Systematic Review and Meta-Analysis

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Comparative effectiveness of prostate cancer treatments for patient-centered outcomes

A systematic review and meta-analysis (PRISMA Compliant)

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Abstract

Background: In the context of prostate cancer (PCa) characterized by the multiple alternative treatment strategies, comparative effectiveness analysis is essential for informed decision-making. We analyzed the comparative effectiveness of PCa treatments through systematic review and meta-analysis with a focus on outcomes that matter most to newly diagnosed localized PCa patients.

Methods: We performed a systematic review of literature published in English from 1995 to October 2016. A search strategy was employed using terms "prostate cancer," "localized," "outcomes," "mortality," "health related quality of life," and "complications" to identify relevant randomized controlled trials (RCTs), prospective, and retrospective studies. For observational studies, only those adjusting for selection bias using propensity-score or instrumental-variables approaches were included. Multivariable adjusted hazard ratio was used to assess all-cause and disease-specific mortality. Funnel plots were used to assess the level of bias.

Results: Our search strategy yielded 58 articles, of which 29 were RCTs, 6 were prospective studies, and 23 were retrospective studies. The studies provided moderate data for the patient-centered outcome of mortality. Radical prostatectomy demonstrated mortality benefit compared to watchful waiting (all-cause HR = 0.63 CI = 0.45, 0.87; disease-specific HR = 0.48 CI = 0.40, 0.58), and radiation therapy (all-cause HR = 0.65 CI = 0.57, 0.74; disease-specific HR = 0.51 CI = 0.40, 0.65). However, we had minimal comparative information about tradeoffs between and within treatment for other patient-centered outcomes in the short and long-term.

Conclusion: Lack of patient-centered outcomes in comparative effectiveness research in localized PCa is a major hurdle to informed and shared decision-making. More rigorous studies that can integrate patient-centered and intermediate outcomes in addition to mortality are needed.

Abbreviations: ADT = androgen deprivation therapy, AS = active surveillance, BT = brachytherapy, CI = confidence interval, EBRT = external beam radiation therapy, ED = erectile dysfunction, HR = hazard ratio, HRQoL = health related quality of life, PCa = prostate cancer, PSA = prostate specific antigen, RARP = robot assisted radical prostatectomy, RCT = randomized controlled trial, RP = radical prostatectomy, RT = radiation therapy, UI = urinary incontinence, WW = watchful waiting.

Keywords: comparative effectiveness, informed shared decision, localized prostate cancer, patient centered outcomes, prostate cancer

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1. Introduction

Prostate cancer (PCa) is the most commonly diagnosed cancer, accounting for the 2nd highest cancer mortality among men in the US. In 2017, approximately 161,360 men will be diagnosed with PCa, and an estimated 26,730 will suffer PCa-related deaths.[1] More than 70% of PCa patients have localized disease and face uncertainty in treatment decision-making. Recent prostate specific antigen (PSA) testing guidelines have implications for long-term surveillance, outcomes, and cost of PCa care.[2] With a median age at diagnosis of 68 years, many patients, especially those with localized tumor, die of other illnesses.[1–3] Although PCa-related mortality has been declining since 1994, the aging baby boomers will increase the future absolute burden of PCa.[4]

For localized PCa, active surveillance (AS), radical prostatectomy (RP), and radiation therapy (RT) are the primary treatment choices.[5] The number of men treated with RP remained stable during 1990 to 2013, those treated with AS or watchful waiting (WW) increased and those receiving RT and hormone therapy decreased.[6] WW is distinct from AS in that WW is an unstructured follow-up, usually in men with an actuarial survival of $\leq$10 years, while AS is a structured program of PSA monitoring, physician exam, imaging, and pathological evaluation with biopsy. Decisions about management, especially for early stage PCa, require tradeoffs among multiple outcomes. Thus, shared-decision making is essential to ensure that patients receive the treatment best aligned with their personal preferences.[7–9] However, such decisions take place amidst considerable uncertainty about relative effectiveness of alternative treatments for a range of clinical and patient reported outcomes.

Comparative effectiveness is defined as the synthesis of evidence that compares benefits and harms of alternative methods to prevent, diagnose, or treat a clinical condition, or to improve the delivery of care.[10] In the context of PCa, characterized by the multiple alternative treatments, comparative effectiveness analysis is essential for informed decision-making. Identifying and interpreting the medical literature comparing the effectiveness of treatments can be a daunting task for patients and caregivers alike. Objective of this patient-centered systematic review and meta-analysis is to synthesize current evidence for outcomes to aid newly diagnosed localized PCa patients, caregivers, and healthcare providers in making informed, shared-decisions. Building on the existing comparative effectiveness reviews,[3,11,12] we focus on the patient-centered outcomes (stratified by disease risk classifications) that matter most to the patients.

2. Methods

2.1. Review procedure

We conducted a systematic review of all peer-reviewed, published studies of comparative effectiveness for PCa from 1995 to 2016. We searched Cochrane Library, Medline, PubMed, and Embase using the key terms "prostate cancer," "localized," "treatment," "outcomes," "mortality," "health related quality of life (HRQoL)," "complication," "cancer recurrence," "satisfaction with care," "decision regrets," "radiation therapy," "radical prostatectomy," and "comparative effectiveness," separately and in combination. These outcomes were identified as important outcomes by the patient-stakeholders and providers in our ongoing study.[13] The references of listed studies were also examined. The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses criteria.[14–16] The local institutional review board reviewed and approved the study.

2.2. Study selection

Randomized controlled trials (RCTs), case–control studies, and cohort or cross-sectional studies (prospective or retrospective) were eligible. For observational studies, only those adjusting for selection bias using propensity score or instrumental variable approaches were included. Studies that did not compare different treatment modalities, basic science studies, editorials/comment articles, and study protocols were excluded. Participants of all ages, and those with low, intermediate, and high risk patients per D'Amico criteria[17] were included. Studies were excluded if the intent of treatment was salvage therapy, if participants had clinical stage >T3a or if patient-centered outcomes (mortality, HRQoL, complications, cancer recurrence, satisfaction with care, and decision regrets) were not addressed. Additionally, studies that were irrelevant to current clinical practice (ie, perineal prostatectomy, and androgen deprivation therapy [ADT] alone) were excluded. In case of multiple articles from the same study or database, we favored those reporting longest follow-up, largest sample size, and greatest completeness of information. The review was performed by 3 independent reviewers. When these reviewers did not agree or no definite conclusion was reached, full text was retrieved for further evaluation, and disputes were resolved by a 4th reviewer.

2.3. Patient-centered outcome measures

Primary outcome measures were all-cause and disease-specific mortality; cancer recurrence; disease and treatment complications; side effects; and patient-reported outcomes, including generic and disease-HRQoL, satisfaction with care, and decision regrets. These latter outcomes were identified by patients, stakeholders, and providers in our patient-centered outcomes study as important patient-centered outcomes that aid in treatment choice.[13] Because treatment side-effects can negatively influence satisfaction with treatment, decision regret, or HRQoL,[18] information regarding the likelihood of side-effects is essential for informed decision-making.[19]

2.4. Data extraction

Following information was collected for eligible studies: name of first author, publication year, design, sample-size, patient characteristics, treatment type and duration, follow-up duration, primary and secondary outcomes, disease and treatment complications, side effects, and analytical strategy.

2.5. Analysis

We analyzed all-cause mortality, disease-specific mortality, cancer recurrence, complications and side-effects, HRQoL, satisfaction with care, and decision regret. We used Stata software, version 14.1 (StataCorp LP, College Station, TX) to perform 4 sets of meta-analyses of studies that compared mortality across treatment groups. Treatment data were pooled across study design to increase sample size and statistical power. Meta-regression was applied to test for heterogeneity due to study design. Pooled hazard ratios (HRs) were calculated as the weighted average with weighting assigned according to the inverse of the variance. We used the I^2 statistic to examine the heterogeneity of effect sizes. In general, I^2 values of 25% or

less indicate low heterogeneity, values near 50% indicate moderate heterogeneity, and values 75% or greater indicate high heterogeneity.[20] Random-effects models were used in all analyses.[21] Meta-regression was used to assess sensitivity of the pooled estimates to study characteristic (ie, study design type). To assess the publication bias, we plotted the logarithm of each study's estimated HR against the standard error of the estimate ("funnel plot").[22] Asymmetry in the plot potentially signals that studies with small, nonstatistically significant estimates are not being submitted or accepted for publication.

3. Results

3.1. Study characteristics

Figure 1 depicts study identification strategy. Fifty-eight studies met the inclusion criteria. Table 1 describes the quality of selected articles. To facilitate the use of information in clinical decisions, we summarized our findings based on the study design (Appendix A, http://links.lww.com/MD/B681). Table 2 provides a synthesis of evidence across patient-reported outcomes and PCa risk categories.[23] Next, we discuss the overall and disease-specific survival in relation to treatment, followed by other patient-centered outcomes.

3.2. Survival

Meta-analysis was conducted for mortality outcomes where there were more than 2 studies with the required information. There was moderate-to-high heterogeneity in the HR for disease-specific mortality ($I^2 = 56.0\%$, Appendix-B Fig. e2D, http://links.lww.com/MD/B681) and all-cause mortality ($I^2 = 69.2\%$, Appendix-B Fig. e2C, http://links.lww.com/MD/B681) for RP compared to RT and for all-cause mortality for RP compared to WW ($I^2 = 87.7\%$, Appendix-B Fig. e2A, http://links.lww.com/MD/B681). However, including an indicator for the study design provided no evidence that the study design contributed to the heterogeneity ($P > .09$). Publication bias exists, especially for studies comparing RP to RT in all-cause mortality (Appendix-B Fig. e2, http://links.lww.com/MD/B681).

3.3. Radical prostatectomy versus watchful-waiting

In an RCT of patients with well to moderately well-differentiated tumors, compared to WW, RP showed substantial disease-specific survival advantage in those with greater than 10-year life expectancy.[24] The Scandinavian Prostate Cancer Group Trial Number-4 trial with a 23-year follow-up found lower disease-specific mortality for RP compared to WW.[24–28] When stratified by risk group, disease-specific survival benefit persisted in

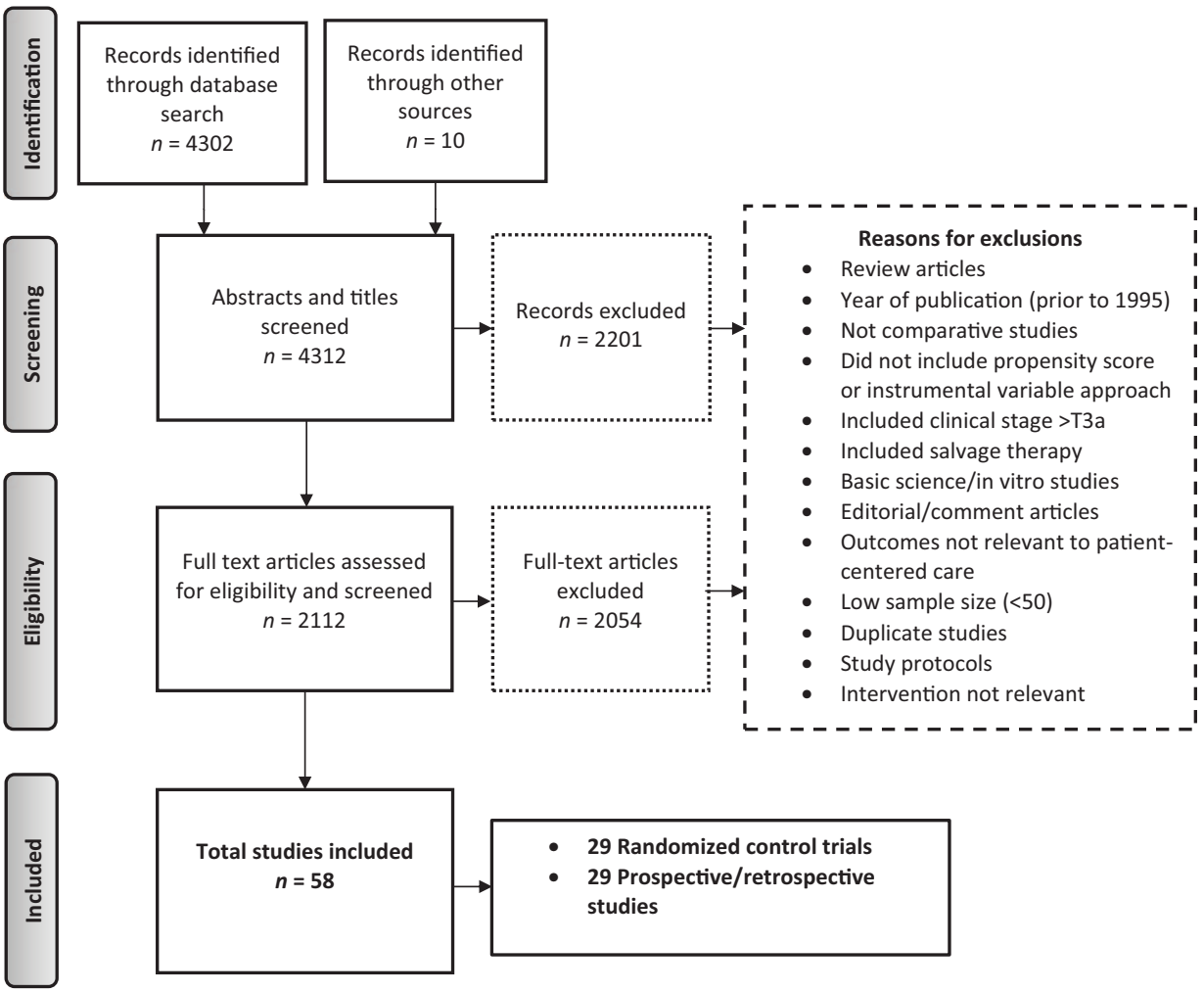

Figure 1. Literature search flow diagram (August 1995–October 2016).

Table 1

Quality assessment of selected review articles.

Study/author, y	Study type	Adequate sample size	Similarity of comparative group	Adequate follow-up (5 years for mortality, 2 for other outcomes)	Primary patient centered outcome/endpoint	Significant HR (or RR) and CI for all primary outcomes/endpoints	Overall risk of bias	Overall study quality GRADE (1–4)
1. Holmberg (2002)	RCT	Yes	Yes	Yes	Disease-specific survival	Yes	Low	4
2. Steineck (2002)	RCT	No	Yes	Yes	HRQoL	No	Intermediate	4
3. Johansson (2009)	RCT	Yes	Yes	Yes	HRQoL	Yes	Intermediate	4
4. Bill-Axelson (2011)	RCT	Yes	Yes	Yes	Disease-specific survival	Yes	Low	4
5. Holmberg (2012)	RCT	Yes	Yes	Yes	Survival, metastasis, HRQoL	Yes	Low	4
6. Wilt (2012)	RCT	Yes	Yes	Yes	Overall survival	No	Low	4
7. Bill-Axelson (2014)	RCT	Yes	Yes	Yes	Disease-specific and overall survival, metastasis	Yes	Low	4
8. Pierro (2011)	RCT	Yes	Yes	Yes	Complications, HRQoL	Yes	Low	3*
9. Asimakopoulos (2011)	RCT	Yes	Yes	No	Erectile function	Yes	Intermediate	1*,†,‡
10. Porpiglia (2012)	RCT	Yes	Yes	Yes	Urinary continence	Yes	Intermediate	2*,‡
11. Van Poppel (1995)	RCT	Yes	Yes	Yes	Side effects	Yes	Low	3*
12. Soloway (1995)	RCT	Yes	Yes	Yes	Complications	Yes	Low	4
13. Dalkin (1996)	RCT	No	Yes	No	Biochemical cancer recurrence	No	Low	3*
14. Goldenberg (1996)	RCT	Yes	Yes	Yes	Complications	Yes	Low	4
15. Aus (1998)	RCT	No	Yes	Yes	Biochemical cancer recurrence	No	Low	3*
16. Klotz (1999)	RCT	Yes	Yes	No	Biochemical cancer recurrence	No	Low	4
17. Gleave (2001)	RCT	Yes.	Yes	Yes	Biochemical cancer recurrence	Yes	Low	4
18. D'Amico (2004)	RCT	Yes	Yes	No	Overall survival	Yes	Low	3†
19. D'Amico (2008)	RCT	Yes	Yes	Yes	Overall survival	Yes	Low	4
20. Yee (2010)	RCT	Yes	Yes	Yes	Biochemical cancer recurrence	No	Low	3*
21. Jones (2011)	RCT	Yes	Yes	Yes	Overall survival	Yes	Low	4
22. Lukka (2005)	RCT	Yes	Yes	Yes	Biochemical cancer recurrence	No	Low	4
23. Norkus (2009)	RCT	Yes	Yes	No	HRQoL, complications	No	Low	2*,†
24. Zietman (2010)	RCT	Yes	Yes	Yes	Biochemical cancer recurrence, overall survival	No	Low	4
25. Yeoh (2011)	RCT	No	Yes	Yes	Biochemical cancer recurrence, overall survival	No	Low	4
26. Fransson (2001)	RCT	No	Yes	Yes	HRQoL	No	Intermediate	3*
27. Hamdy (2016)	RCT	Yes	Yes	Yes	Survival, cancer recurrence, and HRQoL	No	Low	4
28. Yaxley (2016)	RCT	Yes	Yes	Res	HRQoL	No	Low	4
29. Hoffman (2016)	RCT	Yes	Yes	yes	HRQoL	No	Low	4
30. Krygiel (2005)	Prospective	Yes	Propensity score	Yes	Biochemical cancer recurrence	Yes	Intermediate	3§
31. Magheli (2010)	Prospective	Yes	Propensity score	No	Biochemical cancer recurrence	No	Intermediate	2†,§
32. Kibel (2012)	Prospective	Yes	Propensity score	Yes	Overall and disease-specific survival	No	Intermediate	3§
33. Hoffman (2013)	Prospective	Yes	Propensity score	Yes	Overall and disease-specific survival	Yes	Intermediate	3§
34. Nepple (2013)	Prospective	Yes	Propensity score	Yes	Overall and disease-specific survival	No	Intermediate	3§
35. Davison (2014)	Prospective	Yes	Propensity score	No	HRQoL, decision regret	No	High	1†,‡,§
36. Potosky (2000)	Retrospective	Yes	Propensity score	Yes	HRQoL	Yes	Low	3§
37. Wong (2006)	Retrospective	Yes	Propensity score	Yes	Overall survival	Yes	Intermediate	3§
38. Tewari (2007)	Retrospective	Yes	Propensity score	Yes	Overall and disease-specific survival	Yes	Intermediate	3§
39. Albertsen (2007)	Retrospective	Yes	Propensity score	Yes	Overall and disease-specific survival	No	Intermediate	3§
40. Merglen (2007)	Retrospective	Yes	Propensity score	Yes	Disease-specific survival	Yes	Intermediate	3§
41. Abdollah (2011)	Retrospective	Yes	Propensity score	Yes	Overall and disease-specific survival	Yes	Intermediate	3§

(*continued*)

Table 1

(continued).

Study/author, y	Study type	Adequate sample size	Similarity of comparative group	Adequate follow-up (5 years for mortality, 2 for other outcomes)	Primary patient centered outcome/endpoint	Significant HR (or RR) and CI for all primary outcomes/endpoints	Overall risk of bias	Overall study quality GRADE (1–4)
42. Sheets (2012)	Retrospective	Yes	Propensity score	Yes	HRQoL, complications	No	Intermediate	3[§]
43. Trinh (2012)	Retrospective	Yes	Propensity score	Yes	Complications	Yes	Intermediate	3[§]
44. Liu (2013)	Retrospective	Yes	Propensity score	No	Overall and disease-specific survival	Yes	Intermediate	3[†,§]
45. Nakayama (2013)	Retrospective	No	Propensity score	Yes	Overall and disease-specific survival	Yes	Intermediate	2[*,§]
46. Resnick (2013)	Retrospective	Yes	Propensity score	Yes	Survival, HRQoL	No	Intermediate	3[§]
47. Gandaglia (2014)	Retrospective	Yes	Instrumental Variable	Yes	Complications	Yes	Intermediate	3[§]
48. Hu (2014)	Retrospective	Yes	propensity score	Yes	Complications	Yes	Intermediate	3[§]
48. Lu-Yao (2014)	Retrospective	Yes	Instrumental variable	Yes	Overall and disease-specific survival	No	Intermediate	3[§]
50. Sun (2014)	Retrospective	Yes	Instrumental Variable	Yes	Overall and disease-specific survival	Yes	Intermediate	3[§]
51. Sooriakumaran (2014)	Retrospective	Yes	Propensity score	Yes	Overall and disease-specific survival	Yes	Intermediate	3[§]
52. Crandley (2014)	Retrospective	Yes	Propensity score	Yes	HRQoL, complications	Yes	Intermediate	3[§]
53. Daskivich (2014)	Retrospective	Yes	Propensity score	No	Disease-specific survival	No	Intermediate	2[*,§]
54. Lee (2014)	Retrospective	Yes	Propensity score	Yes	Disease-specific survival	Yes	High	2[‡,§]
55. Smith (2015)	Retrospective	Yes	Propensity score	Yes	Biochemical cancer recurrence	Yes	Intermediate	3[§]
56. Basu (2015)	Retrospective	Yes	IV	Yes	Overall survival	No	Intermediate	3[§]
57. Bekelman (2015)	Retrospective	Yes	IV and propensity score	Yes	Overall and disease-specific survival	Yes	Intermediate	3[§]
58. Wallis (2016)	Retrospective	Yes	Propensity score	Yes	Complications	Yes	Intermediate	3[§]

IV = instrumental variable approach, HRQoL = health related quality of life, RCT = randomized controlled trial, HR = hazard ratio.

[*] Reasons for GRADE score downgrade: sparse data ($n < 200$).

[†] Reasons for GRADE score downgrade: inadequate follow-up time period (5-years for survival, 2-years for other outcomes).

[‡] Reasons for GRADE score downgrade: restricted population.

[§] Reason for GRADE score upgrade: adjustment for confounders/effect size.

Table 2

Synthesis of evidence across risk groups and patient centered outcomes.

Treatments	Mortality	Cancer recurrence and metastasis	Complications	Side effects and health related quality of life
D'Amico risk group – low risk – PSA < 10, Gleason score ≤6, clinical stage T1 – 2a				
WW	Overall survival: RP or RT improved survival in men aged 65 to 80 y compared to WW (Wong 2006). With <10 y life expectancy, WW associated with lower 10-y survival compared to RP and RT (Sun 2014). Disease-specific survival: In men ≤ 75 y, RP improved survival than WW (Albertsen 2007).	Bone metastasis was more common with WW compared to RP (Wilt 2012).	Weak urinary stream was reported by 28% RP and 44% of WW men after mean 4 y follow-up (Steineck 2002)	After a mean follow-up of 4 y, bowel function, well-being, anxiety, depression, and subjective quality of life was comparable between RP and WW (Steineck 2002). WW patients had higher prevalence of satisfactory erectile function and urinary control in the initial 2 to 5 y after diagnosis (Potosky 2000, Steineck 2002).
RP, RARP, LRP	Overall survival: Survival benefit with RP compared to WW (Bill-Axelson 2014). Survival benefit with RP compared to RT and WW (Sun 2014). Disease-specific survival: With ≥10 y life expectancy, improved survival with RP compared to WW (Holmberg 2012). With ≥10 y life expectancy, RP improved survival compared to RT (Sun 2014).	RP was associated with a reduced risk of metastasis compared to WW (Bill-Axelson 2014).	Most common complications in the first 30 days of RP are - wound infection, followed by urinary tract infection, surgical repair, bleeding, and urinary catheterization (Wilt 2012).	Higher side effects with RP compared to WW, including erectile dysfunction, urinary incontinence, constipation, defecation urgency, blood/mucus in stools, diarrhea, fecal leakage, distress from symptoms (Holmberg 2012, Steineck 2002, Potosky 2000). Ability for intercourse and time to ability for intercourse significantly lower for RARP compared to LRP (Asimakopoulos 2011). No difference in HRQoL outcomes at 12 mo between LRP and RARP (Davison 2014). Continence rates and recovery of erectile function were higher in RARP vs LRP (Porpiglia 2013).
RT, EBRT, IMRT, BT, or PT	Overall survival: Survival advantage with RP over EBRT and BT (Kibel 2012). Improved survival with BT compared to EBRT (Smith 2015). Survival between high-dose and low-dose RT were comparable (Zietman 2010). With <10 y of life expectancy, RP and RT had comparable survival (Sun 2014). Disease-specific survival: RP improved survival over RT (Albertsen 2007).	Superior long-term cancer control with high dose RT compared to convention RT (Zietman 2010).	Gastrointestinal and genitourinary toxicities did not differ amongst RT dose schedules (Yeoh 2010). Acute GI/GU toxicity higher in shorter schedule vs longer, late toxicity was low in both (Lukka 2005).	Comparable disease-specific urinary, sexual and bowel outcomes with RT compared to RP (15-y following treatment) (Resnick 2013). No significant differences observed between RT and WW in terms of fatigue, nausea/vomiting, and pain symptom scales (Fransson 2001). RT men shown to have decreased social functioning compared to WW due to hematuria, urinary incontinence, mucus, and planning of daily activity because of intestinal problems (Fransson 2001).

(*continued*)

Table 2
(continued).

Treatments	Mortality	Cancer recurrence and metastasis	Complications	Side effects and health related quality of life
ADT	Overall survival: Comparable survival for primary ADT vs WW (Lu-Yao 2014). Comparable survival for ADT prior to RP vs RP alone (Jones 2011). Disease-specific survival: Comparable survival for primary ADT vs WW (Lu-Yao 2014). Survival rates for ADT prior to RP vs RP alone were comparable (Jones 2011).	No improvement in biochemical recurrence or metastasis with neoadjuvant ADT (prior to RP) vs RP alone (Soloway 1995, Aus 1998, Klotz 1999, Yee 2010).	No difference in perioperative blood loss, operating time, need for transfusion or length of stay with neoadjuvant ADT (prior to RP) when compared to RP alone (Soloway 1995).	Most common side effects with ADT included hot flashes, diarrhea, nausea with or without vomiting, and abnormalities in liver function tests (Soloway 1995). Compared with EBRT, neoadjuvant ADT with EBRT showed increase in mild to moderate gynecomastia and severe impotence (D'Amico 2004).
D'Amico risk group – medium risk – PSA 10–20, Gleason score of 7, or are in clinical stage T2b				
WW	Overall survival: Survival advantage with RP or RT in men aged 65–80 y compared to WW (Wong 2006). With <10 y life expectancy, WW associated with lower 10-y survival compared to RP and RT (Sun 2014). Disease-specific survival: Survival benefit with RP over WW (Albertsen 2007).	Bone metastasis was more common with WW compared to RP (Wilt 2012).	Weak urinary stream was reported by 28% RP and 44% of WW men after mean 4 y follow-up (Steineck 2002).	After a mean follow-up of 4 y, bowel function, well-being, anxiety, depression, and subjective quality of life was comparable between RP and WW (Steineck 2002). WW patients had higher prevalence of satisfactory erectile function and urinary control in the initial 2 to 5 y after diagnosis (Potosky 2000, Steineck 2002).
RP, RARP, LRP	Overall survival: Survival benefit was shown for stage T2a/b tumors with RP over RT and WW (Sun 2014). Disease-specific survival: Survival benefit of RP was largest in men ≤65 compared to WW (Bill-Axelson 2014).	RP reduces risk of Metastasis by 19.9% compared to WW (Bill-Axelson 2014).	Most common complications in the first 30 days of RP are - wound infection, followed by urinary tract infection, surgical repair, bleeding, and urinary catheterization (Wilt 2012).	Higher side effects with RP compared to WW, including erectile dysfunction, urinary incontinence, constipation, defecation urgency, blood/ mucus in stools, diarrhea, fecal leakage, distress from symptoms (Holmberg 2012, Steineck 2002, Potosky 2000). No difference in HRQoL outcomes at 12 mo between LARP and RARP (Davison 2014).Continence rates and recovery of erectile function were higher in RARP vs LRP (Porpiglia 2013). Ability for intercourse and time to ability for intercourse significantly lower for RARP compared to LRP (Asimakopoulos 2011).
RT, EBRT, IMRT, BT, or PT	Overall survival: Overall survival benefit with RP over EBRT and BT (Kibel 2012). BT was associated with improved in biochemical free survival compared to EBRT (Smith 2015). Men with <10 y life expectancy, survival rates between RP and RT were comparable (Sun 2014). Disease-specific survival: Survival rate was higher with RP compared to RT (Albertsen 2007).	Superior long-term cancer control with high dose RT compared to convention RT (Zietman 2010).	Gastrointestinal and genitourinary toxicities did not differ amongst RT dose schedules (Yeoh 2010). Acute GI/GU toxicity higher in shorter schedule vs longer, but late toxicity was low in both (Lukka 2005).	Comparable disease-specific urinary, sexual and bowel outcomes with RT compared to RP (15-y following treatment) (Resnick 2013). No significant differences observed between RT and WW in terms of fatigue, nausea/vomiting, and pain symptom scales (Fransson 2001). RT men shown to have decreased social functioning compared to WW due to hematuria, urinary incontinence, mucus, and planning of daily activity because of intestinal problems (Fransson 2001).

(*continued*)

Table 2
(continued).

Treatments	Mortality	Cancer recurrence and metastasis	Complications	Side effects and health related quality of life
ADT	Overall survival: Primary ADT showed no survival benefit over 5-y compared to WW (Lu-Yao 2014). No difference in post-op mortality with neoadjuvant ADT (prior to RP) when compared to RP alone (Soloway 1995). Disease-specific survival No survival benefit with primary ADT compared to WW (Lu-Yao 2014).	No improvement in biochemical recurrence or metastasis with neoadjuvant ADT (prior to RP) vs RP alone (Soloway 1995, Aus 1998, Klotz 1999, Yee 2010).	No difference in perioperative blood loss, operating time, need for transfusion or length of stay with neoadjuvant ADT (prior to RP) when compared to RP alone (Soloway 1995).	Most common side effects with ADT included hot flashes, diarrhea, nausea with or without vomiting, and abnormalities in liver function tests (Soloway 1995). Compared with EBRT alone, patients who underwent neoadjuvant ADT with EBRT experienced significant increases in mild to moderate gynecomastia and severe impotence (in men potent at baseline) (D'Amico 2004).
D'Amico risk group – high risk – PSA > 20, Gleason score ≥8, or clinical stage T2c-3a				
WW	Overall survival: With <10 y life expectancy, WW associated with lower overall 10-y survival compared to RP and RT (Sun 2014). Disease-specific survival: Survival benefits with RP over WW (Albertsen 2007).	Bone metastasis was more common with WW compared to RP (Wilt 2012).	Weak urinary stream was reported by 28% RP and 44% of WW men after mean 4 y follow-up (Steineck 2002).	After a mean follow-up of 4 y, bowel function, well-being, anxiety, depression, and subjective quality of life was comparable between RP and WW (Steineck 2002). WW patients had higher prevalence of satisfactory erectile function and urinary control in the initial 2 to 5 y after diagnosis (Potosky 2000, Steineck 2002).
RP, RARP, LRP	Overall survival: Absolute risk of mortality was comparable between RP and WW (Bill-Axelson 2014). Survival benefit with RP compared to RT and WW (Sun 2014). Disease-specific survival: Mortality was comparable between RP and WW (Bill-Axelson 2014). RP decreases mortality compared to RT (Lee 2014). With >10-y life expectancy, RP improves survival compared to RT and WW (Sun 2014). Higher 10-y survival with RP compared to RT and WW (Albertsen 2007).	The risk of metastasis was comparable between RP and WW (Bill-Axelson 2014). RP has provided good long-term clinical outcomes and avoided the use of ADT in 70% patients (Liu 2013).	Most common complications in the first 30 days of RP are - wound infection, followed by urinary tract infection, surgical repair, bleeding, and urinary catheterization (Wilt 2012).	Higher side effects with RP compared to WW, including erectile dysfunction, urinary incontinence, constipation, defecation urgency, blood/mucus in stools, diarrhea, fecal leakage, distress from symptoms (Holmberg 2012, Steineck 2002, Potosky 2000). RARP showed improved surgical margins, less use of post-surgery ADT and RT compared to RP (Hu 2014). No difference in HRQoL outcomes at 12 m between LARP and RARP (Davison 2014). Continence rates and recovery of erectile function were higher in RARP vs LRP (Porpiglia 2013). Ability for intercourse and time to ability for intercourse significantly lower for RARP compared to LRP (Asimakopoulos 2011).

(*continued*)

Table 2

(continued).

Treatments	Mortality	Cancer recurrence and metastasis	Complications	Side effects and health related quality of life
RT, EBRT, IMRT, BT, or PT	Overall survival: Overall survival advantage with RP compared to BT (Kibel 2012). In men with <10 y life expectancy, survival rates between RP and RT were comparable (Sun 2014).	Superior long-term cancer control with high dose RT compared to convention RT (Zietman 2010).	Gastrointestinal (GI) and genitourinary (GU) toxicities did not differ amongst RT dose schedules (Yeoh 2010). GI/GU toxicity higher in shorter schedule vs longer, but late toxicity was low in both (Lukka 2005).	Comparable disease-specific urinary, sexual and bowel outcomes with RT compared to RP (Resnick 2013). No differences between RT and WW in terms of fatigue, nausea/vomiting, and pain symptom scales (Fransson 2001). RT men shown to have decreased social functioning compared to WW due to hematuria, urinary incontinence, mucus, and planning of daily activity because of intestinal problems (Fransson 2001).
ADT	Overall survival: No survival benefit with primary ADT compared to WW (Lu-Yao 2014). Increased survival with ADT plus RP compared to ADT alone (Bekelman 2015). Addition of 6-mo of ADT to RT resulted in increased survival (D'Amico 2008). PCa-specific survival: No survival benefits with primary ADT compared to WW (Lu-Yao 2014). Increased survival with ADT plus RP compared to ADT alone (Bekelman 2015).	No improvement in biochemical recurrence or metastasis with neoadjuvant ADT (prior to RP) vs RP alone (Soloway 1995, Aus 1998, Klotz 1999, Yee 2010).	No difference in perioperative blood loss, operating time, need for transfusion or length of stay with neoadjuvant ADT (prior to RP) when compared to RP alone (Soloway 1995).	Most common side effects with ADT included hot flashes, diarrhea, nausea with or without vomiting, and abnormalities in liver function tests (Soloway 1995). Compared with EBRT alone, patients who underwent neoadjuvant ADT with EBRT experienced significant increases in mild to moderate gynecomastia and severe impotence (in men potent at baseline) (D'Amico 2004).

ADT = androgen deprivation therapy, BT = brachytherapy, EBRT = external beam radiation therapy, IMRT = intensity modulated radiation therapy, LRP = laparoscopic radical prostatectomy, PT = proton therapy, RARP = robotic assisted radical prostatectomy, RP = radical prostatectomy, RT = radiation therapy, WW = watchful waiting.

intermediate-risk group[25] while overall survival advantage was higher in low and intermediate-risk groups.[25] In contrast, the US-based Prostate Cancer Intervention Versus Observation Trial showed no benefits for RP compared to WW in all-cause and disease-specific mortality.[28] The recent ProtecT trial reported that 10-year disease-specific and all-cause mortality were comparable across AS, RP, and RT groups.[29]

In one retrospective study, both RP and RT exhibited improved survival compared to WW in men aged 65 to 80 years and with low or intermediate-risk.[30] Another retrospective study reported an approximate 50% reduction in 10 year disease-specific mortality compared to WW in patients aged 65 or older.[31] Disease-specific survival benefit from RP or RT compared to WW for early-stage PCa diminished with increasing comorbidity.[32] In contrast, in another retrospective study, RP did not improve 11 year overall morality compared to WW in older men when stratified by age, race, grade, and stage nor did disease-specific mortality in those aged 65 or older.[33] Consistent with these findings, our pooled analysis showed a reduced risk of disease-specific mortality (pooled-HR = 0.48, 95% confidence interval [CI] = 0.40, 0.58) and all-cause mortality (HR = 0.63, CI = 0.45, 0.87) with RP, compared to WW (Fig. 2).

3.4. Radical prostatectomy, radiation therapy, and watchful-waiting

Compared to both external beam radiation therapy (EBRT) and WW, RP was associated with survival advantage.[34–36] Risk of disease-specific mortality post-RP was 68% lower than WW, and 49% lower than RT.[36] Two other studies also reported better overall survival for RP than RT or WW over 10 to 15 year follow-up.[37] Regardless of tumor stage, RP had improved survival compared with RT[38] and WW, in patients with >10 years of life expectancy.[39] However, when life expectancy was <10 years, survival was comparable between RP and RT.[36]

As RT for PCa varies in terms of modality, length, and dosage schedules and has changed over time, we stratified comparison involving RT by modalities. In men without comorbidity, RP was associated with better overall survival than both brachytherapy (BT) and EBRT.[40] Three other retrospective studies reported improved overall survival benefit for RP compared to EBRT.[41,42] The latter study also found a small but significant benefit in disease-specific survival for RP compared to EBRT.[43] Similarly, as shown in Fig. 2, our pooled estimates found that RP was associated with reduced disease-specific mortality (HR = 0.51, CI = 0.40, 0.65) and all-cause mortality (HR = 0.65, CI = 0.57, 0.74) compared to EBRT.

Although compared to conventional dose EBRT, biochemical relapse-free survival was improved at 90-months with a hypofractionated (higher dose of radiation over a shorter time period) dose schedule, overall survival between RT and EBRT was comparable.[44] Compared to EBRT, BT was associated with improved biochemical-free survival in PCa patients with low or intermediate-risk.[45] Among RT patients, a delay in treatment of 6 months or greater after biopsy was associated with increased risk of biochemical progression.[46]

3.5. Androgen deprivation therapy (ADT) alone or in combination with RT or RP

To date, there is no evidence of any clinical benefit of primary ADT without RP or RT for localized PCa.[47–50] Compared to

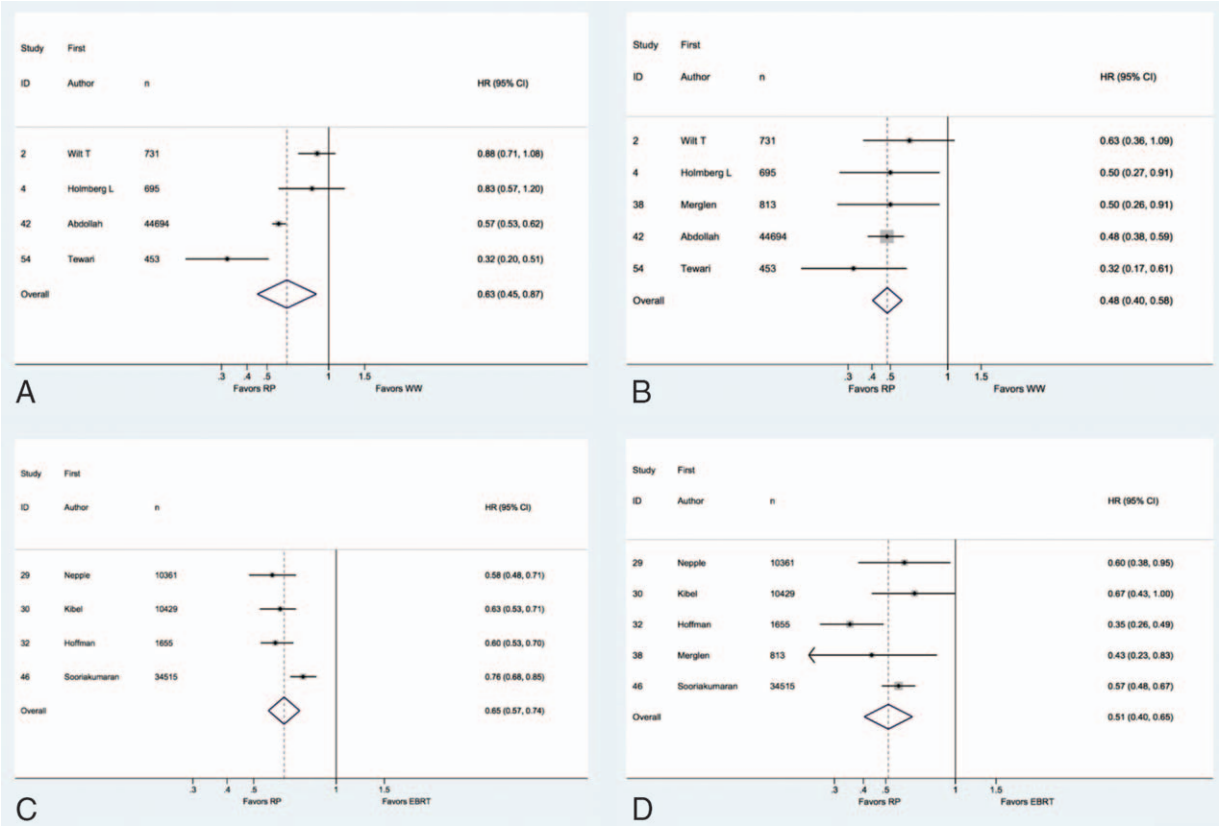

Figure 2. Forrest-plots summarizing meta-analysis results.

RP, primary ADT was associated with higher all-cause and disease-specific mortality.[49,51] Although some earlier studies compared RP with and without ADT,[52–57] currently use of ADT with RP is not recommended.[17] Neoadjuvant-ADT prior, during, or post-RT is primarily recommended for high or intermediate risk groups.[17,58] One retrospective study found that the optimal duration of ADT was longer than 3 months.[59] Men undergoing neoadjuvant ADT showed lower disease-specific mortality and higher overall survival compared to RT alone in high and intermediate-risk groups.[60,61]

3.6. Cancer recurrence or metastasis

There are few comparative effectiveness studies with recurrence as primary endpoint. Two qualifying studies found higher recurrence/metastatic disease in WW compared to RP patients. In localized tumor patients, bone metastases were less common in RP (4.7%) compared to WW patients (10.6%).[28] A study with 15-year follow-up found that 21.7% of RP versus 33.4% of WW patients had distant metastasis.[25,26,62]

3.7. Treatment complications and side effects

No difference in perioperative results and complications were observed between laparoscopic and robot assisted radical prostatectomy (RARP) patients.[63] Although 1 trial found comparable rates of 60 and 90 day complications in RP or RARP patients,[64] most studies found RARP associated with fewer adjusted perioperative outcomes compared to open RP.[65,66] In one trial, RARP offered slightly better results for positive tumor margins, major complications, urinary continence, and erectile function, compared to open retro-pubic RP.[67] However, in a recent RCT, functional outcomes were comparable at 3 months follow-up for RARP and RP.[68] Another study reported benefit of RARP in improving surgical margin status relative to open RP for intermediate and high-risk disease and less use of ADT and RT post-RP.[69] In one RCT comparing RP alone to RP preceded by ADT, there was no group difference in operating time, blood loss, need for transfusion, postoperative morbidity, or length of stay.[54]

Prevalence of erectile dysfunction (ED), urinary incontinence (UI), bowel dysfunction (eg, constipation, fecal urgency, blood/mucus in stool, incontinence, and diarrhea), and symptoms related distress was higher in RP compared to WW patients.[24,70] Although WW patients had high prevalence of satisfactory erectile function, they had weaker urinary streams and more negative psychological symptoms compared to RP patients.[70] Despite comparable need for frequent urination, a higher proportion of RP patients reported leaking urine ≥2 per day and wearing pads compared to RT patients.[19] Men undergoing RP were more likely to suffer from UI and ED, compared to RT patients.[35,40,71] Compared to laparoscopic-RP and open-RP, RARP had better short-term outcomes, continence, and erectile function.[63,72,73]

Compared to RP, those with RT experienced more bowel symptoms, with twice as many RT patients reporting diarrhea, bowel urgency, or painful hemorrhoids.[19] Bowel dysfunction was most prominent within 4 months of treatment, and improved somewhat overtime.[19] Gastrointestinal and genitourinary toxicity persisted up to 60 months post-RT, and did not differ by dose schedules.[44,74] However, a recent study using the Surveillance, Epidemiology, and End Results-Medicare data showed that those treated with RT rather than RP had higher rates of complications requiring urologic and rectal–anal procedures but lower rates of open surgeries.[75] One RCT reported less toxicity for hypofractionated schedule than for conventional fractionation schedule.[76] Studies comparing different forms of RT showed less gastrointestinal morbidity, fewer hip fractures, but impaired UI and higher rates of ED with intensity-modulated RT compared with conformal RT.[71,77,78] Most common adverse effects of ADT were sexual function side effects including loss of libido and ED,[18] followed by physiologic effects.[79,80]

3.8. Health related quality of life

Compared to RP, WW patients had significantly impaired HRQoL after follow-up of 6 to 8 years.[18] More RP patients reported ED (80% vs 45%) and UI (49% vs 21%), compared to WW, and fewer had urinary obstruction (28% vs 44%). Bowel function, anxiety, depression, well-being, and HRQoL were comparable between RP and WW patients.[70] In an RCT, RP patients reported greater psychological effects compared to WW.[24,27] In a recent ProtecT trial, 5 year patterns of severity, recovery and decline in urinary, bowel, and sexual functions and associated HRQoL, differed among AS, RP, and RT patients.[81]

Within RP, HRQoL was comparable between laparoscopic and RARP groups,[82] whereas RARP reported fewer short-term adverse outcomes compared to RP.[73] A higher proportion of RP patients were bothered by urinary function and had a "big" or "moderate" problem with dripping/leaking urine, compared to RT patients.[19] Compared to RP patients, those with RT were more likely to report overall health as fair or poor (22.7% vs 11.5%).[19,83] Despite higher prevalence of bowel complications in RT compared to RP, proportion of those bothered by frequent, painful, or urgent bowel movements was comparable across groups. Except for lower social functioning, RT and RP patients reported similar HRQoL, compared to WW.[84] Patients with EBRT had HRQoL similar to RP patients,[19] while, HRQoL was adversely affected by ADT.[18]

An RCT comparing hypofractionated and conventional radiotherapy showed comparable outcomes for urinary, bowel, and sexual symptom burden.[85]

3.9. Satisfaction with care and decision regret

A lower proportion of RP patients reported being delighted, satisfied, or pleased with their treatment decision, compared to RT patients (81% vs 90%).[19] However, 92% of all patients said they would make the same treatment decision again.[19] Decision regret was comparable in surgical patients undergoing open-RP or RARP.[82]

4. Discussion

Inadequate information exists about comparative effectiveness of alternative treatment options, especially for patient-centered outcomes beyond survival, and thus inhibits optimal PCa care.[13,86] Focus of this meta-analysis was on the comparative effectiveness of PCa treatment studies that include outcomes most important to patients for decision making, that is, symptomology, functional status, and HRQoL, in addition to survival and cancer recurrence.[61] Our systematic review revealed relatively few studies with patient-centered approach for assessing outcomes. Although low-risk PCa has small effect on mortality, most studies qualified for inclusion in our review compared mortality, often with inadequate statistical power. For low-risk patients, we noted that compared to RP alone, ADT alone or when

administered prior to RP, did not provide a mortality benefit. However, for intermediate risk patients, though primary ADT has no survival benefit, neoadjuvant ADT (prior to RT) improved survival compared to RT alone for selected patients. For both low-risk and high-risk patients, RP was associated with reduced risk of metastases compared to WW. For low- and intermediate-risk groups, among RT modalities, BT was associated with improved biochemical-free survival compared to EBRT.

Treatment-related complications are common after RP or RT. Compared with RP, RT is associated with higher risk of hospitalization, increased need for open surgical procedures, and development of secondary malignancy, mostly of the bladder and rectum.[87] Although RP showed a survival advantage for all 3 risk groups, RP had greater risk of side effects compared to WW, especially ED and urinary leakage. ED following RP often improves over time, as opposed to RT where symptoms appear gradually and worsen with time. Open-RP and RARP showed similar peri- and postoperative short-term functional outcomes.[68] Compared to RP, RT patients reported overall health as fair or poor, and comparable decision regrets.[19] Men with multiple comorbidities are at risk for overtreatment, especially those with early-stage PCa.[32] Survival benefit associated with RP or RT decreased exponentially with increasing comorbidity.[32] Despite important implications for treatment choice, comorbidity remains understudied. Additionally, in the absence of strong evidence of benefits and harms, ADT for localized-PCa has limited value. Because of substantial PSA screening in the US, number of men who are candidates for AS is increasing.[88] However, since 1990, the percentage of men initially managed with observation has remained at approximately 9%.[88] Furthermore, a greater proportion of low-risk patients are undergoing treatment with advanced technologies including intensity-modulated RT and RARP, adding to the cost of treating disease that could otherwise be managed with AS.[88]

4.1. Limitations

The shift in PCa risk induced by PSA screening may account for the lack of benefit observed in the Prostate Cancer Intervention Versus Observation Trial that showed no overall or PCa-specific survival benefit to RP compared to WW after 12-year follow-up.[26] However, the Scandinavian Prostate Cancer Group Trial Number-4 randomized trial of RP versus WW, initiated in Scandinavia before PSA screening era, showed benefits to active treatment.[24] Although men are still diagnosed due to symptoms, this number has drastically declined since routine adoption of PSA-screening.[89–92] Pathological classification of PCa and the Gleason grading system was updated in 2005 and often varies between sites.[93] Thus, PCa risk classification has changed throughout the timeline of our review which emphasizes the need for updated studies on current treatment options. Despite numerous publications related to localized PCa treatment and outcomes, the overall methodological quality and lack of comparative groups limited our synthesis due to exclusion of some important studies. As we only discussed comparative treatments for localized PCa, studies with stage T3b or higher were excluded. Although these studies met our clinical stage inclusion criteria, results were not stratified by risk or grade, and therefore could not be separated for localized tumors. Three large RCTs that were excluded due to staging criteria were the hypofractionated versus conventionally fractionated radiotherapy for patients with localized prostate cancer, Radiation Therapy Oncology Group 92-02, and European Organisation for Research and Treatment of Cancer 22961 trials.[76,94–96] Additionally, we excluded studies with chemotherapy because chemotherapy is mainly used for advanced or metastatic disease. Newer treatments such as proton therapy and stereotactic-body were not included due to lack of comparative evidence on mortality and other patient-centered outcomes. Finally, as the treatments for localized PCa are changing rapidly, WW is being replaced by AS and therefore more studies of comparative effectiveness of AS are needed.

5. Conclusions

Active patient participation is central to medical decision-making. Patient-centered care is a challenge for physicians who have limited time, receive little relevant training, and often are disincentivized to engage in shared decision-making. Our comparative effectiveness study is novel in that to our knowledge, it represents the first patient-centered approach to summarize and stratify the existing literature by PCa risk groups and will facilitate informed decision-making. AS is emerging as an alternative management strategy for PCa. In a new RCT, AS was comparable in-terms of disease-specific and all-cause mortality, though had higher incidence of disease progression, metastasis, and differential HRQoL outcomes compared to surgery and RT.[2,29,81,97] RP has shown to improve survival across all risk groups but with undesirable short-term HRQoL outcomes. Although RT is comparable to RP for intermediate and high-risk patients, there is lack of evidence regarding effectiveness of ADT. Our study demonstrates the dearth of comparative effectiveness studies for patient-centered outcomes. Future research must focus on integrating patient-centered outcomes to facilitate shared decision-making in PCa care.

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