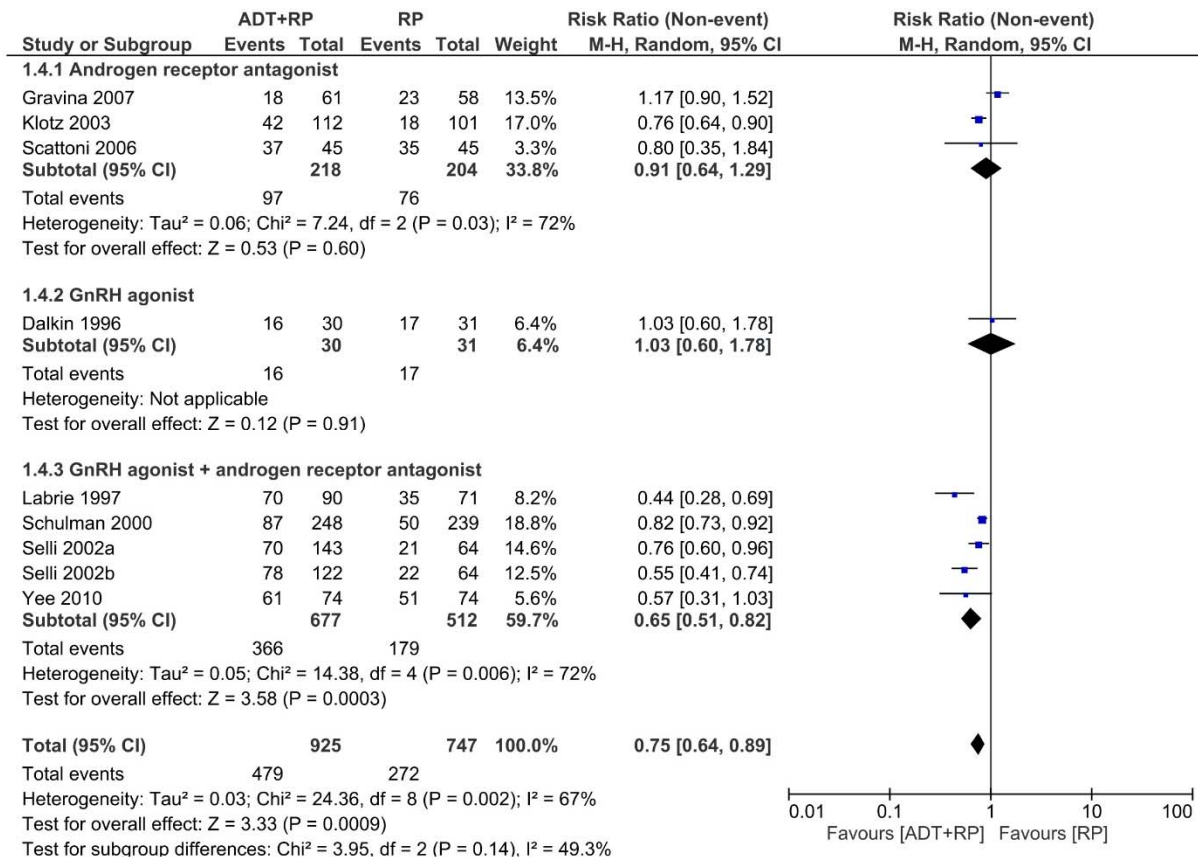
Nayak et al. Do androgen-directed therapies improve outcomes in prostate cancer patients undergoing radical prostatectomy? A systematic review and meta-analysis

Supplementary Fig. 3. Forest plot of positive surgical margins for neoadjuvant androgen-directed therapy (ADT) with prostatectomy (RP) vs. RP alone. *Selli 2002a corresponds to 3 months of neoadjuvant ADT; Selli 2002b corresponds to 6 months of neoadjuvant ADT. As both treatment groups were compared to the same control group, this analysis divided the control group in half for comparisons. **Selli 2002 did not present the total number of patients randomized to each group, therefore, the total number analyzed was used in this analysis. CI: confidence interval.



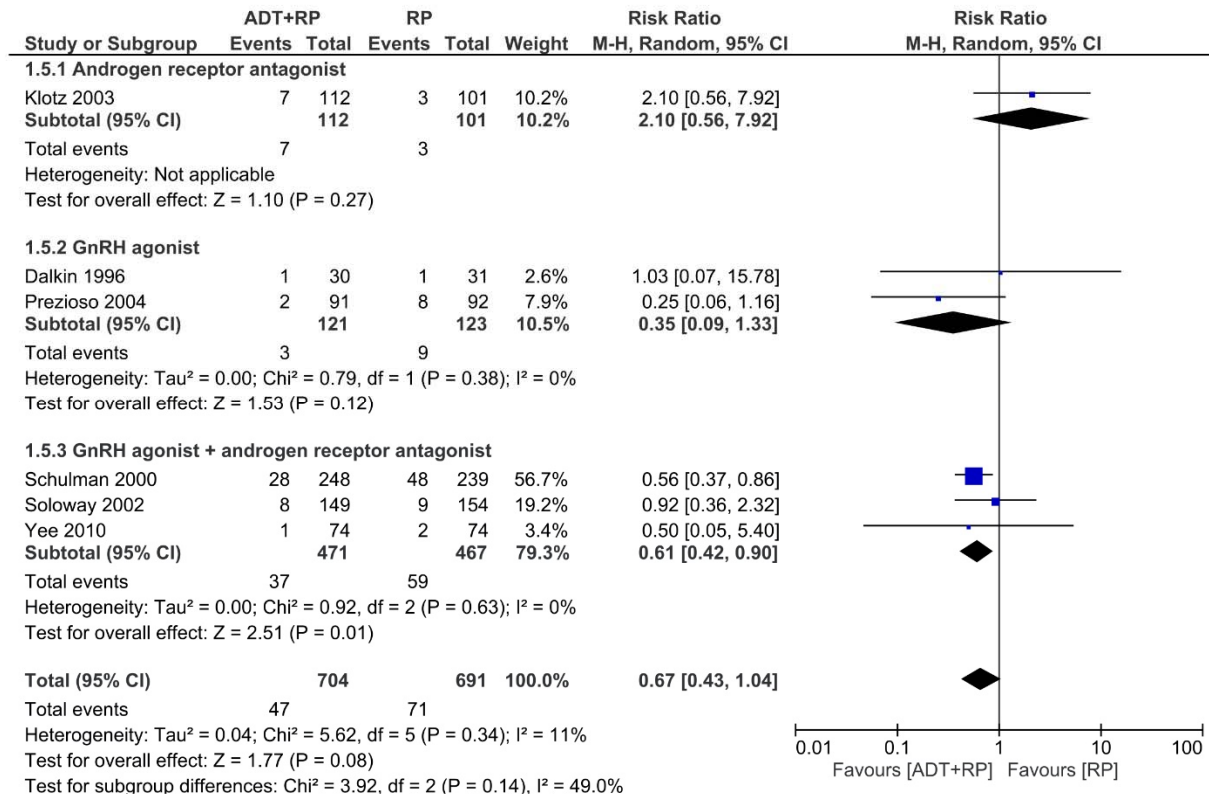
Nayak et al. Do androgen-directed therapies improve outcomes in prostate cancer patients undergoing radical prostatectomy? A systematic review and meta-analysis

Supplementary Fig. 4. Forest plot of pathological extraprostatic extension for neoadjuvant androgen-directed therapy (ADT) with prostatectomy (RP) vs. RP alone. *Selli 2002a corresponds to 3 months of neoadjuvant ADT; Selli 2002b corresponds to 6 months of neoadjuvant ADT. As both treatment groups were compared to the same control group, this analysis divided the control group in half for comparisons. **Selli 2002 did not present the total number of patients randomized to each group, therefore, the total number analyzed was used in this analysis. CI: confidence interval.



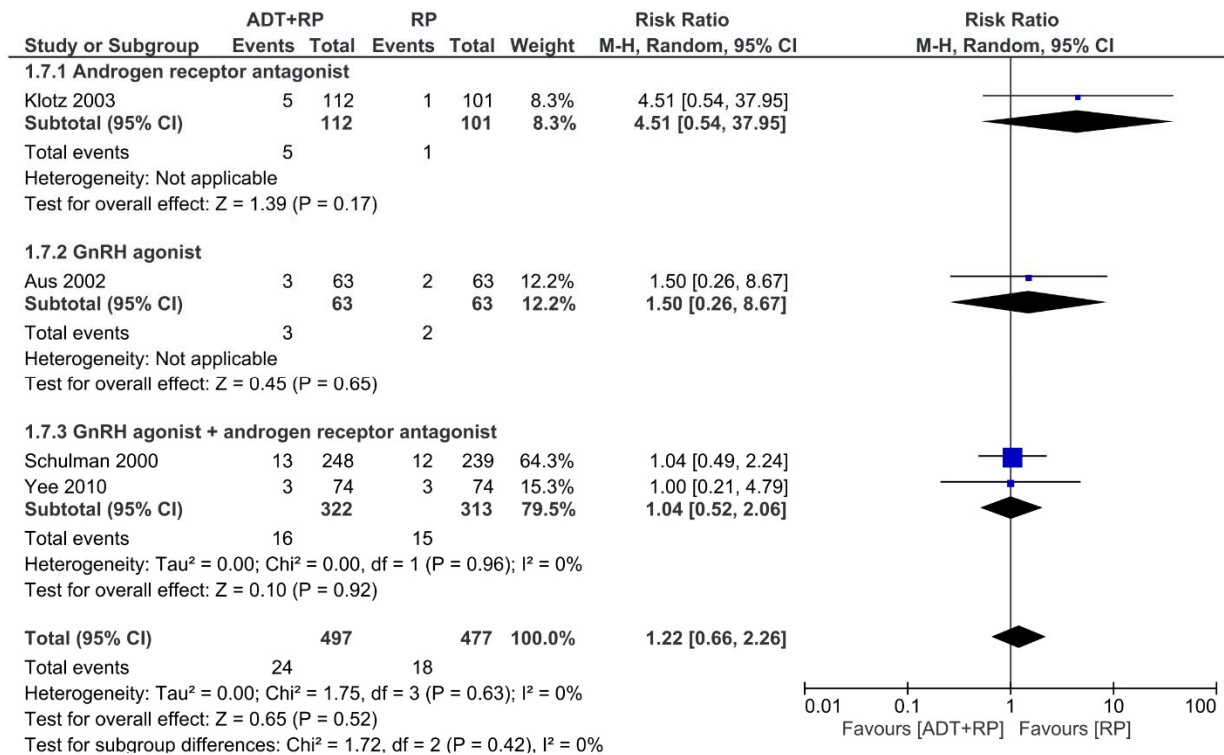
Nayak et al. Do androgen-directed therapies improve outcomes in prostate cancer patients undergoing radical prostatectomy? A systematic review and meta-analysis

Supplementary Fig. 5. Forest plot of pathologic lymph node metastases for neoadjuvant androgen-directed therapy (ADT) with prostatectomy (RP) vs. RP alone. CI: confidence interval.



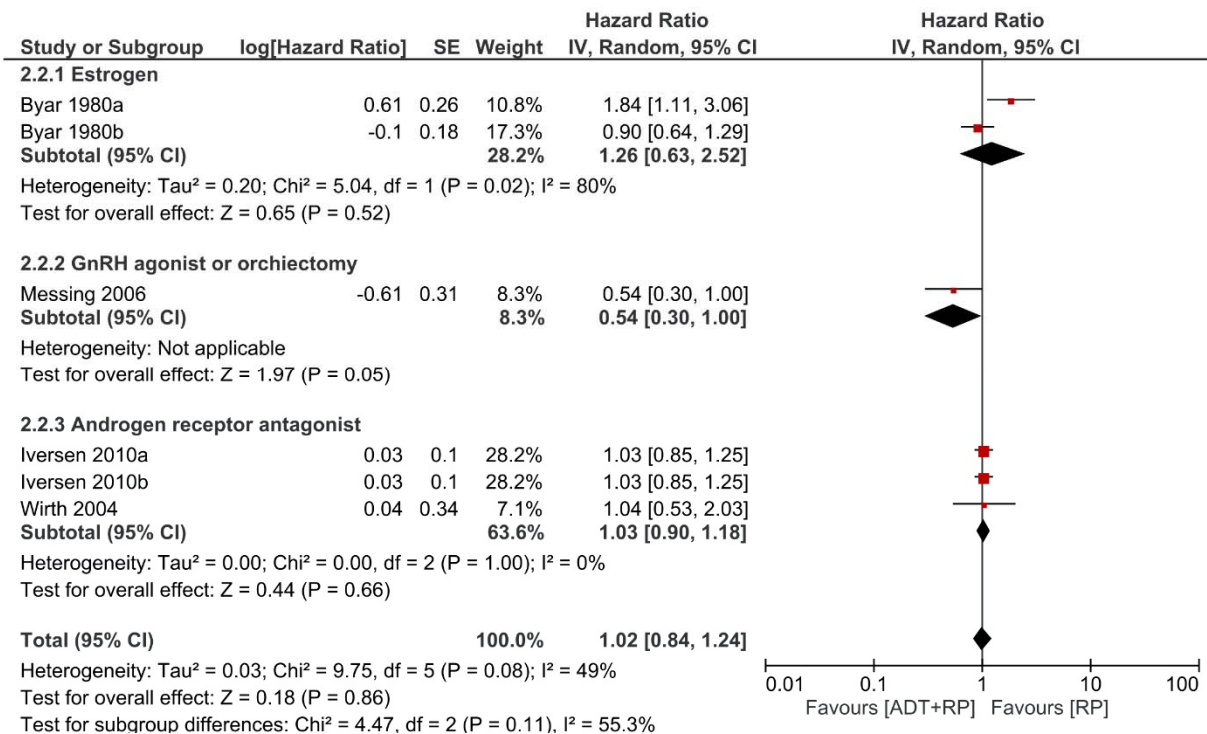
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Supplementary Fig. 6. Forest plot of distant metastases for neoadjuvant androgen-directed therapy y (ADT) with prostatectomy (RP) vs. RP alone. CI: confidence interval.



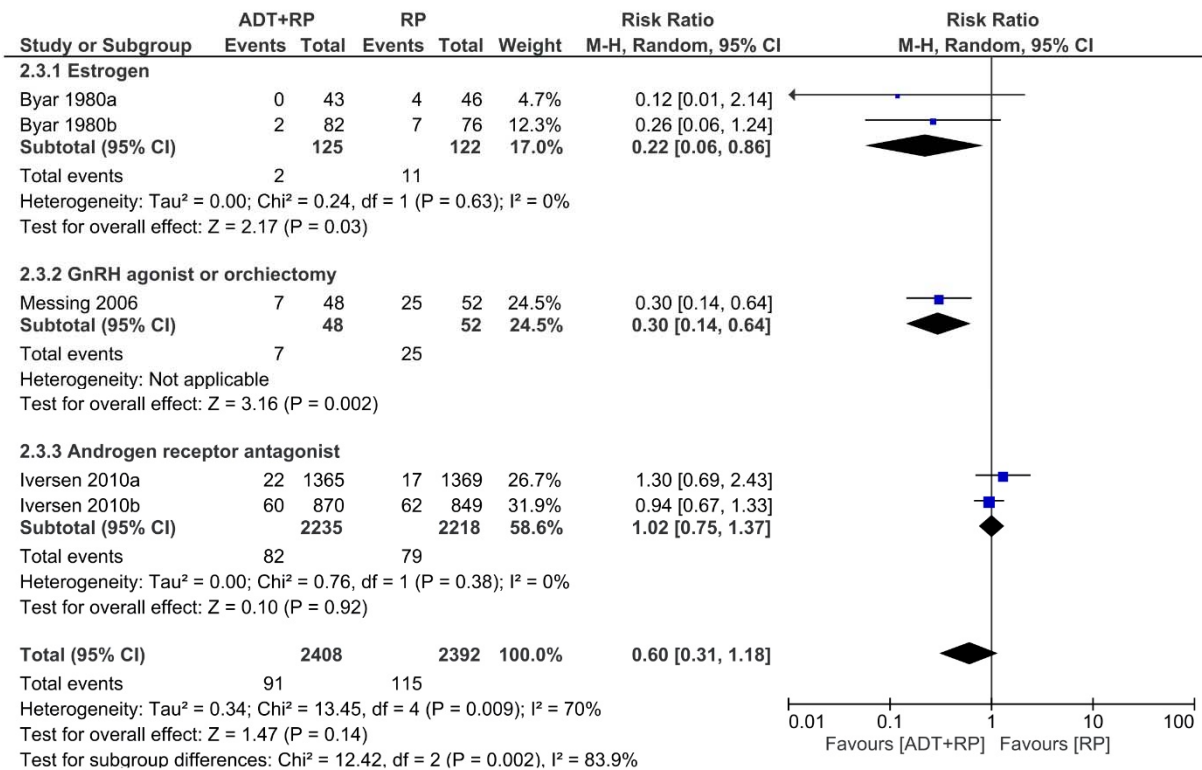
Nayak et al. Do androgen-directed therapies improve outcomes in prostate cancer patients undergoing radical prostatectomy? A systematic review and meta-analysis

Supplementary Fig. 7. Forest plot of hazard ratios of overall survival for adjuvant androgen-directed therapy (ADT) with prostatectomy (RP) vs. RP alone. *Byar 1980a corresponds to stage I prostate cancer; Byar 1980b corresponds to stage II prostate cancer. **Iversen 2010a corresponds to clinically localized prostate cancer; Iversen 2010b corresponds to locally advanced prostate cancer. CI: confidence interval.



Nayak et al. Do androgen-directed therapies improve outcomes in prostate cancer patients undergoing radical prostatectomy? A systematic review and meta-analysis

Supplementary Fig. 8. Forest plot of prostate cancer death for adjuvant androgen-directed therapy (ADT) with prostatectomy (RP) vs. RP alone. *Byar 1980a corresponds to stage I prostate cancer; Byar 1980b corresponds to stage II prostate cancer. This study did not present the total number of patients randomized to each group, therefore the total number analyzed was used in this analysis. **Iversen 2010a corresponds to clinically localized prostate cancer; Iversen 2010b corresponds to locally advanced prostate cancer. CI: confidence interval.



Nayak et al. Do androgen-directed therapies improve outcomes in prostate cancer patients undergoing radical prostatectomy? A systematic review and meta-analysis

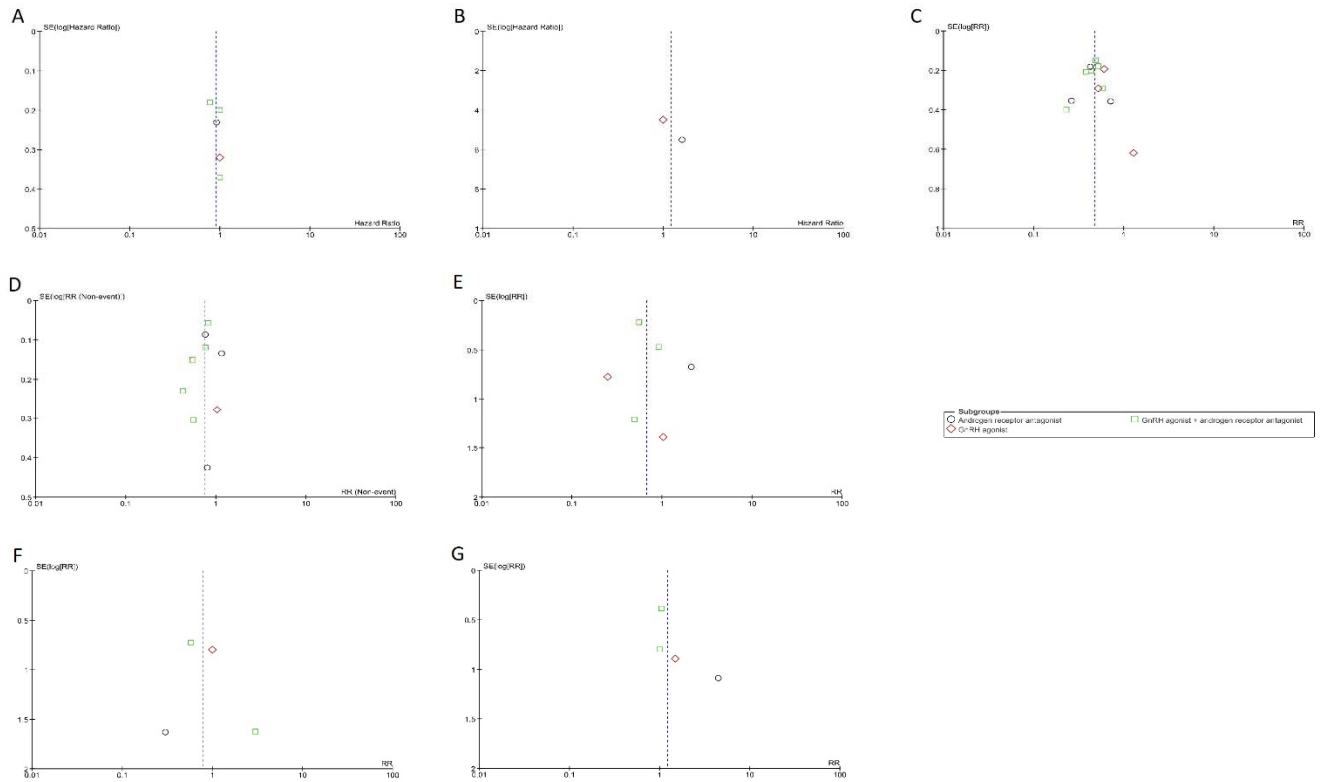
Supplementary Fig. 9. Risk of bias of included studies.

Study ID	Randomization process	Deviations from intended inte	Missing outcome data	Measurement of the outcome	Selection of the reported resul	Overall
Overall survival						
Byar 1980	?	+	+	+	+	!
Iversen 2010	+	+	+	+	+	+
Messing 2006	+	+	+	+	?	+
Wirth 2004	?	?	-	+	?	-
Aus 2002	?	+	+	+	?	!
Klotz 2003	+	?	+	+	?	!
Progression						
Byar 1980	?	?	+	?	?	!
Iversen 2010	+	+	+	?	+	!
Messing 2006	+	+	+	?	?	!
Wirth 2004	?	?	-	?	?	-
Aus 2002	?	+	+	?	?	!
Klotz 2003	+	?	+	?	?	!
Schulman 2000	?	?	?	+	+	!
Soloway 2002	?	?	+	+	+	!
Yee 2010	+	+	+	+	?	!
Surgical outcomes						
Aus 2002	?	+	+	+	?	!
Dalkin 1996	?	+	+	?	?	!
Gravina 2007	+	+	+	?	+	!
Klotz 2003	+	?	+	?	?	!
Labrie 1997	?	?	+	+	+	!
Prezioso 2004	?	?	+	?	+	!
Scattoni 2006	?	+	+	+	?	!
Schulman 2000	?	?	?	?	+	!
Selli 2002	?	?	+	?	?	!
Soloway 2002	?	?	+	+	+	!
Yee 2010	+	+	+	?	?	!



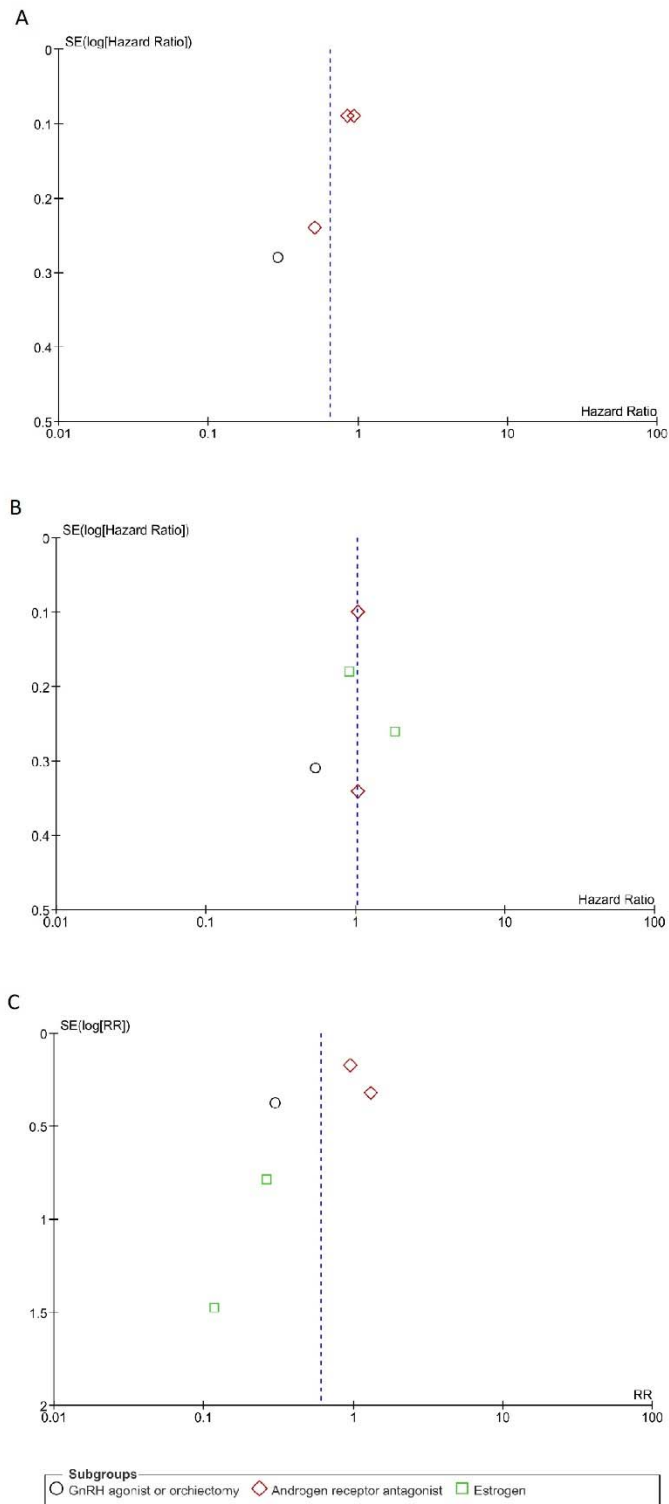
Nayak et al. Do androgen-directed therapies improve outcomes in prostate cancer patients undergoing radical prostatectomy? A systematic review and meta-analysis

Supplementary Fig. 10. Funnel plots of neoadjuvant androgen-directed therapy (ADT) study outcomes: (A) recurrence-free survival; (B) overall survival; (C) positive surgical margins; (D) pathologic extraprostatic extensions; (E) pathologic lymph node metastases; (F) prostate cancer death; and (G) distant metastasis.



Nayak et al. Do androgen-directed therapies improve outcomes in prostate cancer patients undergoing radical prostatectomy? A systematic review and meta-analysis

Supplementary Fig. 11. Funnel plots of adjuvant androgen-directed therapy (ADT) study outcomes: (A) recurrence-free survival; (B) overall survival; and (C) prostate cancer death.



Nayak et al. Do androgen-directed therapies improve outcomes in prostate cancer patients undergoing radical prostatectomy? A systematic review and meta-analysis

Supplementary Table 1. Definition of disease progression in relevant trials		
Study	PSA recurrence threshold	Definition of progression
Neoadjuvant ADT		
Schulman (2000) ²²	>1ng/mL	PSA recurrence, stage pT4 or pN2 disease, metastasis or local recurrence before PSA>1ng/mL
Aus (2002) ¹⁵	>0.5ng/mL	PSA recurrence
Soloway (2002) ²⁴	>0.4ng/mL	PSA recurrence
Klotz (2003) ¹⁹	>0.2ng/mL	PSA recurrence, retreatment, or death from prostate cancer
Yee (2010) ²⁵	>0.1ng/mL	PSA recurrence
Adjuvant ADT		
Byar (1980) ²⁸	N/A	First metastases, rise in acid phosphatase >2.0 King Armstrong Units, or death due to prostatic cancer
Iversen (2010) ²⁶	N/A	Earliest occurrence of objectively confirmed progression or death from any cause
Wirth (2004) ²⁷	>5ng/mL OR 2 values greater than 2ng/mL more than 3 months apart with increasing tendency OR 3 values greater than 1ng/mL more than 3 months apart with increase tendency	PSA recurrence or any clinical recurrence
Messing (2006) ²⁹	≥0.4ng/mL	PSA, clinical progression, or death from any cause

ADT: androgen-directed therapy; PSA: prostate-specific antigen.

Nayak et al. Do androgen-directed therapies improve outcomes in prostate cancer patients undergoing radical prostatectomy? A systematic review and meta-analysis

Supplementary Table 2. GRADE evidence profile								
Outcome	No of participants (studies)	Effect Estimate (95% CI)	Certainty of evidence					Quality
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	
Neoadjuvant ADT								
Positive surgical margins	2284 (11 RCTs)	RR 0.48 (0.41–0.56)	Serious ¹	No serious inconsistency	No serious indirectness	No serious imprecision	No serious publication bias	High
Pathologic extraprostatic extension	1672 (8 RCTs)	RR 0.75 (0.64–0.89)	Serious ¹	Serious inconsistency ²	No serious indirectness	No serious imprecision	No serious publication bias	Low
Pathologic lymph node metastases	1395 (6 RCTs)	RR 0.67 (0.43–1.03)	Serious ¹	No serious inconsistency	No serious indirectness	No serious imprecision	No serious publication bias	Moderate
Progression-free survival	1461 (5 RCTs)	HR 0.90 (0.74–1.11)	Serious ¹	No serious inconsistency	Serious indirectness ³	No serious imprecision	No serious publication bias	Low
Overall survival	339 (2 RCTs)	HR 1.22 (0.62–2.41)	Serious ¹	No serious inconsistency	No serious indirectness	Serious imprecision ⁴	No serious publication bias ⁵	Low
Distant metastases	974 (4 RCTs)	RR 1.22 (0.66–2.26)	Serious ¹	No serious inconsistency	No serious indirectness	Serious imprecision ⁴	Suspected publication bias ⁶	Low
Prostate cancer death	974 (4 RCTs)	RR 0.77 (0.30–2.01)	Serious ¹	No serious inconsistency	No serious indirectness	Serious imprecision ⁴	No serious publication bias	Low
Adjuvant ADT								
Progression-free survival	4906 (3 RCTs)	HR 0.60 (0.42–0.87)	Serious ¹	Serious inconsistency ²	Serious indirectness ³	No serious imprecision	Suspected publication bias ⁶	Low

Nayak et al. Do androgen-directed therapies improve outcomes in prostate cancer patients undergoing radical prostatectomy? A systematic review and meta-analysis

Overall survival	5205 (4 RCTs)	HR 1.02 (0.84– 1.24)	Serious ¹	No serious inconsistency	No serious indirectness	No serious imprecision	No serious imprecision	Moderate
Prostate cancer death	5205 (4 RCTs)	RR 0.60 (0.31– 1.18)	Serious ¹	Serious inconsistency ²	No serious indirectness	No serious imprecision	Suspected publication bias ⁶	Low

¹Majority of trials at unclear risk of bias across at least one domain. ²Substantial statistical heterogeneity ($I^2 > 50\%$). ³Cumulation of differences including outcome measurements (PSA threshold), patient population (cancer T stage), and forms of treatment. ⁴Wide 95% confidence interval. ⁵Unclear bias due to few trials reporting time-to-event; judgement is based off overall death rates reported across 4 RCTs. ⁶Observed small asymmetry in funnel plots. ADT: androgen-directed therapy; HR: hazard ratio; PSA: prostate-specific antigen; RCT: randomized controlled trial; RR: risk ratio.

Nayak et al. Do androgen-directed therapies improve outcomes in prostate cancer patients undergoing radical prostatectomy? A systematic review and meta-analysis

Supplementary Table 3. Ongoing clinical trials in studying ADT in prostate cancer patients undergoing radical prostatectomy			
Study ID	Population	Arms and interventions	Primary outcomes
Neoadjuvant ADT			
NCT04220398	Locally advanced, hormone-sensitive prostate cancer (cT3a-cT4, or any cT,cN1)	i) 4–6 months docetaxel, prednisone, bicalutamide and goserelin, followed by RP+PLND ii) 3–6 months bicalutamide and goserelin, followed by RP+PLND iii) RP + PLND	Biochemical progression-free survival
NCT02949284*	High risk prostate cancer (Gleason score >8 OR PSA>20, ≤cT3)	i) 3 months apalutamide, followed by RP ii) 3 months apalutamide, abiraterone acetate, GnRH agonist and prednisone, followed by RP iii) RP	Post-surgical potency
Adjuvant ADT			
NCT04295447	High risk prostate cancer treated with RP (Gleason ≥8 or Gleason 6-7 and ≥pT2c or pre-RP PSA>20ng/mL)	i) 30 cycles apalutamide 240 mg ii) Observation	Progression-free survival
NCT01442246	High risk prostate cancer treated with RP (R0, N0 or Nx or N+, M0 and Gleason ≥7, pT3b)	i) 24 months leuprorelin acetate 45 mg ii) Surveillance	Metastases-free survival
NCT01753297**	High risk prostate cancer treated with RP (Gleason ≥8 and/or pre-RP PSA≥20ng/mL and/or pT3a)	i) 9 months triptorelin 11.25 mg ii) Active surveillance	Biochemical progression-free survival

*Interim results of 24 patients have been published but are not included in this review.³⁶ **Complete, awaiting results. ADT: androgen-directed therapy; GnRH: gonadotropin-releasing hormone PLND: pelvic lymph node dissection PSA: prostate specific antigen; RP: radical prostatectomy.