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Radical prostatectomy versus deferred treatment for localised prostate cancer (Review)

Vernooij RWM, Lancee M, Cleves A, Dahm P, Bangma CH, Aben KKH

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[Intervention Review]

Radical prostatectomy versus deferred treatment for localised prostate cancer

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ABSTRACT

Background

Prostate cancer is a common cancer but is oftentimes slow growing. When confined to the prostate, radical prostatectomy (RP), which involves removal of the prostate, offers potential cure that may come at the price of adverse events. Deferred treatment, involving observation and palliative treatment only (watchful waiting (WW)) or close monitoring and delayed local treatment with curative intent as needed in the setting of disease progression (active monitoring (AM)/surveillance (AS)) might be an alternative. This is an update of a Cochrane Review previously published in 2010.

Objectives

To assess effects of RP compared with deferred treatment for clinically localised prostate cancer.

Search methods

We searched the Cochrane Library (including CDSR, CENTRAL, DARE, and HTA), MEDLINE, Embase, AMED, Web of Science, LILACS, Scopus, and OpenGrey. Additionally, we searched two trial registries and conference abstracts of three conferences (EAU, AUA, and ASCO) until 3 March 2020.

Selection criteria

We included all randomised controlled trials (RCTs) that compared RP versus deferred treatment in patients with localised prostate cancer, defined as T1-2, N0, M0 prostate cancer.

Data collection and analysis

Two review authors independently assessed the eligibility of references and extracted data from included studies. The primary outcome was time to death from any cause; secondary outcomes were: time to death from prostate cancer; time to disease progression; time to metastatic disease; quality of life, including urinary and sexual function; and adverse events. We assessed the certainty of evidence per outcome using the GRADE approach.

Main results

We included four studies with 2635 participants (average age between 60 to 70 years). Three multicentre RCTs, from Europe and USA, compared RP with WW (n = 1537), and one compared RP with AM (n = 1098).

Radical prostatectomy versus watchful waiting

RP probably reduces the risk of death from any cause (hazard ratio (HR) 0.79, 95% confidence interval (CI) 0.70-0.90; 3 studies with 1537 participants; moderate-certainty evidence). Based on overall mortality at 29 years, this corresponds to 764 deaths per 1000 men in the RP group compared to 839 deaths per 1000 men in the WW group. RP probably also lowers the risk of death from prostate cancer (HR 0.57, 95% CI 0.44-0.73; 2 studies with 1426 participants; moderate-certainty evidence). Based on prostate cancer-specific mortality at 29 years, this corresponds to 195 deaths from prostate cancer per 1000 men in the RP group compared with 316 deaths from prostate cancer per 1000 men in the WW group. RP may reduce the risk of progression (HR 0.43, 95% CI 0.35-0.54; 2 studies with 1426 participants; I^2 = 54%; low-certainty evidence); at 19.5 years, this corresponds to 391 progressions per 1000 men for the RP group compared with 684 progressions per 1000 men for the WW group) and probably reduces the risk of developing metastatic disease (HR 0.56, 95% CI 0.46-0.70; 2 studies with 1426 participants; I^2 = 0%; moderate-certainty evidence); at 29 years, this corresponds to 271 metastatic diseases per 1000 men for RP compared with 431 metastatic diseases per 1000 men for WW.

General quality of life at 12 years' follow-up is probably similar for both groups (risk ratio (RR) 1.0, 95% CI 0.85-1.16; low-certainty evidence), corresponding to 344 patients with high quality of life per 1000 men for the RP group compared with 344 patients with high quality of life per 1000 men for the WW group. Rates of urinary incontinence may be considerably higher (RR 3.97, 95% CI 2.34-6.74; low-certainty evidence), corresponding to 173 incontinent men per 1000 in the RP group compared with 44 incontinent men per 1000 in the WW group, as are rates of erectile dysfunction (RR 2.67, 95% CI 1.63-4.38; low-certainty evidence), corresponding to 389 erectile dysfunction events per 1000 for the RP group compared with 146 erectile dysfunction events per 1000 for the WW group, both at 10 years' follow-up.

Radical prostatectomy versus active monitoring

Based on one study including 1098 participants with 10 years' follow-up, there are probably no differences between RP and AM in time to death from any cause (HR 0.93, 95% CI 0.65-1.33; moderate-certainty evidence). Based on overall mortality at 10 years, this corresponds to 101 deaths per 1000 men in the RP group compared with 108 deaths per 1000 men in the AM group.

Similarly, risk of death from prostate cancer probably is not different between the two groups (HR 0.63, 95% CI 0.21-1.89; moderate-certainty evidence). Based on prostate cancer-specific mortality at 10 years, this corresponds to nine prostate cancer deaths per 1000 men in the RP group compared with 15 prostate cancer deaths per 1000 men in the AM group. RP probably reduces the risk of progression (HR 0.39, 95% CI 0.27-0.56; moderate-certainty evidence; at 10 years, this corresponds to 86 progressions per 1000 men for RP compared with 206 progressions per 1000 men for AM) and the risk of developing metastatic disease (RR 0.39, 95% CI 0.21-0.73; moderate-certainty evidence; at 10 years, this corresponds to 24 metastatic diseases per 1000 men for the RP group compared with 61 metastatic diseases per 1000 men for the AM group).The general quality of life during follow-up was not different between the treatment groups. However, urinary function (mean difference (MD) 8.60 points lower, 95% CI 11.2-6.0 lower) and sexual function (MD 14.9 points lower, 95% CI 18.5-11.3 lower) on the Expanded Prostate Cancer Index Composite-26 (EPIC-26) instrument, were worse in the RP group.

Authors' conclusions

Based on long-term follow-up, RP compared with WW probably results in substantially improved oncological outcomes in men with localised prostate cancer but also markedly increases rates of urinary incontinence and erectile dysfunction. These findings are largely based on men diagnosed before widespread PSA screening, thereby limiting generalisability. Compared to AM, based on follow-up to 10 years, RP probably has similar outcomes with regard to overall and disease-specific survival yet probably reduces the risks of disease progression and metastatic disease. Urinary function and sexual function are probably decreased for the patients treated with RP.

PLAIN LANGUAGE SUMMARY

Radical prostatectomy versus deferred treatment for the treatment of localised prostate cancer

Review question

How does surgery to remove the entire prostate compare to deferred treatment for patients with prostate cancer?

Background

Prostate cancer is a common cancer, especially in older men. Although infrequent, it can cause complaints such as blood in the urine or trouble urinating. It can spread to other organs such as lymph nodes and/or bones. At advanced stages, prostate cancer cannot be cured, can cause other symptoms, and will ultimately lead to death.

Radical prostatectomy removes the entire prostate. It is a procedure used to treat men in case prostate cancer appears to be limited to the prostate and has not spread beyond. Men may choose not to have treatment at first and to later treat the complications. This is called

watchful waiting. Some men will choose not to be treated at first, to monitor their cancer until it becomes more aggressive, and to later have treatment for cure. This is called active surveillance.

Study characteristics

We searched the medical literature until 3 March 2020. We found four randomised controlled trials, including 2635 men with prostate cancer, that compared radical prostatectomy with watchful waiting (3 studies) and one study that compared radical prostatectomy with active monitoring, which is an earlier form of active surveillance.

Key results

Radical prostatectomy versus watchful waiting

Radical prostatectomy probably reduces the risk of dying for any reason, reduces the risk of dying from prostate cancer, reduces the risk of cancer becoming more aggressive, and reduces the risk of cancer spreading to other parts of the body (like lymph nodes and bones) after 29 years' follow-up.

The number of patients reporting high general quality of life is probably similar after 12 years. Risks of urine leakage and problems with erections are probably greater for patients who receive surgery.

Radical prostatectomy versus active monitoring

There is probably little to no difference between radical prostatectomy and active monitoring for the risk of dying for any reason and the risk of dying from prostate cancer after 10 years. Radical prostatectomy probably reduces the risk of cancer becoming more aggressive and the risk of cancer spreading to other parts of the body.

General quality of life during follow-up is probably similar. At two years' follow-up, patients who have radical prostatectomy may be more likely to have incontinence and erectile dysfunction.

Certainty of the evidence

The certainty of evidence was mostly moderate for cancer outcomes. This means that the true results are likely similar to those described in this review. For outcomes for which the certainty of evidence was low, the true result may be quite different.

Summary of findings 1. Radical prostatectomy compared to watchful waiting for localised prostate cancer

Radical prostatectomy compared to watchful waiting for localised prostate cancer

Patient or population: men with localised prostate cancer
Setting: multicentre hospitals in USA and Europe
Intervention: radical prostatectomy
Comparison: watchful waiting

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with watchful waiting	Risk with radical prostatectomy				
Time to death from any cause Median follow-up: range 12.8 to 23.6 years	**22.1 years** [a]		HR 0.79 (0.70 to 0.90)	1537 (3 RCTs)	⊕⊕⊕⊖ MODERATE[b]	Radical prostatectomy likely reduces time to death from any cause
	733 per 1000	648 per 1000 (603 to 695)				
	29 years [c]					
	839 per 1000	764 per 1000 (722 to 807)				
Time to death from prostate cancer Median follow-up: range 12.8 to 23.6 years	**19.5 years** [a]		HR 0.57 (0.44 to 0.73)	1426 (2 RCTs)	⊕⊕⊕⊖ MODERATE[b]	Radical prostatectomy likely reduces time to death from prostate cancer
	114 per 1000	67 per 1000 (52 to 85)				
	29 years [c]					
	316 per 1000	195 per 1000 (154 to 242)				
Time to disease progression Median follow-up: range 12.8 to 13.4 years	**18 years** [c]		HR 0.43 (0.35 to 0.54)	1426 (2 RCTs)	⊕⊕⊖⊖ LOW[b,d]	Radical prostatectomy may reduce time to disease progression
	674 per 1000	382 per 1000 (324 to 454)				
	19.5 years [a]					

	684 per 1000	391 per 1000 (332 to 463)				
Time to metastatic disease Median follow-up: range 12.7 to 23.6 years	**19.5 years** [a]		HR 0.56 (0.46 to 0.70)	1426 (2 RCTs)	⊕⊕⊕⊖ MODERATE[b]	Radical prostatectomy likely reduces time to metastatic disease
	147 per 1000	85 per 1000 (71 to 105)				
	29 years [c]					
	431 per 1000	271 per 1000 (228 to 326)				
Quality of life assessed with dichotomous quality of life item (event: high quality of life) Median follow-up: 12.7 years	Study population		RR 1.00 (0.85 to 1.16)	339 (1 RCT)	⊕⊕⊖⊖ LOW[b,e]	Radical prostatectomy may result in little to no difference in quality of life
	344 per 1000	344 per 1000 (292 to 399)				
Urinary function: incontinence assessed with adverse events requiring treatment Median follow-up: 12.7 years	Study population		RR 3.97 (2.34 to 6.74)	731 (1 RCT)	⊕⊕⊖⊖ LOW[b,e]	Radical prostatectomy may result in a large increase in incontinence
	44 per 1000	173 per 1000 (102 to 294)				
Sexual function: erectile dysfunction assessed with adverse events requiring treatment Median follow-up: 12.7 years	Study population		RR 2.67 (1.63 to 4.38)	731 (1 RCT)	⊕⊕⊖⊖ LOW[b,e]	Radical prostatectomy may result in a large increase in erectile dysfunction
	146 per 1000	389 per 1000 (237 to 638)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; HR: hazard ratio; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Absolute numbers of time-to-event outcomes are based on the 19.5-years or 22.1-years event rate of the PIVOT study.
[b]Downgraded one level due to indirectness (differences in years of recruitment period, interventions, and comparators between included studies and current clinical practice).
[c]Absolute numbers of time-to-event outcomes are based on the 18-years or 29-years event rate of the SPCG-4 study.

[d]Downgraded one level due to inconsistency (I^2 = 54%).
[e]Downgraded one level due to risk of bias (lack of blinding).

Summary of findings 2. Radical prostatectomy compared to active monitoring for localised prostate cancer

Radical prostatectomy compared to active monitoring for localised prostate cancer

Patient or population: localised prostate cancer
Setting: multicentre hospitals in UK
Intervention: radical prostatectomy
Comparison: active monitoring

Outcomes	Anticipated absolute effects* (95% CI)[a]		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with active monitoring	Risk with radical prostatectomy				
Time to death from any cause Median follow-up: 10 years	Study population		HR 0.93 (0.65 to 1.33)	1098 (1 RCT)	⊕⊕⊕⊖ MODERATE[b]	Radical prostatectomy likely results in little to no difference in time to death from any cause
	108 per 1000	101 per 1000 (72 to 141)				
Time to death from prostate cancer Median follow-up: 10 years	Study population		HR 0.63 (0.21 to 1.89)	1098 (1 RCT)	⊕⊕⊕⊖ MODERATE[b]	Radical prostatectomy likely results in little to no difference in time to death from prostate cancer
	15 per 1000	9 per 1000 (3 to 28)				
Time to disease progression Median follow-up: 10 years	Study population		HR 0.39 (0.27 to 0.56)	1098 (1 RCT)	⊕⊕⊕⊖ MODERATE[c]	Radical prostatectomy likely reduces time to disease progression
	206 per 1000	86 per 1000 (60 to 121)				
Incidence of metastatic disease Median follow-up: 10 years	Study population		RR 0.39 (0.21 to 0.73)	1098 (1 RCT)	⊕⊕⊕⊖ MODERATE[c]	Radical prostatectomy likely reduces incidence of metastatic disease
	61 per 1000	24 per 1000 (13 to 44)				
Health-related quality of life assessed with SF-12 (Mental Health Subscale). High scores indicate better outcomes.	Mean health-related quality of life was 53 points	MD 0.5 points higher (0.65 lower to 1.65 higher)	-	856 (1 RCT)	⊕⊕⊕⊖ MODERATE[c]	Radical prostatectomy likely results in little to no difference in health-related quality of life

Median follow-up: 6 years						
Urinary function assessed with ICIQ score. High scores indicate better outcomes. Median follow-up: 6 years	Mean urinary function was 88.9 points	MD 8.6 points lower (11.19 lower to 6.01 lower)	-	782 (1 RCT)	⊕⊕⊖⊖ LOW[c,d]	Radical prostatectomy may result in a large reduction in urinary function
Sexual function assessed with EPIC sexual summary score. High scores indicate better outcomes. Median follow-up: 6 years	Mean sexual function was 48.2 points	MD 14.9 points lower (18.54 lower to 11.26 lower)	-	756 (1 RCT)	⊕⊕⊖⊖ LOW[c,e]	Radical prostatectomy may result in a large reduction in sexual function

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; HR: hazard ratio; MCID: minimal clinically important difference; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Absolute numbers of time-to-event outcomes are based on the 10-years event rate of the ProtecT study.
[b]Downgraded one level due to imprecision (wide confidence interval or low event rate).
[c]Downgraded one level due to risk of bias (lack of blinding).
[d]Downgraded one level due to imprecision due to inclusion of the effect estimates (and confidence interval) in the range of MCID values for the urinary incontinence domain (6 to 9) (Skolarus 2015).
[e]Downgraded one level due to imprecision due to inclusion of the effect estimates (and confidence interval) in the range of MCID values for the sexual domain (10 to 12) (Skolarus 2015).

BACKGROUND

Description of the condition

Prostate cancer is the second most commonly diagnosed cancer among men worldwide, especially in developed countries, with a relatively higher number of elderly men (IARC France). In the USA, prostate cancer accounts for more than 160,000 new cases annually - approximately 19% of all new cancer cases - and the lifetime risk of prostate cancer is estimated to be approximately one in six (Siegel 2017). Similar numbers regarding the incidence of prostate cancer are found in Europe (Cancer Research UK; Netherlands Cancer Registry). The most prevailing risk factors for prostate cancer include ethnicity, family history, and older age (Albright 2015; Hemminki 2012; Jansson 2012; Kamangar 2006). Other reported risk factors are chronic inflammation of the prostate, diet (including alcohol consumption), sexual behaviour, exposure to ultraviolet radiation, and use of statins (Esposito 2013; Freedland 2013; Leitzmann 2012; Nelson 2003). Although the incidence of prostate cancer is high, the mortality of prostate cancer is relatively low (IARC France). Approximately 8% of all deaths due to cancer among men in the USA result from prostate cancer (Siegel 2017). An increase in survival rates has been noted in recent years, largely due to the widespread use of prostate-specific antigen (PSA) testing, resulting in a more favourable stage distribution (De Angelis 2014; Etzioni 2013; Hayes 2014).

Population screening, defined as the systematic examination of men at risk of prostate cancer in the general population, is mainly based on evaluation of the patient's PSA level. However, population screening for prostate cancer remains a controversial topic amidst concerns about overdiagnosis and overtreatment (Ilic 2013; Ilic 2017), and shared decision-making is considered crucial in the decision to undergo screening (Carter 2013; Force 2018; Moyer 2012; Tikkinen 2017). Despite this controversy, PSA screening remains widespread. This has resulted in an increase in the diagnosis of prostate cancer at earlier stages. Today, non-palpable disease is detected in most men diagnosed with prostate cancer due to an elevated PSA level. Many of these tumours are considered at low or very low risk for progression with very low metastatic potential. It is unclear whether increased use of multi-parametric imaging and novel biomarkers will increase or reduce the occurrence of overdiagnosis and overtreatment.

Description of the intervention

Depending on the clinical stage of prostate cancer and individual patient circumstances, which include estimated life expectancy, as well as personal values and preferences, different treatment options are available (Mottet 2017). These are broadly categorised as options aimed at completely eradicating the cancer with a chance of cure and include radical prostatectomy and various forms of local radiation therapy. Further investigation of focal therapy is required to establish this as a treatment option.

Active surveillance refers to an approach by which local treatment with curative intent is delayed as long as possible to avoid the side effects of treatment, but local treatment is ultimately intended if necessary.

An alternative approach is watchful waiting or observation, which defers treatment with no plans for curative treatment. This approach avoids the burden of local treatment and is particular suitable for men with a slow growing cancer and/or a relatively short life expectancy.

Men with locally advanced or metastatic disease who are at high risk of disease-related complications and death from prostate cancer have traditionally been treated with systemic androgen ablation, recently supplemented by others forms of systemic treatment such as docetaxel-based chemotherapy or abiraterone treatment.

Treatment modalities most relevant to this review are further described below.

Radical prostatectomy

Radical prostatectomy involves removal of the entire prostate gland along with sufficient surrounding tissue with the aim of obtaining negative margins. The goal of radical prostatectomy is to completely remove the tumour and avoid surgical morbidity, for example, urinary incontinence and decreased sexual function (Bianco 2005). Retropubic prostatectomy used to be the standard surgical approach. In many countries, it has since been supplanted by robot-assisted laparoscopic prostatectomy, which may offer the advantage of lower risk of transfusion and shorter re-convalescence (Ilic 2017). Regardless of the approach chosen, surgeons' skills and experience have been shown to be important predictors of surgical outcomes (Augustin 2003; Eastham 2003; Lepor 2001; Maffezzini 2003; Potosky 1999; Vickers 2009).

Deferred treatment

Many prostate cancers have a long and indolent natural history. Treating all men would therefore result in overtreatment, exposing these men to the side effects of treatment (Loeb 2014). In response, two alternative treatment approaches have been formulated, which are referred to as watchful waiting (or observation) and active surveillance (or active monitoring). Although these definitions are often used inconsistently in the literature (Adolfsson 2008), we will interpret them as follows in this review.

Active surveillance

Active surveillance or active monitoring is defined as close follow-up that involves periodic clinical examination, assessment of symptoms, and PSA testing and repeat biopsy. 'Active monitoring', which was one of the interventions of ProtecT, represents an early form of active surveillance in which monitoring was mostly PSA-based (but did not include follow-up biopsies). Recently, magnetic resonance imaging (MRI) has been added to the follow-up routine of active surveillance. The purpose of active surveillance is to postpone curative treatment as long as possible, typically when evidence of relevant disease progression is found (Filson 2015). Disease progression is commonly defined as a change in the biopsy score (upgrading of the Gleason score) or progression in tumour size or extent. Active surveillance with delayed intervention for patients with disease progression might reduce overtreatment for low-risk prostate cancer. Additionally, active surveillance intends to regulate and improve the timing by which the patient receives curative treatment based on a threshold, which should be pre-defined in a protocol (PRIAS), taking life expectancy into account. The objective of active surveillance is to avoid or defer treatment-related complications in men with prostate cancer that is unlikely to progress.

Watchful waiting

Watchful waiting is defined as a conservative approach to the management of prostate cancer whereby the decision is made to provide no initial treatment and local treatment with curative intent is not planned. In the setting of progression and impending prostate cancer-related complications, palliative treatment is instituted. Watchful waiting is most often provided to elderly or comorbid patients with a limited life expectancy (Filson 2015). Watchful waiting is based on the assumption that local treatment with curative intent is not necessary, thereby avoiding side effects of treatment (Dahabreh 2012).

How the intervention might work

Radical prostatectomy aims to eradicate prostate cancer by its complete removal. This is accomplished only if prostate cancer is limited to the prostate gland and has not spread beyond that, for example, to regional lymph nodes and/or distant sites such as bones. Whether patients with regional lymph node metastases or even distant metastases benefit from radical prostatectomy remains a topic of controversy. Patients at increased risk for spread of cancer beyond the prostate usually undergo staging studies, which traditionally have consisted of computed tomography (CT) imaging and bone scan. In recent times, MRI and positron emission tomography (PET) imaging are gaining a role in this setting. In men with distant metastases, radical prostatectomy may be futile and may expose patients to the risks of side effects.

Despite advances in how radical prostatectomy is performed, it remains associated with significant short-term (e.g. postoperative pain, need for inpatient stay, Foley placement, risk of medical complications such as deep vein thrombosis (DVT)/pulmonary embolus (PE)) and long-term complications (e.g. urinary incontinence, erectile dysfunction, bladder neck contractures) that may impair quality of life. Given these side effects, radical surgery should be reserved for individuals who are most likely to benefit from the procedure.

Why it is important to do this review

Radical prostatectomy, active surveillance, and watchful waiting all have a place in the current armamentarium for treating clinically localised prostate cancer; however, their comparative effectiveness is not well established (AUA 2017; Chen 2016; Chin 2010). Since publication of the original review updated here (Hegarty 2010), several relevant trials have been published, making the original review out-of-date. The same goes for two comprehensive systematic reviews on clinically localised prostate cancer that were funded by the Agency for Healthcare Research and Quality (AHRQ) (Sun 2014). In addition, methodological expectations for systematic reviews have increased. One review stands out for its rigorous methods, which include a published protocol, a comprehensive search of multiple databases for published and unpublished studies, and use of the GRADE approach with focus on patient-important outcomes and consideration of clinically important effect sizes in a contextualised approach to the certainty of evidence rating (Hultcrantz 2017). We expect this up-to-date evidence report to provide important information for patients, clinicians, and policy-makers alike.

OBJECTIVES

To assess effects of radical prostatectomy compared with deferred treatment, including active surveillance/active monitoring and watchful waiting, for clinically localised prostate cancer.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCTs) and quasi-RCTs for inclusion. We considered studies for inclusion irrespective of their publication status or language of publication. We considered cross-over studies for inclusion; however, we extracted and analysed data solely from the first treatment period of these studies.

Types of participants

We included trials of adult male patients with confirmed localised prostate cancer (as verified by cytological or histological examination).

Diagnostic criteria for localised prostate cancer

We considered for inclusion studies that included participants with stage I or II prostate cancer as defined as follows by the tumour-node-metastasis (TNM) classification (Sobin 2010).

1. Stage I.
   a. T1a-c or T2a tumour: T1 is further divided into T1a (tumour incidental histological finding in ≤ 5% of tissue resected), T1b (tumour incidental histological finding in > 5% of tissue resected), and T1c (tumour identified by needle biopsy, e.g. because of elevated PSA). T2a is defined as a tumour involving one-half of one lobe or less.
   b. N0: no regional lymph node metastasis.
   c. M0: no distant metastasis.
2. Stage II.
   a. T2b-c tumour: T2b is defined as a tumour involving more than one-half of one lobe but not both lobes; T2c is defined as a tumour involving both lobes.
   b. N0: no regional lymph node metastasis.
   c. M0: no distant metastasis.

We contacted trial authors if we needed clarification to determine the health status or diagnostic criteria of included patients. If we received no response, clinical experts in our review group classified the trials, or we listed the studies as 'Studies awaiting classification'.

Types of interventions

We investigated the following experimental intervention compared with the comparator intervention.

Experimental intervention

1. Radical prostatectomy involving removal of the entire prostate gland and the seminal vesicles via any surgical approach (e.g. radical retropubic, radical perineal, robot-assisted, laparoscopic radical prostatectomy) with or without nerve-sparing procedures. We included studies that did and studies

that did not perform a limited or extended pelvic lymph node dissection.

Comparator interventions

For the purpose of this review, we broadly defined deferred management as watchful waiting or active surveillance/active monitoring.

1. Watchful waiting (or conservative management) refers to any observant approach in which there is no intent to cure the patient of prostate cancer. If treatment is implemented, it is directed at avoiding or alleviating disease-specific morbidity (such as bone pain, hydronephrosis, or bladder neck obstruction). Palliative treatment measures include androgen deprivation therapy (surgical or medical castration, antiandrogens), radiation treatment for bone pain, systemic chemotherapy, or transurethral resection of the prostate (TURP) to alleviate bladder outlet obstruction.
2. Active surveillance (or active monitoring) refers to an approach that defers local treatment with curative intent. Patients may be monitored in a variety of ways through serial PSA testing, digital rectal examinations, imaging studies such as MRI, and/or prostate biopsies. Treatments such as radical prostatectomy or radiation therapy may be implemented at a later time in the setting of suspected disease progression and/or according to patient preference.

We excluded studies that did not involve any form of deferred treatment. We also excluded studies that combined the experimental intervention with any other form(s) of intervention, unless the additional intervention was provided in a standardised manner to both experimental and control groups.

Comparisons

1. Radical prostatectomy versus watchful waiting
2. Radical prostatectomy versus active monitoring

Types of outcome measures

We did not exclude studies from the review solely because no outcomes of interest were reported. In cases where none of our outcomes of interest were reported in the included studies, we reported information about these studies in an additional table.

Primary outcomes

1. Time to death from any cause (time-to-event outcome)

Secondary outcomes

1. Time to death from prostate cancer (time-to-event outcome)
2. Time to disease progression (time-to-event outcome)
3. Time to metastatic disease (time-to-event outcome)
4. Health-related quality of life (continuous outcome)
   a. Urinary function (continuous outcome).
   b. Sexual function (continuous outcome).
   c. Bowel function (continuous outcome).
5. Adverse events (dichotomous outcome)

Method and timing of outcome measurement

Primary outcome

1. Time to death from any cause (time-to-event outcome): measured as the date of randomisation to the date of death due to any cause

Secondary outcomes

1. Time to death from prostate cancer (time-to-event outcome): measured as the date of randomisation to the date of death due to prostate cancer
2. Time to disease progression (time-to-event outcome): measured as the date of randomisation to the date of disease progression as determined by physical exam findings (e.g. increase in clinical tumour stage), PSA increase, and/or imaging studies (e.g. development of new metastases)
3. Time to metastatic disease (time-to-event outcome): measured as the date of randomisation to the date of metastatic disease as established by imaging findings
4. Quality of life (continuous outcome): measured as the construct quality of life by a validated instrument (e.g. European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), 12-Item Short Form Health Survey (SF-12))
   a. Health-related quality of life measured by a validated instrument (e.g. EORTC QLQ-C30, SF-12)
   b. Urinary domain in the quality of life construct including incontinence and lower urinary tract symptoms measured by a validated instrument (e.g. International Consultation on Incontinence Questionnaire (ICIQ), International Continence Society Male Short-Form (ICSmaleSF))
   c. Sexual function in the quality of life construct including erectile dysfunction and overall sexual function measured by a validated instrument (e.g. Expanded Prostate Cancer Index Composite (EPIC))
   d. Bowel function in the quality of life construct including bowel function, faecal incontinence, and bloody stools measured by a validated instrument (e.g. EPIC)
5. Adverse events (dichotomous outcome): we defined adverse events as those rated as grade III or IV according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) (National Cancer Institute 2009)

If we had been unable to retrieve the necessary information to analyse time-to-event outcomes, we planned to assess the number of events per total patients analysed for dichotomised outcomes at five-year intervals. The main time point of interest in our study was the end of the trial (defined as the time point with the longest follow-up duration as measured from randomisation). Additionally, we extracted and presented outcome data reported at other time points after randomisation.

Main outcomes for 'Summary of findings' tables

We will present 'Summary of findings' tables reporting the following outcomes listed according to priority.

1. Time to death from any cause.
2. Time to death from prostate cancer.
3. Time to disease progression.
4. Time to metastatic disease.

5. Quality of life.
6. Quality of life: urinary domain.
7. Quality of life: sexual function.

Search methods for identification of studies

We conducted a comprehensive search with no restrictions on language of publication or publication status. See Appendix 1 for the full search strategy for each database.

Electronic searches

We searched the following databases from inception.

1. The Cochrane Library (Wiley) (2020 Issue 3).
   a. *Cochrane Database of Systematic Reviews* (CDSR).
   b. Cochrane Central Register of Controlled Trials (CENTRAL).
   c. Database of Abstracts of Reviews of Effects (DARE).
   d. Health Technology Assessment Database (HTA).
2. MEDLINE (OVIDSP): 1946 to 3 March 2020.
3. MEDLINE-in-Process and Epubs ahead of print (OVIDSP): searched on 3 March 2020.
4. Embase (OVIDSP): 1947 to 3 March 2020.
5. Allied and Complementary Medicine Database (AMED) (OVIDSP): 1985 to 3 March 2020.
6. Web of Science (Thomson Reuters).
   a. Science Citation Index - Expanded: 1900 to 3 March 2020.
   b. Conference Proceedings Citation Index - Science: 1990 to 3 March 2020.
7. Latin American Caribbean Health Sciences Literature (LILACS) (Virtual Health Library): 1982 to 3 March 2020.
8. Scopus (Elsevier): 1960 to 3 March 2020.
9. OpenGrey (Native Interface): 1980 to 3 March 2020.

We searched the following trial registries.

1. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (apps.who.int/trialsearch/) (from 2009 to 2020; last searched 3 March 2020).
2. ClinicalTrials.gov (www.clinicaltrials.gov/) (from 2008 to 2020; last searched 3 March 2020).

We also searched electronically available abstracts of the following national and international urology cancer meetings via Embase (OVIDSP) and Web of Science (Thomson Reuters).

1. Annual Meeting of the European Association of Urology (EAU) (www.uroweb.org; last searched 3 March 2020).
2. Annual Meeting of the American Society of Clinical Oncology (ASCO) (jco.ascopubs.org; last searched 3 March 2020).
3. American Urological Association Annual Meeting (AUA) (www.jurology.com; last searched 3 March 2020).

We applied a MEDLINE email alert service to identify newly published trials using the search strategy as described for MEDLINE (Appendix 1). Should we identify new trials for inclusion, we will evaluate these, incorporate these studies into our review, and update this Cochrane Review.

Searching other resources

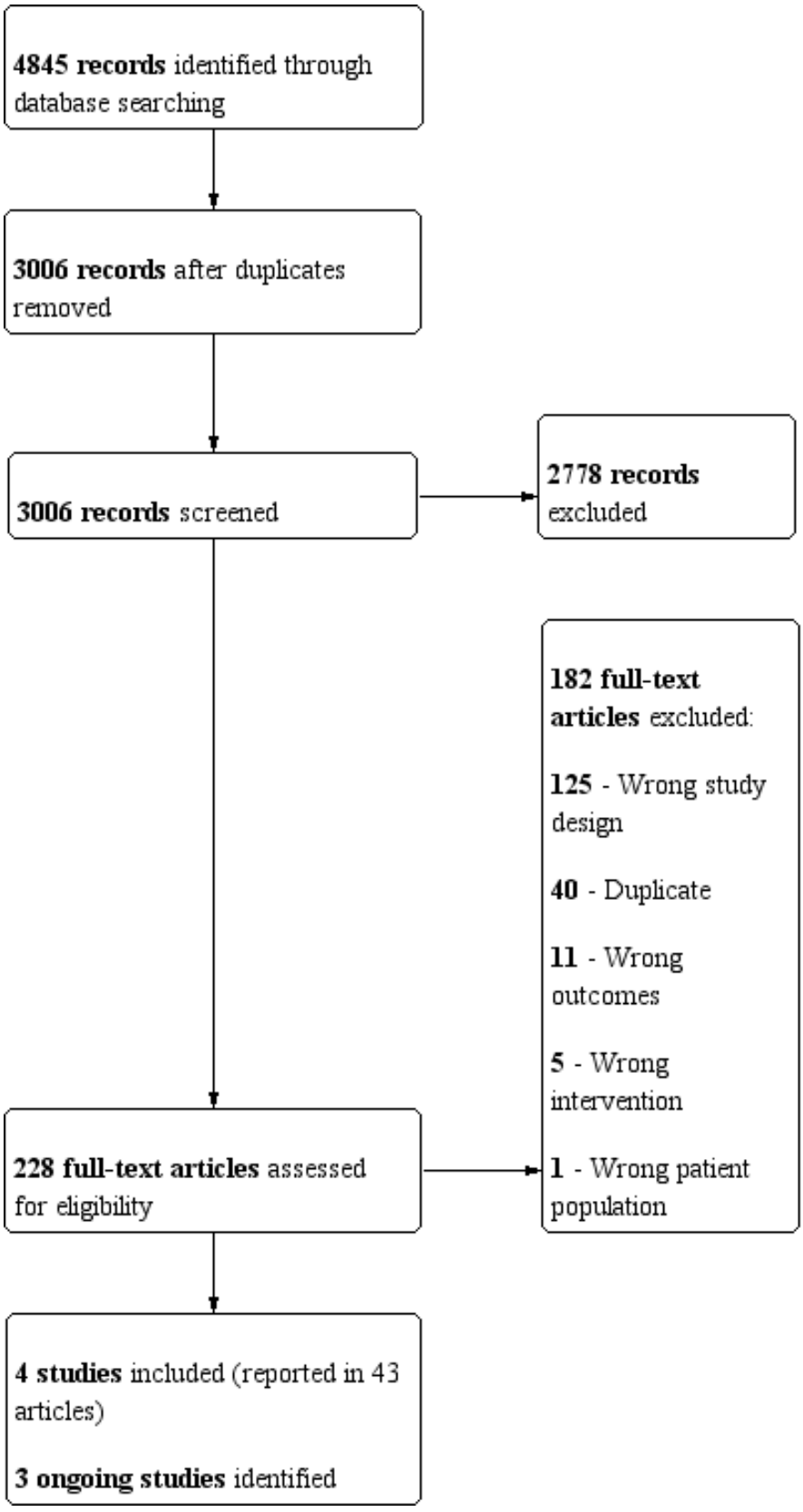
We screened the reference lists of other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials, reviews, and meta-analyses. Additionally, we contacted study authors of included trials to identify any studies that we may have missed.

Data collection and analysis

Selection of studies

We used reference management software (EndNote and Covidence) to identify and remove potential duplicate records based on trial author names, locations and settings, details of intervention, numbers of participants, baseline data, study date, and study duration. Two review authors (RV, ML) independently scanned the abstract, the title, or both, of remaining records retrieved, to determine which studies should be assessed further using Covidence (www.covidence.org). Two review authors (RV, ML) investigated all potentially relevant records as full text, mapped records to studies, and classified studies as included studies, excluded studies, studies awaiting classification, or ongoing studies, in accordance with the criteria for each as provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We resolved any disagreement through discussion and consensus or by recourse to a third review author (KA). We documented the reasons for exclusion of studies that were screened during the full-text evaluation in the Characteristics of excluded studies table. We included an adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the process of study selection (Figure 1) (Liberati 2009).

Figure 1. Study flow diagram



Data extraction and management

For studies that fulfilled inclusion criteria, two review authors (RV, ML) tried to independently extract the following information, which we provide in the Characteristics of included studies table.

Study characteristics

1. Study design
2. Study dates
3. Study settings and country
4. Study funding sources
5. Declarations of interest by primary investigators

Participant characteristics

1. Participant inclusion and exclusion criteria
2. Participant details
   a. Baseline demographics
      i. Age
      ii. Gender
      iii. Comorbidities
      iv. Performance status
   b. Disease characteristics
      i. TNM classification
      ii. PSA value at diagnosis
      iii. Gleason score
3. Numbers of participants by study and by study arm

Intervention characteristics

1. Details of relevant experimental and comparator interventions such as surgical approach or type and intensity of monitoring

Outcomes

1. Definitions of relevant outcomes, method and timing of outcome measurement, and any relevant subgroups

We extracted outcome data relevant to this review as needed for calculation of summary statistics and measures of variance. For dichotomous outcomes, we attempted to obtain numbers of events and totals for the population in a 2 × 2 table, as well as summary statistics with corresponding measures of variance. For continuous outcomes, we attempted to obtain means and standard deviations or data necessary to calculate this information. For time-to-event outcomes, we attempted to obtain hazard ratios (HRs) with corresponding measures of variance or data necessary to calculate this information. If outcome data were available at multiple time points within an included study, we extracted all time points; however, we presented the time point with the longest follow-up in the meta-analysis with other studies. We resolved any disagreements by discussion or, if required, by consultation with a third review author (KA). We provided information, including trial identifier, about potentially relevant ongoing studies in the Characteristics of ongoing studies table. We attempted to contact authors of included studies to obtain key missing data as needed.

Dealing with duplicate and companion publications

For duplicate publications, companion documents, or multiple reports of a primary trial, we maximised the information yield by collating all available data and using the most complete data set aggregated across all known publications. Multiple reports of primary trials are listed as secondary references under the study ID of the included trial.

Assessment of risk of bias in included studies

Two review authors (RV, ML) independently assessed the risk of bias of each included study using Cochrane's 'Risk of bias' assessment tool (Higgins 2011b). Disagreement was resolved by consensus or by consultation with a third review author (KA). We assessed the following domains.

1. Random sequence generation (selection bias due to inadequate generation of a randomised sequence).
2. Allocation concealment (selection bias due to inadequate concealment of allocation before assignment).
3. Blinding of participants and personnel (performance bias due to awareness of the allocated interventions by participants and personnel during the trial).
4. Blinding of outcome assessment (detection bias due to awareness of the allocated interventions by the outcome assessor).
5. Incomplete outcome data (attrition bias due to the quantity, nature, or handling of incomplete outcome data).
6. Selective reporting (reporting bias due to selective outcome reporting).
7. Other sources of bias (bias due to problems not covered elsewhere).

We judged risk of bias domains as 'low risk', 'high risk', or 'unclear risk', and we evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

We justified risk of bias judgements (low, unclear, or high risk) and indicated the source of information for risk of bias judgements by providing a quotation from the study text in the Risk of bias in included studies section. Additonally, we provided a risk of bias summary figure to illustrate these findings.

Random sequence generation, allocation concealment, selective reporting, and other sources of bias were evaluated at trial level. Blinding of participants and personnel, blinding of outcome assessment, and incomplete outcome data were evaluated at outcome level.

With regards to performance bias, we considered all outcomes to be similarly susceptible to performance bias and therefore rated them as one group.

With regards to detection bias, we defined overall survival as an objective outcome (not susceptible to detection bias). The outcomes time to death from prostate cancer, time to disease progression, time to metastatic disease, and adverse events were considered subjective when blinding was important. Quality of life was considered subjective and was rated separately from the other subjective outcomes because it is most likely self-reported by patients.

We assessed the risk of attrition bias separately by outcome but subsequently grouped our assessments in three groups as follows due to identical judgements.

1. Oncological outcomes.

2. Adverse events.
3. Quality of life outcomes (general, urinary, and sexual domains).

Measures of treatment effect

The measure of treatment effect for continuous outcomes was mean difference (MD) with 95% confidence intervals (95% CIs). We expressed the treatment effect for dichotomous outcomes as risk ratio (RR) with 95% CIs. Time-to-event data are expressed as hazard ratios (HRs) with 95% CIs.

Unit of analysis issues

The unit of analysis of included studies was the individual participant. We did not identify any cross-over trials. The ProtecT included three treatment arms, including radical prostatectomy, active monitoring, and external radiotherapy, in which the latter is not included in this reivew. The outcome measures with the longest follow-up were included in the meta-analyses.

Dealing with missing data

We dealt with missing data in our risk of bias assessments regarding attrition bias. We contacted study authors in the case of missing data. When possible, we analysed data using the intention-to-treat (ITT) approach. We carefully evaluated important numerical data such as screened, randomly assigned participants as well as intention-to-treat and per-protocol populations. We did not impute any missing data. Additionally, as missing data in an individual trial might put effect estimates at high risk and may lower the overall certainty of evidence according to the Grading or Recommendations Assessment, Development, and Evaluation (GRADE) Working Group (Guyatt 2008), we took the quantity of missing data into account in our certainty of evidence assessment.

Assessment of heterogeneity

We visually inspected forest plots for the presence of heterogeneity (inconsistency). Additionally, we calculated the I^2 statistic, which quantifies inconsistency across studies, to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003). We interpreted the I^2 statistic as follows (Deeks 2011).

1. 0% to 40%: may not be important.
2. 30% to 60%: may indicate moderate heterogeneity.
3. 50% to 90%: may indicate substantial heterogeneity.
4. 75% to 100%: considerable heterogeneity.

We did not find any excessive heterogeneity unexplained by subgroup analyses; therefore, a narrative description of the results of each study was not necessary.

Assessment of reporting biases

We did not identify sufficient randomised controlled trials and therefore did not construct funnel plots with the appropriate statistics to explore reporting biases and other biases related to small-study effects. We obtained the protocols of the included studies to assess possible bias of selective outcome reporting.

Data synthesis

We reported summary and descriptive statistics (means and standard deviations (SDs), RRs, or HRs) for participant and intervention characteristics. Additionally, we synthesised outcome data across trials at the end of the trial using a random-effects model. We interpreted random-effects meta-analyses with due consideration of the whole distribution of effects. For dichotomous outcomes (incidence of progression and incidence of metastatic disease), we used the Mantel-Haenszel method, and for continuous outcomes (quality of life), we used the inverse variance method. Finally, for time-to-event outcomes (all-cause mortality, prostate-cancer mortality, time to disease progression, and time to metastatic disease), we used the generic inverse variance method. We used Review Manager 5 (RevMan) to perform all statistical analyses.

Subgroup analysis and investigation of heterogeneity

We tested clinical heterogeneity through investigation of interaction in subgroups of patients based on the follow characteristics.

1. Patient age: younger than 65 years versus 65 years or older.
2. PSA level at diagnosis: less than or equal to 10 ng/mL versus 10 ng/mL or more.
3. Gleason score at diagnosis: 6 or lower versus 7 or higher.
4. Clinical stage at diagnosis: T1c versus T2 as defined by the TNM classification system (Sobin 2010).

We used the test for subgroup differences in RevMan to compare subgroup analyses.

Sensitivity analysis

We performed sensitivity analyses to explore the influence of the following factor (when applicable) on effect sizes.

1. Risk of bias: by excluding studies at 'high risk' or 'unclear risk'.

Summary of findings and assessment of the certainty of the evidence

We present the overall certainty of evidence for each outcome according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. We defined quality as the degree of confidence that we have in the estimates of treatment benefits and harms. The certainty of evidence takes five criteria into account related not only to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity (directness of results) (Guyatt 2008). For each comparison, two review authors (RV, ML) independently rated the certainty of evidence for each outcome as 'high', 'moderate', 'low', or 'very low' using GRADEpro GDT. In cases of disagreement, we consulted a third review author (KA).

For each comparison, we present a summary of evidence for the main outcomes in 'Summary of findings' tables, which provide key information about the best estimate of the magnitude of effect in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and ratings of overall confidence in effect estimates for each outcome (Guyatt 2011; Schünemann 2011). We created 'Summary of findings' tables based on the methods detailed in the *Cochrane Handbook for Systematic Reviews of Interventions,* and we justified all decisions to downgrade quality by using footnotes.

RESULTS

Description of studies

For a comprehensive description of trials, more details are provided in the Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies sections and are briefly summarised below.

Results of the search

For detailed information on results of the search, see Figure 1. We identified 4845 references in total through database searching. Following title and abstract screening by two review authors, we considered 228 articles for full-text screening. After full-text evaluation, we included four studies (reported in 43 articles) in this Cochrane Review (PIVOT; ProtecT; SPCG-4; VACURG).

Included studies

Trial design and population

All included studies were randomised controlled trials.

1. Three studies compared radical prostatectomy to watchful waiting (PIVOT; SPCG-4; VACURG); these studies informed this comparison (Summary of findings 1). Respectively, 61 and 50 patients were randomised to receive radical prostatectomy or watchful waiting in the VACURG study. In the PIVOT study, 364 patients were randomised to prostatectomy and 367 patients to watchful waiting. SPCG-4 randomised 347 patients to radical prostatectomy and 348 patients to watchful waiting. Median follow-up ranged from 12.7 years in PIVOT to 23 years in VACURG to 23.6 years in SPCG-4.
2. One three-armed trial compared radical prostatectomy versus active monitoring versus radiotherapy and informed the second comparison (Summary of findings 2) (ProtecT). Relevant to this review, 553 patients were randomised to receive radical prostatectomy and 545 patients active monitoring. Median follow-up was 10 years.

Setting

1. In the VACURG trial, participants were recruited from 15 hospitals located in the USA between May 1967 and March 1975
2. In the PIVOT study, participants were recruited from 44 Department of Veterans Affairs sites and eight National Cancer Institute centres in the USA between November 1994 and January 2002
3. Fourteen centres from Sweden, Finland, and Iceland enrolled participants in the SPCG-4 trial between October 1989 and Feburary 1999
4. ProtecT recruited participants from 337 primary centres in the UK between late 1999 and 2009

Participants

1. VACURG included participants with clinically diagnosed, untreated localised prostate cancer with normal acid phosphatase and no evidence of metastases. Participants who were randomised to the radical prostatectomy arm had a mean age of 67 years compared with 61 years in the control arm. This study pre-dates the PSA era, and participants did not have their PSA levels measured. A Gleason score of 5 to 6 was reported for 72.1% of participants treated with prostatectomy compared with 66% of those on watchful waiting. A Gleason score of 7 to 10 was reported in 11.5% and 8% of participants treated with prostatectomy and placebo, respectively
2. SPCG-4 included men younger than 75 years, most with clinically diagnosed (or diagnosed at the time of transurethral resection of the prostate) adenocarcinoma of the prostate verified by cytological examination, histological status, or both. Participants had to have prostate cancer of clinical stage T1 or T2 and a PSA level lower than 50 ng/mL. Mean participant age was 65 (SD 5) years. Mean PSA was 13.5 ng/mL (no SD reported). In all, 47.6% and 47.7% of participants treated with prostatectomy and watchful waiting, respectively, had a Gleason score at baseline of 5 or 6. Similarly, 22.2% and 23.6% of participants in the prostatectomy and watchful waiting arms had a Gleason score at baseline of 7
3. PIVOT enrolled participants with histologically confirmed, clinically localised prostate cancer (defined as T1-T2, NX, M0), with a PSA level less than 50 ng/mL, 75 years of age or younger, with a life expectancy of at least 10 years from the time of randomisation. Mean participant age was 67 (SD 5) years. Mean PSA was 10.1 (SD 7.4) ng/mL. Mean Gleason score was 5.5 (SD 1.6) in the watchful waiting group and 5.6 (SD 1.5) in the prostatectomy group
4. ProtecT included participants with histologically confirmed, clinically localised prostate cancer (defined as T1-T2, NX, M0), with a PSA level between 3.0 and 19.99 ng/mL, who were between 50 and 69 years of age with a life expectancy of at least 10 years. Participants were recruited from men diagnosed with prostate cancer through the Comparison Arm for ProtecT (CAP) cluster-randomised controlled trial (Martin 2018). Participants had a median age of 58 (range 50 to 69) years. Median PSA was 4.7 (inter-quartile range: 3.7 to 6.7) ng/mL and 4.9 (inter-quartile range: 3.7 to 6.7) ng/mL in, respectively, the active monitoring and prostatectomy group. In the radical prostatectomy arm, 76% and 22% of participants had a Gleason score of 6 and 7, respectively. Similarly, 77% and 20% of those in the active monitoring group had a Gleason score of 6 and 7, respectively

Interventions

1. VACURG
   a. Radical prostatectomy was performed via a retropubic approach. Participants also received a placebo
   b. Participants in the watchful waiting arm received placebo only
2. SPCG-4
   a. Radical prostatectomy was performed via a retropubic approach with bilateral pelvic lymph node dissection
   b. Participants in the watchful waiting arm received no intervention. For symptom-producing local tumour growth in the watchful waiting arm, transurethral resection of the prostate was standard procedure. For symptom-producing recurrence and/or uraemia, orchidectomy was considered
3. PIVOT
   a. The choice of surgical approach (retropubic, perineal) and the decision of whether to perform a node dissection were left to the surgeon's discretion
   b. Watchful waiting was defined as palliative therapies whenever tumour progression or metastatic disease occurred (e.g. transurethral resection of the prostate for

local progression, androgen deprivation, and/or targeted radiation therapy)

4. ProtecT
   a. Radical prostatectomy was performed via a retropubic approach in conjunction with a pelvic node dissection. Nerve sparing was performed at the discretion of the individual surgeon
   b. Active monitoring was described as a personalised plan of management including regular PSA level determinations, digital rectal examinations, and investigation of clinical symptoms suggestive of disease progression

Outcomes

This review focuses on reporting of the most important pre-defined outcomes. Additional outcomes reported by individual trials are reported in the Characteristics of included studies section.

Primary outcomes

Time to death from any cause

This outcome was reported by all three studies (PIVOT; SPCG-4; VACURG), informing the comparison of prostatectomy versus watchful waiting, but reporting differed.

1. VACURG reported the HR of all-cause mortality at 15 years' follow-up and median survival times of both groups; however, this study provided no measurement of variability for median survival estimates.
2. In SPCG-4, all-cause mortality was reported with an event rate of death during follow-up, a difference in cumulative mortality, and the risk ratio of death between the two groups.
3. PIVOT reported all-cause mortality with HR and cumulative incidence of death when radical prostatectomy was compared with watchful waiting.

This outcome was also reported by ProtecT, which was the only study informing the comparison of prostatectomy versus active monitoring.

Secondary outcomes

Time to death from prostate cancer

Two trials informing the comparison of radical prostatectomy versus watchful waiting reported this outcome (PIVOT; SPCG-4).

1. VACURG did not report this outcome.
2. SPCG-4 reported the cumulative incidence of death from prostate cancer at 18 years' follow-up and the risk ratio of death due to prostate cancer for both groups.
3. PIVOT reported HR and the cumulative incidence of death due to prostate cancer for both radical prostatectomy and watchful waiting groups.

ProtecT was the only study informing the comparison of prostatectomy versus active monitoring that also reported this outcome.

Time to disease progression

Two trials informing the comparison of radical prostatectomy versus watchful waiting reported this outcome (PIVOT; SPCG-4).

1. VACURG did not report this outcome.
2. SPCG-4 defined disease progression according to increased elevation in a patient's PSA level, development of metastases, and the need for hormonal treatments and palliative treatment.
3. PIVOT defined disease progression as asymptomatic local disease progression/persistence (e.g. rise in PSA), symptomatic local disease progression, symptomatic regional disease progression, asymptomatic metastatic disease progression, symptomatic metastatic disease progression, or asymptomatic progression of tumour biomarkers.

ProtecT defined disease progression as any of the following: evidence of metastases, diagnosis of clinical T3/T4 disease, initiation of long-term androgen deprivation therapy, ureteric obstruction, rectal fistula, or the need for a urinary catheter due to local tumour growth.

Time to metastatic disease

Two trials informing the comparison of radical prostatectomy versus watchful waiting reported this outcome (PIVOT; SPCG-4).

1. VACURG did not report this outcome.
2. SPCG-4 reported the cumulative incidence of distant metastases at 18 years' follow-up including the risk ratio compared between radical prostatectomy and watchful waiting groups.
3. PIVOT reported the rate of systemic progression as well as the HR for time to development of metastases.

In ProtecT the incidence of metastases was included in the time to disease progression outcome and was combined with other reasons for clinical progression (i.e. T3/T4 disease or initiation of long-term androgen deprivation therapy). We were not able to isolate the information for time to metastasis to perform this analysis.

Quality of life

Two trials informing the comparison of radical prostatectomy versus watchful waiting reported this outcome (PIVOT; SPCG-4).

1. VACURG did not report this outcome.
2. SPCG-4 collected health-related quality of life data on a seven-point visual digital scale, which was validated in an unpublished pilot study. The questionnaires explored psychological symptoms (anxiety, depressed mood), sense of well-being, and quality of life. Additionally, several categories of physical symptoms were assessed: erectile dysfunction, weak urinary stream, urinary leakage, and nocturia.
3. PIVOT reported information regarding urinary and sexual quality of life by collecting patient-reported outcomes of urinary incontinence, erectile and sexual dysfunction, worry about health, 'bother' due to prostate cancer or treatment, physical discomfort, satisfaction with sexual functioning, and functional limitations due to prostate cancer or treatment. Patient-reported overall health and physical or mental health was assessed with the use of the Medical Outcomes Study 12-Item Short-Form General Health Survey (SF-12).

ProtecT reported general health-related quality of life using a number of instruments, namely, SF-12, the Hospital Anxiety and Depression Scale (HADS), and the EORTC QLQ-C3021 instrument. Additionally, urinary function and urinary incontinence domains were reported using ICIQ score, the EPIC instrument, and the

ICSmaleSF instrument, as well as the categorical question of whether urinary dysfunction impacted participants' quality of life. The sexual function domain was reported using the EPIC instrument and the categorical question of whether sexual dysfunction impacted participants' quality of life. Finally, bowel function domains were reported using the EPIC instrument, categorical questions about faecal incontinence, and the impact of bowel habits on quality of life.

Adverse events

1. VACURG did not report this outcome
2. SPCG-4 did not report this outcome
3. PIVOT was the only study to inform this outcome for the comparison of radical prostatectomy versus watchful waiting
4. ProtecT also provided this information, which informed the comparison of radical prostatectomy versus active monitoring

Excluded studies

We excluded 182 studies after evaluating the full-text articles. We excluded most of these studies (n = 125) due to non-randomised study design. Furthermore, we excluded 11 studies for reporting solely costs or cost-effectiveness outcomes without any clinical outcomes of our interest (Andersson 2011; Corcoran 2010; Eldefrawy 2013; Hayes 2013; Kim 2012; Koerber 2014; Lavelle 2011; Molinier 2011; Penson 2011; Reinhold 2016; Schwartz 1995). We excluded five studies for not comparing deferred treatment with radical prostatectomy (Dall'Era 2008; Dall'Era 2012; Eifler 2017; NCT02914873; Xia 2012). We excluded one study for investigating first-line treatment options solely in high-risk prostate cancer patients (Lei 2015). More details regarding reasons for study exclusion are described in the Characteristics of excluded studies table.

Ongoing studies

We identified three ongoing trials in trial registers; more details can be found in the Characteristics of ongoing studies table.

Risk of bias in included studies

For details on risk of bias of the included trials, see the Characteristics of included studies table. For an overview of our evaluations of each risk of bias item, see Figure 2, Figure 3, and the two summary of findings tables (Summary of findings 1; Summary of findings 2).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

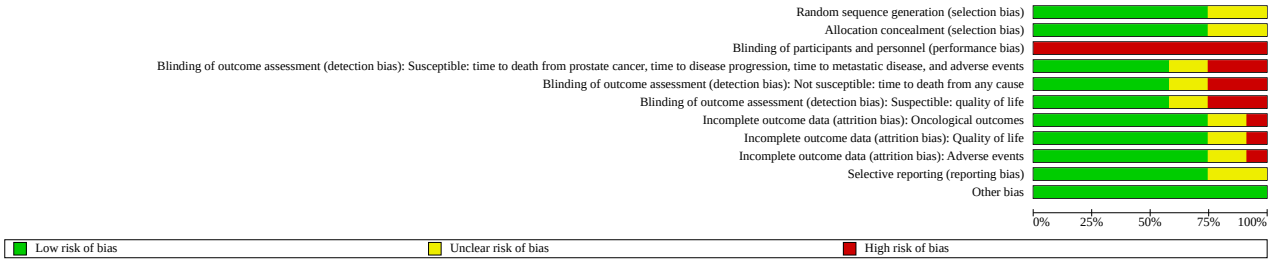
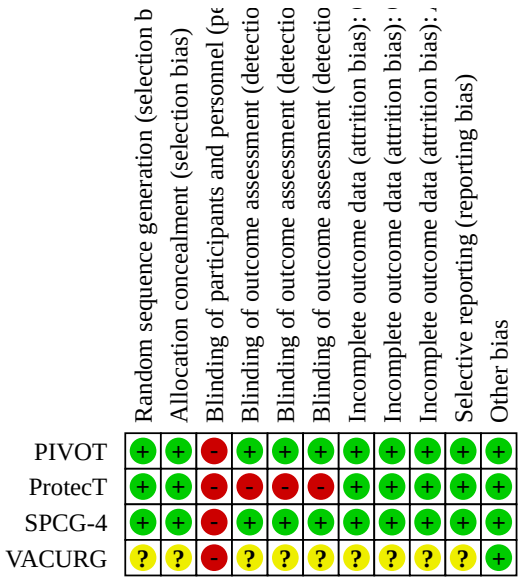


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 3. (Continued)



Allocation

We rated three studies as having low risk of selection bias due to adequate random sequence generation and allocation concealment (PIVOT; ProtecT; SPCG-4).

We considered VACURG as having unclear risk for selection bias because neither methods for random sequence generation nor methods for allocation concealment was described.

Blinding

Performance bias

The nature of the trial interventions largely precluded blinding of patients and their physicians, and no special measures suggesting the use of sham surgery were reported. Therefore, we considered all included studies to have high risk of performance bias (PIVOT; ProtecT; SPCG-4; VACURG).

Detection bias

Not susceptible outcomes: time to death from any cause

Risk of detection bias for the outcome time to death from any cause, which was considered not susceptible for detection bias, was low for all four studies (PIVOT; ProtecT; SPCG-4; VACURG).

Suspectible outcomes: time to death from prostate cancer, time to disease progression, time to metastatic disease, and adverse events

In three studies, risk of detection bias for outcome assessor-dependent outcomes was considered low due to use of anonymised medical records reviewed by an independent endpoint committee masked to the trial assignment (PIVOT; ProtecT; SPCG-4). The other study did not describe whether outcome assessors and/or radiologists assessing subjective outcomes were blinded to group allocation (VACURG).

Suspectible outcomes: quality of life

All studies were downgraded to high risk of detection bias for the outcome quality of life because this is self-reported by patients who were not blinded due to the nature of the intervention (PIVOT; ProtecT; SPCG-4).

Incomplete outcome data

Oncological outcomes

No exclusions post randomisation nor patients lost to follow-up have been reported in the PIVOT trial, which we therefore considered as having low risk of attrition bias for oncological outcomes. ProtecT reported a total of 14 patients who were lost to follow-up, equally divided across treatment arms; however data on death were captured for all patients, which we assessed as showing low risk of attrition bias for oncological outcomes. Post randomisation, two patients were excluded from the radical prostatectomy group (two concurrent malignancies) and one patient from the watchful waiting group (no prostate cancer) in SPCG-4, which we therefore evaluated as having low risk of attrition bias. We assessed VACURG as having high risk of attrition bias across because 19 patients (14%) were lost to follow-up.

Adverse events

No exclusions post randomisation nor patients lost to follow-up have been reported in the PIVOT trial, which we therefore considered as having low risk of attrition bias for adverse events outcomes. ProtecT reported a total of 14 patients who were lost to follow-up, equally divided across treatment arms, which we assessed as showing low risk of attrition bias for adverse events. Post randomisation, two patients were excluded from the radical prostatectomy group (two concurrent malignancies) and one patient from the watchful waiting group (no prostate cancer) in SPCG-4, which we therefore evaluated as having low risk of attrition bias.

Quality of life

No exclusions post randomisation nor patients lost to follow-up have been reported in the PIVOT trial, which we therefore considered as having low risk of attrition bias for the outcome quality of life. ProtecT reported a response rate of at least 85% for quality of life questionnaires during follow-up, which we considered as showing low risk of attrition bias. A response rate of at least 87% was reported in SPCG-4 for the quality of life questionnaire; therefore we evaluated this study as having low risk of attrition bias.

Selective reporting

We considered three studies to have low risk of reporting bias (PIVOT; ProtecT; SPCG-4). All three studies reported a protocol or a trial registry, and we found no differences between reported outcomes nor in the analytical approach between published reports and prior protocols. We rated VACURG as having unclear risk of attrition bias because we identified no protocol and no trial registry.

Other potential sources of bias

We identified no other potential sources of bias for any of the four included studies (PIVOT; ProtecT; SPCG-4; VACURG).

Effects of interventions

See: **Summary of findings 1** Radical prostatectomy compared to watchful waiting for localised prostate cancer; **Summary of findings 2** Radical prostatectomy compared to active monitoring for localised prostate cancer

1. Radical prostatectomy versus watchful waiting

See Summary of findings 1 for the comparison radical prostatectomy versus watchful waiting.

Primary outcomes

1.1. Time to death from any cause

Radical prostatectomy probably reduces the risk of dying from any cause over time (hazard ratio (HR) 0.79, 95% confidence interval (CI) 0.70 to 0.90; 3 studies with 1537 participants; I^2 = 0%; Analysis 1.1). Based on overall mortality at approximately 29 years taken from the watchful waiting arm of SPCG-4, this corresponds to 764 deaths (722 to 807) deaths per 1000 men in the prostatectomy group compared to 839 deaths per 1000 men in the watchful waiting group (Summary of findings 1). Using the overall mortality rate from PIVOT at approximately 22 years' follow-up, this corresponds to 648 deaths (603 to 695) per 1000 compared to 733 deaths per 1000 men in the watchful waiting group. We rated the certainty of evidence as moderate, downgrading by one level due to indirectness, given likely important differences between study participants' disease stage and the interventions they received compared to today's patients.

Secondary outcomes

1.2. Time to death from prostate cancer

Radical prostatectomy probably reduces the risk of dying from prostate cancer over time (HR 0.57, 95% CI 0.44 to 0.73; 2 studies with 1426 participants; I^2 = 0%; Analysis 1.2). Based on prostate cancer-specific mortality at approximately 29 years taken from the watchful waiting arm of SPCG-4, this corresponds to 195 deaths (154 to 242) from prostate cancer per 1000 men in the prostatectomy group compared to 316 deaths from prostate cancer per 1000 men in the watchful waiting group (Summary of findings 1). Using the prostate cancer-specific mortality rate from PIVOT at 19.5 years' follow-up, this corresponds to 67 deaths (52 to 85) from prostate cancer per 1000 men in the prostatectomy group compared to 114 deaths from prostate cancer per 1000 men in the watchful waiting group. We rated once again the certainty of evidence as moderate, downgrading by one level due to indirectness, given likely important differences between study participants' disease stage and the interventions they received compared to today's patients.

1.3. Time to disease progression

Radical prostatectomy probably reduces the risk of progression over time (HR 0.43, 95% CI 0.35 to 0.54; 2 studies with 1426 participants; I^2 = 54%; Analysis 1.3). Based on rates of progression at 19.5 years of SPCG-4, this corresponds to 391 disease progressions (332 to 463) per 1000 men in the prostatectomy group compared with 684 disease progressions per 1000 men in the watchful waiting group. Using the disease progression rate from PIVOT at 18 years' follow-up, this corresponds to 382 disease progressions (324 to 454) per 1000 men in the prostatectomy group compared to 674 disease progressions per 1000 men in the watchful waiting group. We rated the certainty of evidence as low, downgrading by one level due to indirectness and inconsistency.

1.4. Time to metastatic disease

Radical prostatectomy probably reduces the risk of metastatic spread over time (HR 0.56, 95% CI 0.46 to 0.70; 2 studies with 1426 participants; I^2 = 0%; Analysis 1.4). Based on rates of metastatic disease at 29 years of SPCG-4, this corresponds to 271 cases of metastatic disease per 1000 men in the prostatectomy group compared with 431 cases of metastatic disease per 1000 men in the watchful waiting group. Using the disease progression rate from PIVOT at approximately 20 years' follow-up, this corresponds to 85 cases of metastatic disease (71 to 105) per 1000 men in the prostatectomy group compared to 147 cases of metastatic disease per 1000 men in the watchful waiting group. We rated the certainty of evidence as moderate, downgrading by one level due to indirectness, given likely important differences between study participants' disease stage and the interventions they received compared to today's patients.

1.5. General quality of life

1.5.1. Quality of life: health-related quality of life

All information for this outcome was informed by SPCG-4. Different instruments were used and different outcomes were measured.

1.5.1.1. Moderate or high level of anxiety

Radical prostatectomy may result in similar risk of moderate or high levels of anxiety (risk ratio (RR) 1.01, 95% CI 0.79 to 1.29; 1 study with 339 participants; I^2 = 0%; low-certainty evidence).

1.5.1.2. Moderate or high level of depressed mood

Radical prostatectomy may result in similar risk of moderate or high levels of depressed mood (RR 0.92, 95% CI 0.74 to 1.14; 1 study with 339 participants; I^2 = 100%; low-certainty evidence).

1.5.1.3. High level of self-perceived well-being

Radical prostatectomy may result in a similar probability of high levels of self-perceived well-being (RR 1.06, 95% CI 0.88 to 1.27; 1 study with 340 participants; I^2 = 0%; low-certainty evidence).

The effects of radical prostatectomy compared with watchful waiting in terms of health-related quality of life have been reported solely in the SPCG-4 trial with several dichotomous items (Analysis 1.5; Analysis 1.6; Analysis 1.7; Analysis 1.8; Analysis 1.9).

Across the different analyses below, it is likely that there are no differences in overall quality of life between patients who underwent radical prostatectomy and those treated with watchful waiting.

The analysis regarding moderate or high anxiety included low-certainty evidence (downgraded because of risk of bias and indirectness) and showed no difference in scores at the end of follow-up between the radical prostatectomy group and the watchful waiting group (end of follow-up: RR 1.01, 95% CI 0.79 to 1.29; 1 study with 339 participants; Analysis 1.5). Similarly, no differences were found in the number of patients with a moderate or high depressed mood between intervention and control arms (end of follow-up: RR 0.92, 95% CI 0.74 to 1.14; 1 study with 339 participants; Analysis 1.6 low-certainty evidence due to risk of bias and indirectness). In total, 73 of the 179 patients treated with radical prostatectomy and 71 of the 161 watchful waiting patients were indicated to have high overall well-being, resulting in no differences between the two groups for this item (end of follow-up: RR 0.92, 95% CI 0.72 to 1.18; 1 study with 340 participants; Analysis 1.7 low-certainty evidence due to risk of bias and indirectness). The analysis regarding high quality of life included low-certainty evidence (downgraded because of risk of bias and indirectness) and showed no differences in scores at the end of follow-up between the radical prostatectomy group and the watchful waiting group (end of follow-up: RR 1.01, 95% CI 0.75 to 1.35; 1 study with 339 participants; Analysis 1.8).

1.5.2. Quality of life: urinary function - incontinence and lower urinary tract symptoms

Two trials reported information on quality of life using different measures that could not be combined in a meaningful way; therefore, the results of key measures are presented separately for each of these trials. The effect of urinary function (including incontinence and lower urinary tract symptoms) has been reported in the PIVOT study by one dichotomous outcome, defined as incontinence as an adverse event requiring treatment, and in the SPCG-4 trial by several dichotomous items (Analysis 1.11; Analysis 1.12; Analysis 1.13; Analysis 1.14; Analysis 1.15; Analysis 1.16; Analysis 1.17; Analysis 1.18; Analysis 1.19; Analysis 1.20; Analysis 1.21). Below, a narrative description of the (sub-)scale scores of items regarding urinary emptying symptoms, urinary storing symptoms, and urinary leakage has been provided. Across the different analyses below, it is likely that patients who underwent surgery have more deteriorated urinary function than those treated with watchful waiting.

Radical prostatectomy may cause a large increase in the number of men who experienced incontinence as an adverse event requiring treatment (RR 3.97, 95% CI 2.34 to 6.74; 1 study with 731 participants; Analysis 1.10). This corresponds to 129 more men per 1000 (95% CI 58 more to 250 more). We rated the certainty of evidence as very low, downgrading for study limitations, imprecision, and indirectness.

1.5.3. Quality of life: overall sexual function and erectile dysfunction

The effect of sexual function (including erectile dysfunction) has been reported in the PIVOT and SPCG-4 trial by several dichotomous items (Analysis 1.23; Analysis 1.24; Analysis 1.25; Analysis 1.26; Analysis 1.27; Analysis 1.28; Analysis 1.29; Analysis 1.30; Analysis 1.31; Analysis 1.32; Analysis 1.33; Analysis 1.34; Analysis 1.35; Analysis 1.36; Analysis 1.37; Analysis 1.38). The effect of radical prostatectomy versus watchful waiting on sexual function in the PIVOT trial has been reported for several time points (i.e. 6, 12, 24, 36, 48, 70, and 72 months). Below, a narrative description is provided of the (sub-)scale scores for items regarding sexual activity or intercourse, level of interest in sexual activities, physical discomfort, desire, sexuality, penile stiffness, and orgasms. Across the different analyses below, it is likely that patients who underwent surgery have more deteriorated sexual function than those treated with watchful waiting.

A lower incidence of erectile dysfunction at the end of follow-up was found for the watchful waiting group compared with the radical prostatectomy group (RR 2.67, 95% CI 1.63 to 4.38; 1 study with 731 participants; 91 more per 1000, 95% CI 34 more to 184 more; Analysis 1.22 very low-certainty evidence due to risk of bias, imprecision, and indirectness). Similarly, in total, 146 of the 173 patients treated by radical prostatectomy and 122 of the 153 patients treated by watchful waiting in the SPCG-4 trial were indicated to never have sufficient erectile function for intercourse, resulting in no differences between groups (RR 1.06, 95% CI 0.96 to 1.17; 1 study with 326 participants; 48 more per 1000, 95% CI 32 more to 136 more; Analysis 1.31 low-certainty evidence due to risk of bias and indirectness).

1.5.4. Quality of life: overall bowel function and faecal incontinence

No evidence was identified regarding overall bowel function and faecal incontinence in the radical prostatectomy versus watchful waiting comparison.

1.6. Adverse events

Radical prostatectomy may have rates of adverse events similar to watchful waiting (RR 1.11, 95% CI 0.74 to 1.65; 1 study with 731 participants). We rated the certainty of evidence as very low, downgrading for study limitations, imprecision, and indirectness

Other adverse events were reported by 45 of the 364 patients (12.4%) treated by radical prostatectomy and by 41 of the 367 patients (11.2%) treated by watchful waiting. Therefore, the analysis regarding adverse events included very low-certainty evidence (downgraded due to risk of bias, imprecision, and indirectness) and showed no differences in event rates of adverse events at end of follow-up for the radical prostatectomy group compared with the watchful waiting group (RR 1.11, 95% CI 0.74 to 1.65; 1 study with 731 participants; Analysis 1.39).

1.7. Subgroup analyses

1.7.1. Patient age: younger than 65 years versus 65 years and older

1.7.1.1. All-cause mortality

The subgroup analysis indicated no subgroup effect on patient age regarding the outcome all-cause mortality (P = 0.07), where

the survival benefit for radical prostatectomy was greatest among younger men (Analysis 3.1.

1.7.1.2. Prostate cancer mortality

The subgroup analysis did not give any indication of a subgroup effect on patient age regarding the outcome prostate cancer mortality (Analysis 3.2).

1.7.1.3. Time to disease progression

The subgroup analysis indicated a possible subgroup effect on patient age regarding the outcome time to disease progression (P = 0.04), where the survival benefit of radical prostatectomy was greatest among younger men. For men younger than 65 years, an HR of 0.39 (95% CI 0.29 to 0.52; 1 study with 323 participants; Analysis 3.3), and for men 65 years and older, an HR of 0.60 (95% CI 0.45 to 0.80; 1 study with 372 participants), were found when prostatectomy was compared with watchful waiting. The test for interaction indicated a P value of 0.04.

1.7.1.4. Time to metastatic disease

The subgroup analysis did not give any indication of a subgroup effect on patient age regarding the outcome prostate cancer mortality (Analysis 3.4).

1.7.2. PSA level at diagnosis: less than or equal to 10 ng/mL versus more than 10 ng/mL

The subgroup analysis did not give any indication of a subgroup effect on PSA level at diagnosis regarding the outcome all-cause mortality (Analysis 4.1), prostate cancer mortality (Analysis 4.2), or time to metastatic disease (Analysis 4.3).

1.7.3. Gleason score at diagnosis: 6 versus 7 or more

The subgroup analysis did not give any indication of a subgroup effect on Gleason score at diagnosis regarding the outcome all-cause mortality (Analysis 5.1), prostate cancer mortality (Analysis 5.2), or time to metastatic disease (Analysis 5.3).

1.7.4. Clinical stage at diagnosis: T1c versus T2

The subgroup analysis did not give any indication of a subgroup effect on clinical stage at diagnosis regarding the outcome all-cause mortality (Analysis 6.1), prostate cancer mortality (Analysis 6.2), or time to metastatic disease (Analysis 6.3).

1.8. Sensitivity analyses

For the first comparison, Radical prostatectomy versus watchful waiting, the only outcome that was changed in the sensitivity analyses was all-cause mortality. Compared with Analysis 1.1, the VACURG trial was deleted from this sensitivity analysis due to high risk of bias. Therefore, the meta-analysis of all-cause mortality (including the PIVOT and SPCG-4 trials) included a difference in time to death from any cause between radical prostatectomy and watchful waiting groups during follow-up (HR 0.77, 95% CI 0.66 to 0.91; 2 studies with 1426 participants; I^2 = 38%; Analysis 11.1).

2. Radical prostatectomy versus active monitoring

See Summary of findings 2 for the comparison radical prostatectomy versus active monitoring.

Primary outcomes

2.1. Time to death from any cause

It is probable that there are no differences between radical prostatectomy and active monitoring in the risk of dying from any cause over time (HR 0.93, 95% CI 0.65 to 1.33; 1 study with 1098 participants; Analysis 2.1). Based on overall mortality at 10 years for ProtecT, this corresponds to 101 deaths (95% CI 72 to 141) per 1000 men in the prostatectomy group compared with 108 deaths per 1000 men in the active monitoring group. We rated the certainty of evidence as moderate, downgrading by one level overall for imprecision.

Secondary outcomes

2.2. Time to death from prostate cancer

Radical prostatectomy probably does not alter the risk of dying from prostate cancer compared to active monitoring (HR 0.63, 95% CI 0.21 to 1.93; 1 study with 1098 participants; Analysis 2.2). Based on prostate cancer-specific mortality at 10 years for ProtecT, this corresponds to 9 prostate cancer-specific deaths (95% CI 3 to 28) per 1000 men in the prostatectomy group compared with 15 prostate cancer-specific deaths per 1000 men in the active monitoring group. The certainty of evidence was downgraded for imprecision.

2.3. Time to disease progression

Radical prostatectomy reduces the risk of progression over time (HR 0.39, 95% CI 0.27 to 0.56; 1 study with 1098 participants; Analysis 2.3). Based on rates of progression at 10 years for ProtecT, this corresponds to 86 disease progressions (95% CI 60 to 121) per 1000 men in the prostatectomy group compared with 206 disease progressions per 1000 men in the active monitoring group. The certainty of evidence was considered moderate due to risk of bias.

2.4. Time to metastatic disease

Time to metastatic disease was included as part of the composite outcome time to disease progression in ProtecT, and only the dichotomous event rate of metastases was reported. Radical prostatectomy reduces the occurrence of metastases at the end of follow-up (RR 0.39, 95% CI 0.21 to 0.73; 1 study with 1098 participants; Analysis 2.4). Based on rates of metastatic disease at 10 years for ProtecT, this corresponds to 24 (95% CI 13 to 44) metastatic diseases per 1000 men in the prostatectomy group compared with 61 metastatic diseases per 1000 men in the active monitoring group. The certainty of evidence was considered moderate due to risk of bias.

2.5. Quality of life

2.5.1. Quality of life: health-related quality of life

Health-related quality of life was measured in ProtecT by the SF-12 instrument, the HADS instrument, and the EORTC QLQ-C30 instrument. The effect of radical prostatectomy versus active monitoring on quality of life has been reported for several time points (i.e. 6, 12, 24, 36, 48, 60, and 72 months). These outcomes are included in Analysis 2.5; Analysis 2.6; Analysis 2.7; Analysis 2.8; Analysis 2.9; Analysis 2.10; and Analysis 2.11. Below a narrative description of the (sub-)scale scores of instruments used to measure health-related quality of life has been provided. Across the different analyses below, it is likely that there are no differences

in overall quality of life between patients who underwent radical prostatectomy and those treated with active monitoring.

It is probable that there are no differences in the quality of life measured with the SF-12 mental health subscale between radical prostatectomy and active monitoring (mean difference (MD): 0.50, 95% CI -0.65 to 1.65; 1 study with 856 participants; Analysis 2.6). The certainty of evidence was downgraded to moderate due to concerns of risk of bias. The analysis regarding quality of life on the HADS anxiety subscale score included moderate-certainty evidence (downgraded because of risk of bias) and showed no differences in scores between surgery and active monitoring groups at any time point of follow-up (end of follow-up: MD -0.40, 95% CI -0.88 to 0.08; 923 participants; Analysis 2.7). Finally, health-related quality of life has been measured on the EORTC QLQ-C30 instrument, and scores on different subscales (including physical, role, emotional, cognitive, and social subscales) at five years' follow-up are provided (Analysis 2.11).

2.5.2. Quality of life: urinary function - incontinence and lower urinary tract symptoms

ProtecT reported effects of radical prostatectomy versus active monitoring on urinary function by several instruments, including ICIQ score, EPIC urinary score, and the ICSmaleSF instrument. Similarly, these outcomes are reported for several time points (i.e. 6, 12, 24, 36, 48, 60, and 72 months). All time points for several outcomes are included in Analysis 2.12; Analysis 2.13; Analysis 2.14; Analysis 2.15; Analysis 2.16; Analysis 2.17; Analysis 2.18; Analysis 2.19; Analysis 2.20; Analysis 2.21; Analysis 2.22; Analysis 2.23; and Analysis 2.24. Below, a narrative description of the (sub-)scale scores of instruments used to measure effects of health-related quality of life on urinary function has been provided. Across the different analyses below, it is likely that patients who underwent surgery have more deteriorated urinary function than those treated with active monitoring.

Radical prostatectomy probably lowers urinary function at two years' follow-up compared with active monitoring (MD -8.6, 95% CI -11.19 to -6.01; 1 study with 782 participants; Analysis 2.12). The certainty of evidence was low to moderate due to concerns of risk of bias and imprecision. Urinary function measured with the EPIC yielded low-certainty evidence (downgraded because of risk of bias and imprecision) and was lower at every time point during follow-up for the surgery group (end of follow-up: MD -4.90, 95% CI -7.44 to -2.36; 895 participants; Analysis 2.13). Similarly, urinary function was measured with the ICSmaleSF instrument (moderate-certainty evidence downgraded due to risk of bias), and a worse score was found for the surgery group at every time point during follow-up (end of follow-up: MD 0.80, 95% CI 0.40 to 1.20; 926 participants; Analysis 2.14).

2.5.3. Quality of life: overall sexual function and erectile dysfunction

The effect of overall sexual function on quality of life was measured by the EPIC sexual function score in ProtecT. The effect of radical prostatectomy versus active monitoring on sexual function has been reported for several time points (i.e. 6, 12, 24, 36, 48, 70, and 72 months). Scores for different time points for these outcomes are included in Analysis 2.25; Analysis 2.26; Analysis 2.27; Analysis 2.28; Analysis 2.29; and Analysis 2.30. Across the different analyses below, it is likely that patients who underwent surgery have more deteriorated sexual function than those treated with active monitoring.

Radical prostatectomy probably lowers sexual function at two years' follow-up compared with active monitoring (MD -14.9, 95% CI -18.54 to -11.26; 1 study with 756 participants; Analysis 2.27). The certainty of evidence was downgraded to low due to concerns of risk of bias and imprecision.

2.5.4. Quality of life: overall bowel function and faecal incontinence

The effect of overall bowel function on quality of life was measured by the EPIC bowel function score in ProtecT. The effect of radical prostatectomy versus active monitoring on bowel function has been reported for several time points (i.e. 6, 12, 24, 36, 48, 70, and 72 months). Different scores at time points for these outcomes are included in Analysis 2.31; Analysis 2.32; Analysis 2.33; Analysis 2.34; Analysis 2.35; Analysis 2.36; Analysis 2.37; and Analysis 2.38. The analysis regarding bowel function measured by the EPIC bowel function score yielded moderate-certainty evidence (downgraded because of risk of bias) and showed no differences in scores at most time points during follow-up for the radical prostatectomy group compared with the active monitoring group (end of follow-up: MD 0.20, 95% CI -1.00 to 1.40; 920 participants; Analysis 2.31).

2.6. Adverse events

No event rate regarding adverse events has been provided by the ProtecT trial for the radical prostatectomy and active monitoring groups. Hence, a meta-analysis for this outcome was impossible and reporting only a narrative statement regarding adverse events for the study is possible. In ProtecT, no deaths related to surgery occurred during follow-up. However, nine men had thromboembolic or cardiovascular events, 14 required transfusion of more than 3 units of blood, one had a rectal injury, and nine required intervention for anastomotic problems.

2.7. Subgroup analyses

2.7.1. Patient age: younger than 65 years versus 65 years and older

The subgroup analyses did not give any indication of a subgroup effect on patient age at diagnosis regarding the outcome prostate cancer mortality (Analysis 7.1).

2.7.2. PSA level at diagnosis: less than or equal to 10 ng/mL versus more than 10 ng/mL

The subgroup analyses did not give any indication of a subgroup effect on PSA level at diagnosis regarding the outcome prostate cancer mortality (Analysis 8.1).

2.7.3. Gleason score at diagnosis: 6 versus 7 or higher

The subgroup analyses did not give any indication of a subgroup effect on Gleason score at diagnosis regarding the outcome prostate cancer mortality (Analysis 9.1).

2.7.4. Clinical stage at diagnosis: T1c versus T2

The subgroup analyses did not give any indication of a subgroup effect on clinical stage at diagnosis regarding the outcome prostate cancer mortality (Analysis 10.1).

2.8. Sensitivity analyses

For comparison 2, Radical prostatectomy versus active monitoring, it was not possible to conduct sensitivity analyses due to the fact that the one included study was evaluated to be at low risk of bias and to have follow-up longer than five years.

Ongoing trials

Two trial registry records of randomised controlled trials that would potentially be eligible for comparison 2, Radical prostatectomy versus active monitoring, were identified (DRKS00004405; NCT00499174). This Cochrane Review will be considered for updating when one of these two trials has been published.

DISCUSSION

Summary of main results

Compared with watchful waiting, patients who underwent radical prostatectomy probably have lower all-cause and prostate cancer mortality after 29 years' follow-up. Similarly, operated patients probably experience longer time to disease progression and longer time to metastatic disease at 18 or 29 years' follow-up. General health-related quality of life, albeit reported in a heterogeneous manner between the included studies, appears to be mostly similar between the radical prostatectomy and watchful waiting groups. Finally, patients treated with radical prostatectomy have worse functional outcomes, including increased rates of erectile dysfunction and urinary incontinence. Younger men had higher overall survival and time to disease progression benefit for radical prostatectomy compared with older men. No other differences in patient or disease characteristics were identified by subgroup analyses.

Radical prostatectomy is not associated with lower all-cause mortality or prostate cancer mortality compared with active monitoring at 10 years' follow-up. However, patients treated with radical prostatectomy probably have longer time to disease progression compared with patients treated with active monitoring. Patients treated with radical prostatectomy may have similar general health-related quality of life as patients treated with active monitoring; however, patients treated with active monitoring may have better functional outcomes, including urinary and sexual function. It should be noted that all the above mentioned results of radical prostatectomy versus active monitoring are based on only one randomised controlled trial. No differences in patient or disease characteristics were identified by subgroup analyses.

Overall completeness and applicability of evidence

The following issues appear relevant to interpretation of our study findings.

Radical prostatectomy versus watchful waiting

1. All three studies informing this comparison pre-date the current prostate-specific antigen (PSA) screening era, and participants were not exposed to use of other biomarkers or modern magnetic resonance imaging techniques (PIVOT; SPCG-4; VACURG). However, actual benefit for today's patients may be less, given that this study stems from the early PSA era
2. Radical prostatectomy has dramatically evolved since the accrual periods of the three included trials, as reflected in reduced patient length of stay, transfusion rates, and duration of catheterisation. Functional outcomes, in particular related to urinary continence and erectile function, have likely improved considerably over the last three decades due to better understanding of the surgical anatomy, including the development of neurovascular bundle-sparing approaches. Contemporarily, especially in the USA but also in many other affluent countries, prostatectomy is performed most often as robot-assisted laparoscopic prostatectomy with demonstrated advantages in terms of length of stay and transfusion rates (Ilic 2017). Observational studies suggest additional advantages over the standard open retropubic approach in terms of functional and quality of life outcomes, in particular in the hands of experienced, high-volume surgeons (De Carlo 2014; Heer 2011; Moran 2013; Novara 2012; Tooher 2006)
3. Both SPCG-4 and PIVOT were pragmatic trials that compared radical prostatectomy to deferred management in the form of watchful waiting, which was not well defined but usually consisted of initiation of surgical or medical castration when patients developed radiographic or clinical evidence of locoregional or distant metastases. Until the introduction of docetaxel, additional treatment options for these patients were very limited, and their effectiveness was not supported by high-quality evidence. This has recently changed dramatically, with several drugs such as abiraterone demonstrating large effect sizes in patients with advanced prostate cancer. As medical treatment for advanced prostate cancer becomes more effective, the future role of local treatment may be mitigated

Radical prostatectomy versus active monitoring

1. Trial evidence for this comparison was limited to ProtecT, which recruited from the Comparison Arm for ProtecT (CAP) screening trial and provided follow-up of only 10 years. In light of PSA screening, modern imaging, and stage migration, these patients had low risk of prostate cancer-related morbidity and mortality, as reflected in low event rates across all three treatment arms. Future follow-up will be valuable for placing results into context
2. Patients in the control arm underwent 'active monitoring' that is distinct from active surveillance as practiced today. Current active surveillance protocols call for an initial confirmation biopsy to confirm pathological grade, follow-up PSA monitoring at three- to six-month intervals, and repeat biopsies as frequently as once per year. In addition, magnetic resonance imaging is finding a role in active surveillance protocols. This results in a considerably higher treatment burden than is seen with PSA monitoring alone, thereby adding to the burden of overtreatment. At the same time, it may provide additional assurances, especially for younger patients for whom local treatment with curative intent can be safely postponed. It is notable that over half of patients in the active surveillance arm elected to undergo local treatment during the 10-year follow-up period; recent efforts at multi-disciplinary management with psychological support may improve future adherence (Kinsella 2018). Whereas a number of large prospective observational cohort studies are ongoing to inform the prognosis of patients in active surveillance (PRIAS), no randomised trials are ongoing, with the START trial having been stopped due to failure to accrue
3. Even today, the terms 'active surveillance' and 'watchful waiting' are not always well distinguished in routine clinical practice (Bruinsma 2016; Bruinsma 2017). An international expert panel has recently proposed a set of defined terms to allow practitioners to appropriately define the intended treatment approach (Bruinsma 2017)

Quality of the evidence

We downgraded the certainty of evidence to moderate (by one level) and low (by two levels) due to concerns over a combination of study limitations, indirectness, and imprecision.

1. The main reason for rating down for study limitations was concern over performance bias, given lack of blinding of participants, which was not practical in any of the included trials.
2. We downgraded all outcomes of the radical prostatectomy versus watchful waiting comparison for indirectness, given that all included trials were substantially different from today's practice in terms of study participants (tumour stage, size, grade) and intervention (open prostatectomy).
3. When confidence intervals around (pooled) effect sizes crossed presumed thresholds of clinical significance, we further rated down for imprecision.

Potential biases in the review process

Strengths of this updated review include its comprehensive search of multiple databases, including clinical trial registries, and contact with study authors to inform whether there are additional studies that we might have potentially missed. Therefore, we believe it is not likely that we have overlooked further relevant published or unpublished randomised controlled trials. We did not detect publication bias; however, we cannot rule it out completely because we cannot formally assess it in funnel plot evaluations due to the small number of identified studies. We applied a standard, high-quality method to complete our Cochrane Review. At least two independent review authors assessed the inclusion of every reference, evaluated risk of bias, and extracted data for our Cochrane Review to minimise bias. We followed Cochrane guidance and applied GRADE to assess the certainty of evidence on a per-outcome basis.

This review is an update of a review published in 2010 and a protocol that dates back to 2007 (Hegarty 2010). Since that time, methodological standards have increased substantially, prompting changes to the review format, which are not reflected in the original protocol (which is outdated at this time). Although we have sought to capture the main determinations of differences between the protocol and the review, we recognise lack of a concordant protocol as a potential source of bias. In addition, included trials reported different quality of life measures. Although we have sought to report on these findings in a comprehensive measure, the summary of findings tables focus on a subset of these, which were chosen post hoc. This also represents a potential source of bias.

Agreements and disagreements with other studies or reviews

Non-randomised studies often include more participants, showing increased external validity, and are particularly suitable for evaluation of adverse events and sensible survival data (Gartlehner 2008). However, the existing reviews Bandari 2017, Carter 2015, Dahabreh 2012, Romero-Otero 2016, Thomsen 2014, Wilt 2008, and Yang 2014, which included both randomised controlled trials and observational studies, did not find results different from our Cochrane Review. Other systematic reviews have also assessed available evidence from randomised controlled trials regarding effects of radical prostatectomy versus deferred treatment (both active surveillance and watchful waiting) (Abrahamsson 2009; Adolfsson 1993; Alibhai 2004; Bandari 2017; Carter 2015; Dahabreh 2012; Dall'Era 2017; Hugosson 2011; Kilpeläinen 2019; Romero-Otero 2016; Thomsen 2014; Tikkinen 2017; Wilt 2008; Yang 2014).

Results of this updated Cochrane Review are largely consistent with those of existing reviews but stand out for its rigorous methodology, which includes rating the certainty of evidence using GRADE on a per-outcome basis. It also provides the most up-to-date assessment by including recently published long-term data on all-cause survival for PIVOT.

AUTHORS' CONCLUSIONS

Implications for practice

Men with clinically localised prostate cancer are at relatively low risk for disease-related morbidity and mortality. Whereas the results of this Review demonstrate substantial benefit of radical prostatomy over watchful waiting with regard to oncological outcomes, such benefit is realised only by men with an extended life expectancy of well over 10 years. Given that all men undergoing surgery are at increased risk for urinary incontinence and erectile dysfunction and resulting diminished quality of life, careful patient selection based on disease characteristics, medical comorbidities, and patient expectations appears critical. Ultimately, the decision of radical prostatectomy versus deferred treatment will depend on the values and preferences of each individual patient and the importance that each patient places on the potential for prolonging progression-free life versus the increased risk for potential adverse events, including erectile dysfunction and urinary incontinence. The decision regarding primary treatment of localised or locally advanced prostate cancer depends largely on patient-/disease-specific factors and patients' values and preferences (Lancee 2018). The need to make such difficult trade-offs highlights the importance of a shared approach to decision-making, during which patients and their healthcare providers openly discuss available evidence on potential benefits and potential harms of different treatment options in the context of the patient's personal values, preferences, and specific circumstances.

Implications for research

The findings of this review are based on evidence of moderate or low certainty, indicating that the true effects are likely close to the estimates of effect reported here, although the possibility exists that they may be substantially different. However, the following issues remain to be addressed.

1. Reported evidence on the comparative effectiveness of radical prostatectomy versus active monitoring is based on a single, albeit high-quality, trial. In this study, patients in the deferred treatment arm underwent PSA test-based follow-up referred to as 'active monitoring'. This differs considerably from the current surveillance practice, which also incorporates periodic repeat prostate biopsies and magnetic resonance imaging. Although these active surveillance protocols may increase the patient burden, better risk stratification may allow a greater proportion of patients than in ProtecT to defer local treatment with curative intent and its associated unfavourable effects.
2. Reported trial evidence on active monitoring is limited to 10 years' follow-up. Although no impact was observed with regards to overall and disease-specific survival, a beneficial impact on

time to progression and time to metastatic spread was noted. Longer follow-up for ProtecT is necessary to determine whether or not this will translate into a future mortality benefit.

3. We had anticipated that effects of surgical treatment may differ based on important baseline characteristics such as patient age and disease stage, and we had defined subgroup analyses accordingly. Ultimately, we were unable to conduct many of these pre-planned analyses, leaving the question of any possible interaction as an open question. This appears particularly relevant to the selection of men who can be safely treated with watchful waiting (over either surgery or watchful waiting).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

PIVOT

Study characteristics	
Methods	**Study design:** randomised controlled trial

PIVOT *(Continued)*

	Recruitment period: November 1994 to January 2002 **No. of centres:** 44 Department of Veterans Affairs sites and 8 National Cancer Institute sites **Publication status:** full-text report
Participants	**Country:** USA **Setting:** hospital and other **Sample size:** 731 patients **Mean age (SD)**: 67 ± 5 years **Baseline mean PSA (SD):** watchful waiting: 10.2 (SD 7.9) ng/mL and radical prostatectomy: 10.1 (SD 7.4) ng/mL **Baseline mean Gleason score:** watchful waiting: 5.5 (SD 1.6) and radical prostatectomy: 5.6 (SD 1.5) **Inclusion criteria:** patients had to be medically fit for radical prostatectomy and to have histologically confirmed, clinically localised prostate cancer (T1-T2, NX, M0 in the tumour-node-metastasis classification system according to the American Joint Committee on Cancer) of any grade diagnosed within the previous 12 months. Patients also had to have a PSA level < 50 ng/mL, age 75 years or less, negative results on bone scan for metastatic disease, and a life expectancy of at least 10 years from the time of randomisation **Exclusion criteria:** (1) significant coexisting medical conditions that are acute or debilitating, or are expected to result in a life expectancy < 10 years or to place the patient at unacceptable surgical risk (e.g. evidence of non-dermatologic malignancy within the past 5 years; severe pulmonary, cardiac, renal, or hepatic impairment; myocardial infarction within 6 months; unstable angina, dementia, or other debilitating illness); (2) prior surgical treatment (except TURP), irradiation, or hormonal treatment or chemotherapy for cancer of the prostate; (3) laboratory abnormalities that in the opinion of the participating investigator are expected to result in a life expectancy < 10 years; (4) evidence of clinically non-localised prostate cancer: (a) PSA > 50 (if on finasteride within the previous 3 months, PSA > 25), (b) bone scan consistent with metastatic disease, (c) other imaging or laboratory studies performed at the discretion of the participating investigator indicating that prostate cancer is non-localised; (5) current use of any of the following medications: estrogens, 5' alpha-reductase inhibitors, antiandrogen drugs; (6) inability or unwillingness to give informed consent; (7) reasonable likelihood that the patient cannot be followed during the study period; (8) participation in another intervention research study **Diagnostic criteria:** locally obtained PSA values and biopsy readings
Interventions	**Number of arms:** 2 **Comparison:** radical prostatectomy vs watchful waiting **Randomisation ratio:** 364/367 **Run-in period:** not applicable **Follow-up period:** median follow-up of 18.6 years **Intervention:** radical prostatectomy (defined as the exact type of radical prostatectomy (e.g. retropubic, transperineal, use of lymph node dissection) was left to the discretion of the operating surgeon) **Control:** watchful waiting (defined as palliative (non-curative) therapies (e.g. transurethral resection of the prostate for local progression causing urinary obstruction, androgen deprivation, and/or targeted radiation therapy for evidence of distant spread). Interventions for asymptomatic progression (e.g. change in PSA value) were discouraged)
Outcomes	**Primary outcome:** all-cause mortality

PIVOT *(Continued)*

	Secondary outcomes: prostate cancer-specific mortality; biochemical (PSA), local, and metastatic progression; 30-day perioperative mortality and morbidity; longer-term urinary, bowel, and erectile dysfunction **Composite outcome measures reported:** no
Funding sources	**Funding:** supported by grants from the Department of Veterans Affairs Cooperative Studies Program, the National Cancer Institute, and the Agency for Healthcare Research and Quality
Declarations of interest	Several trial authors report conflicts of interest in the acknowledgements section of the paper
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quotes from publication:** "randomization was stratified according to site and implemented means of a central interactive telephone system"; "patients will be randomized to radical prostatectomy or expectant management. Patients will be stratified by medical center. Baseline data will include clinical stage and grade of the biopsy specimen, PSA level, age, race, presence of prostatic symptoms, health status, demographics, history of other medical conditions, Charlson Comorbidity index, and family history of prostate cancer"; "randomization was stratified according to site and implemented means of a central interactive telephone system" **Comment:** block randomisation with a centralised interactive telephone system was considered to be adequate for the random sequence generation
Allocation concealment (selection bias)	Low risk	**Quote from publication:** "randomization was stratified according to site and implemented means of a central interactive telephone system" **Comment:** a central interactive telephone system was considered to be adequate for the allocation concealment
Blinding of participants and personnel (performance bias)	High risk	**Comment:** the nature of the trial interventions precluded blinding of patients and their physicians
Blinding of outcome assessment (detection bias) Susceptible: time to death from prostate cancer, time to disease progression, time to metastatic disease, and adverse events	Low risk	**Quotes from publication:** "the site investigators and assistants collected and transmitted data to the coordinating center for analysis"; "an end-points committee whose members were unaware of the trial-group assignments determined the cause of death on the basis of information extracted from the patient's medical record" **Comment:** it seems that outcome assessors and radiologists assessing subjective outcomes were blinded to group allocation
Blinding of outcome assessment (detection bias) Not susceptible: time to death from any cause	Low risk	**Quote from publication:** "the site investigators and assistants collected and transmitted data to the coordinating center for analysis" **Comment:** it is unclear whether outcome assessors and radiologists assessing the objective outcomes were blinded to group allocation. However, it is unlikely that these objective outcomes are influenced by the unblinded nature of outcome assessment
Blinding of outcome assessment (detection bias) Suspectible: quality of life	High risk	**Quote from publication:** "we assessed 30-day perioperative harms and the prevalence of urinary incontinence and erectile and bowel dysfunction at 2

PIVOT *(Continued)*

		years, which was based on self-reported dysfunction that was at least moderate in severity" **Comment:** quality of life and functional outcomes are self-reported. Due to the nature of the trial intervention, patients could not be blinded
Incomplete outcome data (attrition bias) Oncological outcomes	Low risk	**Quote:** "the vital status of all the participants was available, although we were unable to ascertain the cause of death in 7 men (2 assigned to surgery and 5 to observation)" **Comment:** no exclusions post randomisation and no losses to follow-up
Incomplete outcome data (attrition bias) Quality of life	Low risk	**Comment:** no exclusions post randomisation and no losses to follow-up
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment:** no exclusions post randomisation and no losses to follow-up
Selective reporting (reporting bias)	Low risk	**Quote:** "ClinicalTrials.gov number: NCT00007644" **Comment:** a complete study protocol is available and no differences were identified between outcomes reported in this protocol and in the articles
Other bias	Low risk	**Comment:** none identified

ProtecT

Study characteristics	
Methods	**Study design:** randomised controlled trial **Recruitment period:** between 1999 and 2009 **No. of centres:** 337 primary care centres **Publication status:** full-text report
Participants	**Country:** UK **Setting:** hospital and primary care **Sample size:** 1643 patients **Median age (range):** 58 years (50 to 69) **Baseline median PSA (range):** active monitoring: 4.6 (3.0 to 20.9) ng/mL and radical prostatectomy: 4.7 (3.0 to 18.4) ng/mL **Baseline Gleason score:** prostatectomy: 6 (76%), 7 (22%), 8 to 10 (2%), missing: < 1%; active surveillance: 6 (77%), 7 (20%), 8 to 10 (2%), missing: 0% **Inclusion criteria:** (1) age 50 to 69 years on the date of Prostate Check Clinic; (2) male gender; (3) able to give informed written consent to participate; (4) fit for any of the 3 treatments. Patients had to have a life expectancy of more than 10 years and clinically localised disease (defined as stage T1-T2, NX, M0, with PSA level between 3.0 and 19.99 ng/mL) **Exclusion criteria:** (1) concomitant or past malignancy (other than a small treated skin cancer); (2) prior treatment for prostate malignancy; (3) serious cardiac problems in the previous 12 months of

ProtecT *(Continued)*

	Prostate Check Clinic (i.e. stroke, MI, heart failure); (4) kidney dialysis or transplantation. Men with benign biopsy samples, or with locally advanced or advanced prostate cancer, were excluded **Diagnostic criteria:** digital rectal examination, PSA, transrectal ultrasound-guided biopsy, isotope bone scanning, or MRI
Interventions	**Number of arms:** 3 **Comparison:** active monitoring vs radical prostatectomy vs external beam radiotherapy (radiotherapy not considered for this Cochrane Review) **Randomisation ratio:** active monitoring: 545 and radical prostatectomy: 553 **Run-in period:** not applicable **Follow-up period:** median follow-up of 10 years **Intervention:** radical prostatectomy (defined as pelvic lymphadenectomy and radical prostatectomy) was performed following the conventional anatomical retropubic approach as described by Walsh. The decision to undertake a nerve-sparing operation was made at the discretion of the individual surgeon, depending on individual cases, and after discussion with participants **Control:** active surveillance (defined as patient's personal plan of management decided jointly by the participant and the urologist or research nurse but likely to include (1) PSA every 3 months in year 1, then 3 to 6 months at clinical or participant request; (2) rapid 'review' appointments in the event of symptoms (urinary or systemic) or unstable PSA; (3) digital rectal examination (DRE) at the review appointment conducted by the urologist)
Outcomes	**Primary outcome:** prostate cancer mortality at a median of 10 years' follow-up **Secondary outcomes:** (1) short-term outcomes (6 months/1 year): disease progression, treatment complications, urinary symptoms, quality of life, sexual function, and anxiety, depression, and other psychosocial effects; (2) medium-term outcomes (5 years): same as short-term outcomes plus survival; (3) long-term outcomes (10 years and 5-yearly thereafter): same as short-term outcomes plus survival **Composite outcome measures reported:** no
Funding sources	UK National Institute for Health Research Health Technology Assessment Programme
Declarations of interest	Several trial authors report conflicts of interest in the acknowledgements section of the paper
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication:** "allocations were computer-generated as required for each participant, originally using Microsoft Excel functions, and subsequently in C++" **Comment:** a computer-generated randomisation list is generally accepted as an adequate method of ensuring a random sequence
Allocation concealment (selection bias)	Low risk	**Quote from publication:** "men discussed treatment options with the specialist nurses, and if they agreed to the three-group randomisation (1:1:1), the nurse telephoned a central system in the Bristol trials' office (Bristol, UK) and logged participant details" **Comment:** a centralised telephone system is generally accepted as an adequate method of adequate allocation concealment

ProtecT *(Continued)*

Blinding of participants and personnel (performance bias)	High risk	**Quote from publication:** "clinicians and participants were not masked to group assignment" **Comment:** the nature of the trial interventions precluded blinding of patients and their physicians
Blinding of outcome assessment (detection bias) Susceptible: time to death from prostate cancer, time to disease progression, time to metastatic disease, and adverse events	Low risk	**Quote from publication:** the medical records of deceased participants were summarised by trained CAP researchers, anonymised, and reviewed by an independent endpoint committee who were masked to ProtecT and CAP trial assignments" **Comment:** it seems that outcome assessors and radiologists assessing the subjective outcomes were blinded to group allocation
Blinding of outcome assessment (detection bias) Not susceptible: time to death from any cause	Low risk	**Quote from publication:** the medical records of deceased participants were summarised by trained CAP researchers, anonymised, and reviewed by an independent endpoint committee who were masked to ProtecT and CAP trial assignments" **Comment:** it seems that outcome assessors and radiologists assessing subjective outcomes were blinded to group allocation
Blinding of outcome assessment (detection bias) Suspectible: quality of life	High risk	**Quote from publication:** "study questionnaires were completed at baseline (i.e. at the time of biopsy, before the diagnosis was known), at 6 and 12 months after randomization, and annually thereafter" **Comment:** quality of life and functional outcomes are self-reported. Due to the nature of the trial intervention, patients could not be blinded
Incomplete outcome data (attrition bias) Oncological outcomes	Low risk	**Quote from publication:** "a total of 14 patients were lost to follow-up for secondary outcomes, but data on deaths were captured for all participants" **Comment:** less than 1% of the total number of patients who underwent randomisation (N = 1643) was lost to follow-up; these patients were equally divided across treatment arms
Incomplete outcome data (attrition bias) Quality of life	Low risk	**Quote from publication:** "the response rates during follow-up were higher than 85% for most measures, including sexual function, and did not decline over time" **Comment:** low number of participants were lost to follow-up after randomisation, and high response rates were achieved for quality of life outcomes
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Quote from publication:** "a total of 14 patients were lost to follow-up for secondary outcomes, but data on deaths were captured for all participants" **Comment:** less than 1% of the total number of patients who underwent randomisation (N = 1643) was lost to follow-up; these patients were equally divided across treatment arms
Selective reporting (reporting bias)	Low risk	**Quote:** "Current Controlled Trials number, ISRCTN20141297; ClinicalTrials.gov number, NCT02044172" **Comment:** a complete study protocol is available, and no differences were identified between outcomes reported in this protocol and in the articles
Other bias	Low risk	**Comment:** none identified

SPCG-4

Study characteristics	
Methods	**Study design:** randomised controlled clinical trial **Recruitment period:** October 1989 through February 1999 **No. of centres:** 14 centres **Publication status:** full-text report
Participants	**Country:** Sweden, Finland, and Iceland **Setting:** hospital **Sample size:** 695 patients **Mean age (SD):** 65 ± 5 years **Baseline mean PSA:** watchful waiting: 12.3 ng/mL and radical prostatectomy: 13.5 ng/mL **Baseline Gleason score:** prostatectomy: 2 to 4 (13%), 5 to 6 (47.6%), 7 (22.2%), 8 to 10 (4%), unknown: 13.3%; watchful waiting: 2 to 4 (13%), 5 to 6 (47.7%), 7 (23.6%), 8 to 10 (6%), unknown: 9.5% **Inclusion criteria:** men under the age of 75 years with a primary, previously untreated, and newly diagnosed adenocarcinoma of the prostate verified by cytological examination, histological examination, or both were eligible. Further prerequisites were a general condition and mental status that were expected to permit a radical prostatectomy and follow-up for at least 10 years. Patients with other cancers were excluded. To be eligible, participants had to have a tumour at stage T0d, T1, or T2. After 1994, men with T1c tumours - according to the revised 1987 International Union Against Cancer classification - were also eligible. All of these were early stage; the prostate cancer was clinically inapparent (T0d, T1), was confined to the prostate (T2), or was diagnosed by needle biopsy performed because of an elevated prostate-specific antigen level (T1c). If the tumour was detected through transurethral resection only, at least 6 blocks of prostatic tissue had to have been studied. The tumour had to be graded as well or moderately well differentiated, as judged according to the World Health Organization classification. Men with a poorly differentiated tumour were not eligible. Patients whose condition was diagnosed with an extended biopsy protocol were accepted if < 25% of the tumour was Gleason grade 4 and < 5% was Gleason grade 5. It was further required that a preoperative bone scan show no signs of metastases, that a bone scan or a urographic examination show no signs of obstruction of the upper urinary tract, and that the prostate-specific antigen level be < 50 ng/mL **Exclusion criteria:** not stated **Diagnostic criteria:** histological or cytological examination
Interventions	**Number of arms:** 2 **Comparison:** watchful waiting vs radical prostatectomy **Randomisation ratio:** 348/347 **Run-in period:** not applicable **Follow-up period:** median 23.6 years **Intervention:** radical prostatectomy (defined as surgery started with dissection of the pelvic lymph nodes). If no nodal metastases were found in a frozen section, a Walsh-Lepor radical prostatectomy was carried out **Control:** watchful waiting (defined as no immediate treatment apart from the transurethral resection that some patients had already undergone)
Outcomes	**Primary outcome:** death from prostate cancer

SPCG-4 *(Continued)*

	Secondary outcomes: metastasis-free survival; progression-free survival after treatment of progression; local tumour progression; transrectal ultrasound and histology/cytology to be evaluated in a special spin-off project; quality of life and health service requirements **Composite outcome measures reported:** no
Funding sources	**Funding:** The Swedish Cancer Society and the National Institutes of Health in the United States
Declarations of interest	Several trial authors report conflicts of interest in the acknowledgements section of the paper
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication:** "the randomization list was computer generated, and the block size was unknown to the investigators" **Comment:** a computer-generated randomisation list is generally accepted as an adequate method of ensuring a random sequence
Allocation concealment (selection bias)	Low risk	**Quote from publication:** "the randomization was performed through a telephone service at offices outside the clinical units. The urologist responsible for the patient's care informed the patient and completed the case-record forms" **Comment:** a centralised telephone system is generally accepted as an adequate method of allocation concealment
Blinding of participants and personnel (performance bias)	High risk	**Comment:** the nature of the trial interventions precluded blinding of patients and their physicians
Blinding of outcome assessment (detection bias) Susceptible: time to death from prostate cancer, time to disease progression, time to metastatic disease, and adverse events	Low risk	**Quote:** "in patients who died, an independent endpoint committee whose members were unaware of the study-group assignments determined the cause of death on the basis of information extracted from the patients' medical records" **Comment:** it seems that outcome assessors and radiologists assessing the subjective outcomes were blinded to group allocation
Blinding of outcome assessment (detection bias) Not susceptible: time to death from any cause	Low risk	**Quote:** "in patients who died, an independent endpoint committee whose members were unaware of the study-group assignments determined the cause of death on the basis of information extracted from the patients' medical records" **Comment:** it seems that outcome assessors and radiologists assessing the subjective outcomes were blinded to group allocation
Blinding of outcome assessment (detection bias) Suspectible: quality of life	High risk	**Quote from publication:** "all patients agreeing in a telephone contact to participate were posted a study-specific questionnaire, distributed between October, 2006, and November, 2008" **Comment:** quality of life and functional outcomes are self-reported. Due to the nature of the trial intervention, patients could not be blinded
Incomplete outcome data (attrition bias) Oncological outcomes	Low risk	**Quote:** "all participants were followed until December 31, 2017, and none of the patients were lost to follow-up"

SPCG-4 *(Continued)*

		Comment: post randomisation, 2 patients were excluded from the radical prostatectomy group (1 with bladder cancer, 1 with concurrent malignancy) and 1 patient from the watchful waiting group (without prostate cancer)
Incomplete outcome data (attrition bias) Quality of life	Low risk	**Quote:** "182 (88%) of 208 participants in the radical prostatectomy group and 167 (87%) of 192 in the watchful-waiting group responded to the questionnaire" **Comment:** low number of participants were lost to follow-up after randomisation, and high response rates were achieved for quality of life outcomes
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Quote:** "all participants were followed until December 31, 2017, and none of the patients were lost to follow-up" **Comment:** post randomisation, 2 patients were excluded from the radical prostatectomy group (1 with bladder cancer, 1 with concurrent malignancy) and 1 patient from the watchful waiting group (without prostate cancer)
Selective reporting (reporting bias)	Low risk	**Comment:** study protocol has been provided by trial authors, and no differences were identified between outcomes reported in this protocol and in the articles
Other bias	Low risk	**Comment:** none identified

VACURG

Study characteristics	
Methods	**Study design:** randomised controlled clinical trial **Recruitment period:** May 1967 to March 1975 **No. of centres:** 15 hospitals **Publication status:** full-text report
Participants	**Country:** United States of America **Setting:** hospitals **Sample size:** 111 patients **Age:** 67 (intervention group) vs 61 years (control group) **Baseline PSA:** not reported **Baseline Gleason score:** prostatectomy: ≤ 4 (18%), 5 to 6 (72.1%), 7 to 10 (11.5%), unknown: 1.6%; placebo: ≤ 4 (20%), 5 to 6 (66%), 7 to 10 (8%), unknown: 6% **Inclusion criteria:** recently diagnosed and untreated localised prostate cancer with normal acid phosphatase and no evidence of metastases **Exclusion criteria:** none reported **Diagnostic criteria:** rectal examination, determination of serum acid phosphatase, histology, skeletal and chest x-ray films
Interventions	**Number of arms:** 2 **Comparison:** retropubic radical prostatectomy plus oral placebo vs oral placebo as initial treatment

VACURG *(Continued)*

	Randomisation ratio: 61/50 **Run-in period:** not applicable **Follow-up period:** median 23 years **Intervention:** retropubic radical prostatectomy plus oral placebo **Control:** oral placebo as initial treatment
Outcomes	**Primary outcomes:** time to progression; overall survival **Secondary outcomes:** none reported **Composite outcome measures reported:** no
Funding sources	**Funding:** Veterans Administration
Declarations of interest	None reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "the patients were randomly and prospectively assigned to either radical prostatectomy plus placebo or to placebo alone" **Comment:** the method used for generating a random sequence is not described in the reviewed publications
Allocation concealment (selection bias)	Unclear risk	**Comment:** the method used for the allocation concealment is not described in the reviewed publications
Blinding of participants and personnel (performance bias)	High risk	**Comment:** the nature of the trial interventions precluded blinding of patients and their physicians
Blinding of outcome assessment (detection bias) Susceptible: time to death from prostate cancer, time to disease progression, time to metastatic disease, and adverse events	Unclear risk	**Comment:** time to death from prostate cancer, time to disease progression, time to metastatic disease, and adverse events are not reported
Blinding of outcome assessment (detection bias) Not susceptible: time to death from any cause	Low risk	**Comment:** it is unclear whether outcome assessors and radiologists assessing the objective outcomes were blinded to group allocation. However, it is unlikely that these objective outcomes are influenced by the unblinded nature of outcome assessors
Blinding of outcome assessment (detection bias) Suspectible: quality of life	Unclear risk	**Comment:** quality of life and functional outcomes are not reported
Incomplete outcome data (attrition bias) Oncological outcomes	High risk	**Comment:** in total, 19 patients were lost to follow-up - approximately 14% of the total sample size

VACURG *(Continued)*

Incomplete outcome data (attrition bias) Quality of life	Unclear risk	**Comment:** quality of life and functional outcomes are not reported
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	**Comment:** adverse events are not reported
Selective reporting (reporting bias)	Unclear risk	**Comment:** no study protocol has been provided by trial authors; therefore no assessment of reporting bias can be conducted
Other bias	Low risk	**Comment:** none identified

CAP: Comparison Arm for ProtecT.
MRI: magnetic resonance imaging.
PSA: prostate-specific antigen.
SD: standard deviation.
TURP: transurethral resection of the prostate.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
[No authors] 2002	Wrong study design
[No authors] 2002a	Wrong study design
[No authors] 2002b	Duplicate
[No authors] 2002c	Wrong study design
[No authors] 2002d	Duplicate
[No authors] 2012	Duplicate
[No authors] 2012a	Duplicate
[No authors] 2013	Wrong study design
[No authors] 2013a	Duplicate
[No authors] 2013b	Wrong study design
[No authors] 2013c	Wrong study design
[No authors] 2014	Duplicate
[No authors] 2016	Wrong study design
[No authors] 2016a	Duplicate
Abdollah 2011	Wrong study design
Abdollah 2018	Wrong study design

Study	Reason for exclusion
Abrahamsson 2009	Wrong study design
Acar 2014	Wrong study design
Adolfsson 1993	Wrong study design
Adolfsson 1995	Wrong study design
Albertsen 2009	Wrong study design
Albertsen 2014	Wrong study design
Alibhai 2004	Wrong study design
Alibhai 2005	Wrong study design
Alrawashdh 2019	Wrong study design
Andersson 2011	Wrong outcomes
Bandari 2017	Wrong study design
Bandari 2017a	Duplicate
Barbosa 2016	Wrong study design
Barocas 2010	Wrong study design
Barocas 2017	Wrong study design
Barry 2001	Wrong study design
Black 2012	Wrong study design
Block 2012	Wrong study design
Boylu 2017	Wrong study design
Caliskan 2016	Wrong study design
Canfield 2011	Wrong study design
Carter 2015	Wrong study design
Cathcart 2013	Wrong study design
Cathcart 2013a	Duplicate
Cathcart 2013b	Duplicate
Chamie 2015	Wrong study design
Chan 2012	Wrong study design
Chen 2017	Wrong study design

Study	Reason for exclusion
Chodak 2006	Wrong study design
Chopra 2012	Wrong study design
Concato 2012	Wrong study design
Cooperberg 2009	Wrong study design
Cooperberg 2015	Wrong study design
Corcoran 2010	Wrong outcomes
Couper 2009	Wrong study design
Dahabreh 2012	Wrong study design
Dahm 2017	Wrong study design
Dahm 2019	Wrong study design
Dalela 2017	Wrong study design
Dalela 2017a	Duplicate
Dall'Era 2008	Wrong intervention
Dall'Era 2012	Wrong intervention
Dall'Era 2017	Wrong study design
Das 2017a	Wrong study design
Das 2017b	Duplicate
Donovan 2016	Duplicate
Dragićević 2012	Wrong study design
Eifler 2017	Wrong intervention
Eldefrawy 2013	Wrong outcomes
Fosså 2014	Wrong study design
Froehner 2019	Wrong study design
Frohmüller 1995	Wrong study design
Gattellari 2009	Wrong study design
Goonewardene 2014	Wrong study design
Griffin 2013	Wrong study design
Hadley 2010	Wrong study design

Study	Reason for exclusion
Haggman 2003	Wrong study design
Hajdenberg 2014	Wrong study design
Hamdy 2016	Duplicate
Hampson 2015	Wrong study design
Hayes 2010	Duplicate
Hayes 2013	Wrong outcomes
Hayes 2013a	Duplicate
Hegarty 2007	Wrong study design
Hegarty 2010	Wrong study design
Hegarty 2010a	Duplicate
Herden 2014	Wrong study design
Holmberg 2002	Duplicate
Holmberg 2012	Duplicate
Hugosson 2011	Wrong study design
Ip 2011	Wrong study design
Iversen 1995	Duplicate
Iversen 1995a	Duplicate
Iversen 2003	Wrong study design
Jeldres 2014	Wrong study design
Jeldres 2015	Wrong study design
Johansson 1991	Wrong study design
Johansson 1991a	Duplicate
Johansson 1994	Wrong study design
Johansson 1994a	Duplicate
Kakehi 2003	Wrong study design
Kakehi 2007	Wrong study design
Khan 2003	Wrong study design
Khurana 2012	Wrong study design

Study	Reason for exclusion
Kim 2012	Wrong outcomes
Kirby 2003	Wrong study design
Klein 2005	Wrong study design
Klotz 2006	Wrong study design
Klotz 2006a	Wrong study design
Klotz 2008	Wrong study design
Koerber 2014	Wrong outcomes
Koerber 2014a	Duplicate
Korfage 2009	Wrong study design
Ladjevardi 2010	Wrong study design
Lane 2014	Duplicate
Lane 2014a	Duplicate
Lane 2016	Duplicate
Lane 2016a	Duplicate
Lavelle 2011	Wrong outcomes
Lei 2015	Wrong patient population
Liu 2008	Wrong study design
Lyth 2012	Wrong study design
Markun 2014	Wrong study design
Maté Mate 2013	Wrong study design
McDermott 2009	Wrong study design
Merglen 2007	Wrong study design
Molinier 2011	Wrong outcomes
Mottet 2017	Wrong study design
Munro 2005	Wrong study design
NCT00007644	Duplicate
NCT00499174a	Duplicate
NCT00499174b	Duplicate

Study	Reason for exclusion
NCT01717677	Duplicate
NCT01717677a	Duplicate
NCT02914873	Wrong intervention
Penson 2009	Wrong study design
Penson 2011	Wrong outcomes
Penson 2011a	Duplicate
Printz 2012	Wrong study design
Randal 1994	Wrong study design
Reinhold 2016	Wrong outcomes
Richie 2005	Wrong study design
Rivera 2006	Wrong study design
Rivera 2006a	Wrong study design
Romero-Otero 2016	Wrong study design
Roobol 2014	Wrong study design
Rosenberg 2017	Wrong study design
Sartor 2012	Wrong study design
Sartor 2012a	Wrong study design
Schulz 2009	Wrong study design
Schulz 2009a	Duplicate
Schwartz 1995	Wrong outcomes
Sharma 2017	Wrong study design
Siemens 2003	Wrong study design
Smith 2017	Wrong study design
Solange 2006	Wrong study design
Sonpavde 2003	Wrong study design
Stattin 2009	Wrong study design
Stattin 2010	Wrong study design
Stone 2014	Wrong study design

Study	Reason for exclusion
Stuart 2005	Wrong study design
Stöckle 2019	Wrong study design
Taneja 2014	Wrong study design
Taneja 2018	Wrong study design
Taneja 2019	Wrong study design
Thomsen 2014	Wrong study design
Tyldesley 2012	Wrong study design
van den Bergh 2012	Wrong study design
Vickers 2012	Duplicate
Vickers 2012a	Wrong study design
Walsh 2003	Wrong study design
Walsh 2009	Wrong study design
Walsh 2009a	Wrong study design
Weissbach 2016	Wrong study design
Wilt 1994	Duplicate
Wilt 1995	Duplicate
Wilt 1997	Duplicate
Wilt 2008	Wrong study design
Wilt 2008a	Wrong study design
Wilt 2012	Duplicate
Wilt 2012a	Wrong study design
Wilt 2012b	Wrong study design
Wilt 2017	Duplicate
Xia 2012	Wrong intervention
Yang 2014	Wrong study design
Yang 2019	Wrong study design
You 2014	Wrong study design

Characteristics of ongoing studies *[ordered by study ID]*

DRKS00004405

Study name	PREFERE (Preference based randomized trial for evaluation of four treatment modalities in prostate cancer with low or "early intermediate" risk)
Methods	**Study design:** randomised controlled trial **Recruitment period:** 2012
Participants	**Country:** Germany **(Anticipated) sample size:** 7600 patients **Inclusion criteria:** (1) newly diagnosed adenocarcinoma of the prostate confirmed by punching biopsy method/histology (punch biopsy according to standardised protocol); (2) at least 8 randomised biopsies; in case of modern imaging methods, a minimum of 6 biopsies have to be taken; lesion-targeted biopsies only are not sufficient; (3) initiation of therapy within 6 months after histological confirmation; (4) locally limited carcinoma ≤ cT2a, NX, or N0, M0 (a tumour detected with needle biopsy in 1 or both lobes that is neither palpable nor visible in imaging is classified as T1c); (5) PSA ≤ 10 ng/mL; (6) Gleason score ≤ 7a (3 + 4); (7) for Gleason 7 tumours: proportion of tumour punching in the total number of extracted stamping (see punching Protocol) ≤ 33% and the largest contiguous tumour stove ≤ 5 mm; (8) men aged 18 to 75 years; (9) ECOG performance status 0 or 1 **Exclusion criteria:** (1) lack of patient suitability for surgery, radiation*, or active surveillance; (2) timely op because of BPH (e.g. TURP, HIFU, cryotherapy) in the anamnesis; (3) timely radiotherapy of the pelvis; (4) life expectancy < 10 years; (5) ASA > 4; (6) IPSS Score > 18*; (7) residual urine > 50 mL*; (8) prostate volume on transrectal ultrasound* > 60 cm^3; (9) prostate volume on transrectal ultrasound* > 60 cm^3; (10) prostate large median lobe* visible in the TRUS; (11) fluoride chronic intestinal inflammation in the rectum area*; (12) application of alpha-reductase inhibitors (finasteride, dutasteride) within 6 months before biopsy because of their influence on PSA level; (13) other active malignancy within the past 5 years (except superficial basal cell carcinoma or non-muscle invasive bladder cancer); (14) patients who are not able to consent; (14) lack of written informed consent
Interventions	**Number of arms:** 4 **Comparison:** radical prostatectomy vs percutaneous radiotherapy vs continuous seed implantation vs active surveillance
Outcomes	**Primary outcome:** prostate cancer-specific survival **Secondary outcomes:** overall survival; time to onset of hormone therapy; occurrence of first progression in hormone therapy; quality of life; complications
Starting date	2012/10/22
Contact information	
Notes	

NCT00499174

Study name	Observation or radical treatment in patients with prostate cancer
Methods	**Study design:** randomised controlled trial **Recruitment period:** 2011 to 2013

NCT00499174 *(Continued)*

	No. of centres: University Medical Center
Participants	**Country:** Canada **(Anticipated) sample size:** 180 patients **Inclusion criteria:** (1) diagnosed within 6 months before randomisation; clinical stage T1b, T1c, T2a, or T2b at the time of diagnosis; (2) clinical (diagnostic biopsy) Gleason score ≤ 6; (3) PSA ≤ 10.0 ng/mL; (4) physical examination, rectal examination, and transrectal ultrasound done within 6 months before randomisation, and radiographic studies, if indicated, negative for metastasis; (5) suitable candidate for radical prostatectomy or radiotherapy; (6) ECOG performance status 0, 1, or 2; (7) minimum life expectancy > 10 years; (8) in centres participating in the quality of life component of the study, patient is able (i.e. sufficiently fluent) and willing to complete quality of life questionnaires in either English or French **Exclusion criteria:** (1) no history of other malignancies, except adequately treated non-melanoma skin cancer, adequately treated superficial bladder cancer, or other solid tumour curatively treated with no evidence of disease for ≥ 5 years from study randomisation; (2) no previous treatment for prostate cancer, including surgery (excluding biopsy and TURP), radiotherapy, or androgen deprivation therapy for longer than 3 months; (3) no planned androgen therapy except in the context of radical therapy
Interventions	**Number of arms:** 2 **Comparison:** radical intervention (radical prostatectomy or radiotherapy (external beam radiotherapy 5 days a week for 4 to 8 weeks; permanent prostate brachytherapy; or high-dose rate temporary brachytherapy), based on patient and physician preference) vs active surveillance
Outcomes	**Primary outcome:** disease-specific survival **Secondary outcomes:** overall survival; quality of life; distant disease-free survival; PSA relapse/progression after radical intervention; initiation of androgen deprivation therapy; proportion of patients on active surveillance arm who receive radical intervention; prognostic significance of PSA doubling time before diagnosis; prognostic significance of molecular biomarkers
Starting date	June 2007
Contact information	
Notes	

NCT03348722

Study name	Active surveillance or radical treatment for newly diagnosed patients with a localized, low risk, prostate cancer (START)
Methods	**Study design:** randomised controlled trial **Recruitment period:** 2017
Participants	**Country:** Italy **(Anticipated) sample size:** 3000 patients **Inclusion criteria:** (1) newly diagnosed low-risk prostate cancer patients, defined according to the presence of all the following criteria: diagnosis of adenocarcinoma of the prostate, prostate cancer clinical stage T1c or T2a, PSA ≤ 10 ng/mL at diagnosis, adequate biopsy sampling according to prostate volume, maximum of 2 positive scores for random sampling and maximum of 2 lesions for target biopsies (even if the number of positive samples is > 2), Gleason grade 3 + 3 (in patients age

NCT03348722 *(Continued)*	
	> 70 Gleason 3 + 4); (2) residence in Piemonte or Valle D'Aosta region; (3) suitable for radical treatment (surgery or radiotherapy); (4) age at diagnosis ≤ 75 years or > 75 years if fragility assessment (measured with G8 score) ≥ 14; (5) patient suitability for expressing valid consent to participate in the study **Exclusion criteria:** (1) previously treated for prostate cancer; (2) not willing to undergo radical treatment (surgery or radiotherapy)
Interventions	**Number of arms:** 4 **Comparison:** active surveillance vs radical prostatectomy vs radiotherapy vs other radical treatment (high-intensity focal ultrasound, cryotherapy, other)
Outcomes	**Primary outcome:** treatment-free survival **Secondary outcomes:** quality of life; cost-effectiveness
Starting date	2017/11/21
Contact information	
Notes	

ASA: American Society of Anesthesiologists.
BPH: benign prostatic hyperplasia.
ECOG: Eastern Cooperative Oncology Group.
HIFU: high-intensity focused ultrasound.
IPSS: International Prostate Symptom Score.
PSA: prostate-specific antigen.
TRUS: transrectal ultrasound.
TURP: transurethral resection of the prostate.

DATA AND ANALYSES

Comparison 1. Radical prostatectomy versus watchful waiting

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Time to death from any cause	3	1537	Hazard Ratio (IV, Random, 95% CI)	0.79 [0.70, 0.90]
1.2 Time to death from prostate cancer	2	1426	Hazard Ratio (IV, Random, 95% CI)	0.57 [0.44, 0.73]
1.3 Time to disease progression	2	1426	Hazard Ratio (IV, Random, 95% CI)	0.43 [0.35, 0.54]
1.4 Time to metastatic disease	2	1426	Hazard Ratio (IV, Random, 95% CI)	0.56 [0.46, 0.70]
1.5 Quality of life: anxiety - moderate or high	1	339	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.79, 1.29]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6 Quality of life: depressed mood - moderate or high	1	339	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.74, 1.14]
1.7 Quality of life: well-being - high	1	340	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.88, 1.27]
1.8 Quality of life: quality of life - high	1	339	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.85, 1.16]
1.9 Quality of life: sense of meaningfulness - high	1	339	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.86, 1.30]
1.10 Urinary function: incontinence - adverse events requiring treatment	1	731	Risk Ratio (M-H, Random, 95% CI)	3.97 [2.34, 6.74]
1.11 Urinary function: urinary emptying symptoms - weak stream - more than half of all occasions	1	334	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.53, 0.97]
1.12 Urinary function: urinary storing symptoms - nocturia - occurrence twice a night or more	1	338	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.64, 0.94]
1.13 Urinary function: urinary storing symptoms - urgency - occurrence once a day or more	1	336	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.65, 1.90]
1.14 Urinary function: urinary storing symptoms - distress from voiding problems - moderate or great distress	1	337	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.61, 1.17]
1.15 Urinary function: urinary leakage - urinary leakage in daytime - occurrence once a week or more	1	337	Risk Ratio (M-H, Random, 95% CI)	2.45 [1.78, 3.37]
1.16 Urinary function: urinary leakage - urinary leakage in daytime - occurrence once a day or more	1	337	Risk Ratio (M-H, Random, 95% CI)	3.74 [2.33, 5.99]
1.17 Urinary function: urinary leakage - subjective estimation of the extent of leakage - at least some leakage	1	341	Risk Ratio (M-H, Random, 95% CI)	1.72 [1.39, 2.14]
1.18 Urinary function: urinary leakage - subjective estimation of the extent of leakage - moderate or severe leakage	1	341	Risk Ratio (M-H, Random, 95% CI)	2.11 [1.27, 3.52]
1.19 Urinary function: urinary leakage - distress from urinary leakage in daytime - moderate to great distress	1	336	Risk Ratio (M-H, Random, 95% CI)	1.79 [1.16, 2.76]
1.20 Urinary function: urinary leakage - urinary leakage at night - occurrence once a week or more	1	340	Risk Ratio (M-H, Random, 95% CI)	2.55 [1.40, 4.63]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.21 Urinary function: urinary leakage - distress from urinary leakage at night - moderate to great distress	1	341	Risk Ratio (M-H, Random, 95% CI)	2.05 [1.13, 3.72]
1.22 Sexual function: erectile dysfunction - adverse events requiring treatment	1	731	Risk Ratio (M-H, Random, 95% CI)	2.67 [1.63, 4.38]
1.23 Sexual function: men with any sexual activity or intercourse during the past month	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.23.1 6 months	1	731	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.26, 0.45]
1.23.2 1 year	1	731	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.40, 0.62]
1.23.3 2 years	1	731	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.43, 0.69]
1.23.4 5 years	1	731	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.51, 0.93]
1.23.5 10 years	1	731	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.49, 1.41]
1.24 Sexual function: level of interest in sexual activities: very low	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.24.1 6 months	1	731	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.97, 2.76]
1.24.2 1 year	1	731	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.72, 2.18]
1.24.3 2 years	1	731	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.87, 2.54]
1.24.4 5 years	1	731	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.63, 2.29]
1.24.5 10 years	1	731	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.56, 2.04]
1.25 Sexual function: physical discomfort because of anything related to prostate cancer or the effect of its treatments: a lot	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.25.1 6 months	1	731	Odds Ratio (M-H, Random, 95% CI)	3.17 [1.40, 7.15]
1.25.2 1 year	1	731	Odds Ratio (M-H, Random, 95% CI)	2.06 [0.87, 4.88]

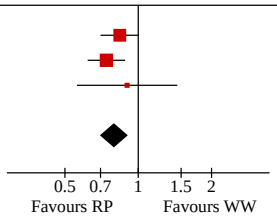
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.25.3 2 years	1	731	Odds Ratio (M-H, Random, 95% CI)	3.11 [1.12, 8.65]
1.25.4 5 years	1	731	Odds Ratio (M-H, Random, 95% CI)	1.71 [0.74, 3.96]
1.25.5 10 years	1	731	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.43, 2.98]
1.26 Sexual function: desire: sexual thoughts - occurrence more than once a month	1	329	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.96, 1.42]
1.27 Sexual function: sexuality: importance of sexuality - moderate or great importance	1	328	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.71, 1.31]
1.28 Sexual function: sexuality: sexuality part of one's manhood - yes	1	322	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.89, 1.30]
1.29 Sexual function: sexuality: ability to sexually satisfy partner - seldom or never	1	230	Risk Ratio (M-H, Random, 95% CI)	1.15 [1.00, 1.33]
1.30 Sexual function: sexuality: distress from decreased sexual ability - moderate to great distress	1	317	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.77, 1.39]
1.31 Sexual function: penile stiffness: erectile function - never sufficient for intercourse	1	326	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.96, 1.17]
1.32 Sexual function: penile stiffness: at awakening - never sufficient for intercourse	1	327	Risk Ratio (M-H, Random, 95% CI)	1.10 [1.02, 1.20]
1.33 Sexual function: penile stiffness: distress from erectile dysfunction - moderate to great distress	1	322	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.01, 1.70]
1.34 Sexual function: penile stiffness: distress on self-esteem: moderate to great distress	1	328	Risk Ratio (M-H, Random, 95% CI)	1.71 [1.21, 2.41]
1.35 Sexual function: intercourse: frequency of intercourse - more than once in past 6 months	1	329	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.46, 1.11]
1.36 Sexual function: intercourse: distress from decreased frequency - moderate to great distress	1	316	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.74, 1.40]
1.37 Sexual function: orgasm: frequency of orgasm - more than once in past 6 months	1	327	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.46, 1.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.38 Sexual function: orgasm: distress from decreased frequency - moderate to great distress	1	318	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.86, 1.79]
1.39 Adverse events	1	731	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.74, 1.65]

Analysis 1.1. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 1: Time to death from any cause

Study or Subgroup	log[Other]	SE	Radical prostatectomy Total	Watchful waiting Total	Weight	Other IV, Random, 95% CI
PIVOT	-0.1744	0.093	364	367	45.3%	0.84 [0.70 , 1.01]
SPCG-4	-0.3011	0.0903	347	348	48.0%	0.74 [0.62 , 0.88]
VACURG	-0.1054	0.2421	61	50	6.7%	0.90 [0.56 , 1.45]
Total (95% CI)			**772**	**765**	**100.0%**	**0.79 [0.70 , 0.90]**

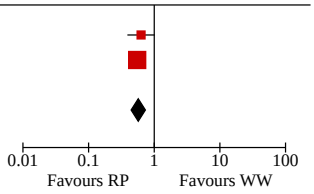
Heterogeneity: Tau² = 0.00; Chi² = 1.24, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 3.69 (P = 0.0002)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 2: Time to death from prostate cancer

Study or Subgroup	log[Other]	SE	Radical prostatectomy Total	Watchful waiting Total	Weight	Other IV, Random, 95% CI
PIVOT	-0.462	0.2447	364	367	27.3%	0.63 [0.39 , 1.02]
SPCG-4	-0.5978	0.1499	347	348	72.7%	0.55 [0.41 , 0.74]
Total (95% CI)			**711**	**715**	**100.0%**	**0.57 [0.44 , 0.73]**

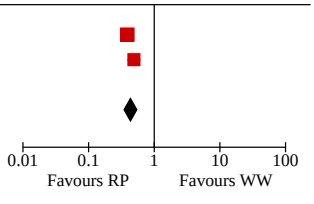
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 4.39 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 3: Time to disease progression

Study or Subgroup	log[Other]	SE	Radical prostatectomy Total	Watchful waiting Total	Weight	Other IV, Random, 95% CI
PIVOT	-0.9416	0.1009	364	367	53.3%	0.39 [0.32 , 0.48]
SPCG-4	-0.7133	0.1165	347	348	46.7%	0.49 [0.39 , 0.62]
Total (95% CI)			**711**	**715**	**100.0%**	**0.43 [0.35 , 0.54]**

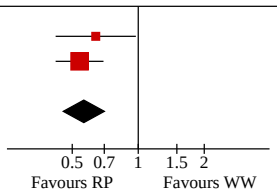
Heterogeneity: Tau² = 0.01; Chi² = 2.19, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 7.33 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 4: Time to metastatic disease

Study or Subgroup	log[Other]	SE	Radical prostatectomy Total	Watchful waiting Total	Weight	Other IV, Random, 95% CI
PIVOT	-0.4463	0.2149	364	367	26.2%	0.64 [0.42 , 0.98]
SPCG-4	-0.6162	0.1282	347	348	73.8%	0.54 [0.42 , 0.69]
Total (95% CI)			**711**	**715**	**100.0%**	**0.56 [0.46 , 0.70]**

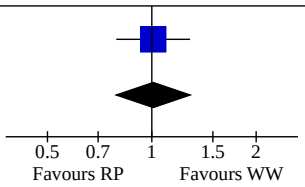
Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 1 (P = 0.50); I² = 0%
Test for overall effect: Z = 5.19 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 5: Quality of life: anxiety - moderate or high

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	77	178	69	161	100.0%	1.01 [0.79 , 1.29]
Total (95% CI)		**178**		**161**	**100.0%**	**1.01 [0.79 , 1.29]**
Total events:	77		69			

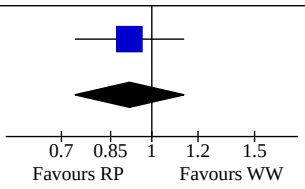
Heterogeneity: Not applicable
Test for overall effect: Z = 0.07 (P = 0.94)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 6: Quality of life: depressed mood - moderate or high

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	85	180	82	159	100.0%	0.92 [0.74 , 1.14]
Total (95% CI)		**180**		**159**	**100.0%**	**0.92 [0.74 , 1.14]**
Total events:	85		82			

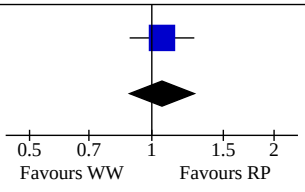
Heterogeneity: Not applicable
Test for overall effect: Z = 0.80 (P = 0.42)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 7: Quality of life: well-being - high

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio (Non-event) M-H, Random, 95% CI
SPCG-4	73	179	71	161	100.0%	1.06 [0.88 , 1.27]
Total (95% CI)		**179**		**161**	**100.0%**	**1.06 [0.88 , 1.27]**
Total events:	73		71			

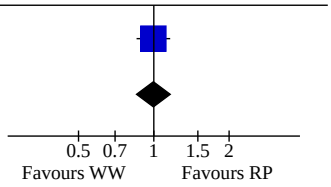
Heterogeneity: Not applicable
Test for overall effect: Z = 0.62 (P = 0.54)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 8: Quality of life: quality of life - high

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio (Non-event) M-H, Random, 95% CI
SPCG-4	62	179	55	160	100.0%	1.00 [0.85 , 1.16]
Total (95% CI)		**179**		**160**	**100.0%**	**1.00 [0.85 , 1.16]**
Total events:	62		55			

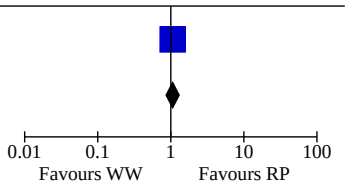
Heterogeneity: Not applicable
Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 9: Quality of life: sense of meaningfulness - high

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio (Non-event) M-H, Random, 95% CI
SPCG-4	83	179	79	160	100.0%	1.06 [0.86 , 1.30]
Total (95% CI)		**179**		**160**	**100.0%**	**1.06 [0.86 , 1.30]**
Total events:	83		79			

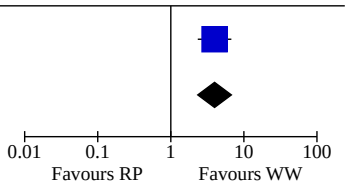
Heterogeneity: Not applicable
Test for overall effect: Z = 0.55 (P = 0.58)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 10: Urinary function: incontinence - adverse events requiring treatment

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
PIVOT	63	364	16	367	100.0%	3.97 [2.34 , 6.74]
Total (95% CI)		**364**		**367**	**100.0%**	**3.97 [2.34 , 6.74]**
Total events:	63		16			

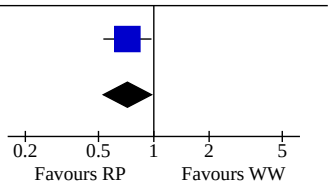
Heterogeneity: Not applicable
Test for overall effect: Z = 5.11 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 11: Urinary function: urinary emptying symptoms - weak stream - more than half of all occasions

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	50	174	64	160	100.0%	0.72 [0.53 , 0.97]
Total (95% CI)		**174**		**160**	**100.0%**	**0.72 [0.53 , 0.97]**
Total events:	50		64			

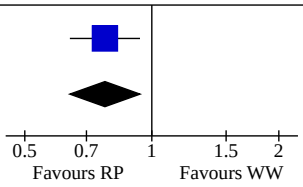
Heterogeneity: Not applicable
Test for overall effect: Z = 2.15 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 12: Urinary function: urinary storing symptoms - nocturia - occurrence twice a night or more

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	87	178	101	160	100.0%	0.77 [0.64 , 0.94]
Total (95% CI)		**178**		**160**	**100.0%**	**0.77 [0.64 , 0.94]**
Total events:	87		101			

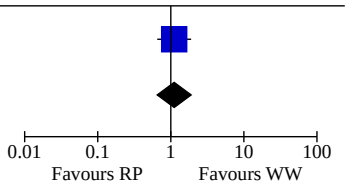
Heterogeneity: Not applicable
Test for overall effect: Z = 2.62 (P = 0.009)
Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 13: Urinary function: urinary storing symptoms - urgency - occurrence once a day or more

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	26	177	21	159	100.0%	1.11 [0.65 , 1.90]
Total (95% CI)		**177**		**159**	**100.0%**	**1.11 [0.65 , 1.90]**
Total events:	26		21			

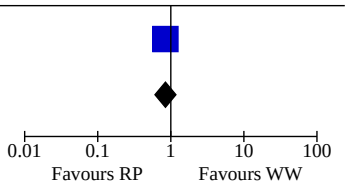
Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)
Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 14: Urinary function: urinary storing symptoms - distress from voiding problems - moderate or great distress

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	48	176	52	161	100.0%	0.84 [0.61 , 1.17]
Total (95% CI)		**176**		**161**	**100.0%**	**0.84 [0.61 , 1.17]**
Total events:	48		52			

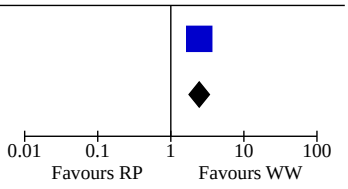
Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)
Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 15: Urinary function: urinary leakage - urinary leakage in daytime - occurrence once a week or more

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	93	173	36	164	100.0%	2.45 [1.78 , 3.37]
Total (95% CI)		**173**		**164**	**100.0%**	**2.45 [1.78 , 3.37]**
Total events:	93		36			

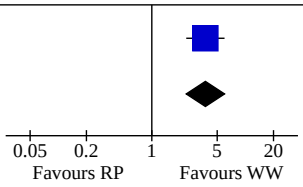
Heterogeneity: Not applicable
Test for overall effect: Z = 5.49 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.16. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 16: Urinary function: urinary leakage - urinary leakage in daytime - occurrence once a day or more

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	71	173	18	164	100.0%	3.74 [2.33 , 5.99]
Total (95% CI)		**173**		**164**	**100.0%**	**3.74 [2.33 , 5.99]**
Total events:	71		18			

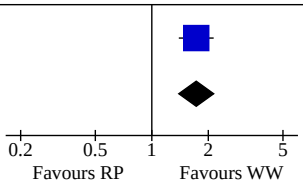
Heterogeneity: Not applicable
Test for overall effect: Z = 5.49 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.17. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 17: Urinary function: urinary leakage - subjective estimation of the extent of leakage - at least some leakage

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	121	177	65	164	100.0%	1.72 [1.39 , 2.14]
Total (95% CI)		**177**		**164**	**100.0%**	**1.72 [1.39 , 2.14]**
Total events:	121		65			

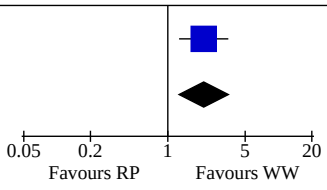
Heterogeneity: Not applicable
Test for overall effect: Z = 5.00 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.18. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 18: Urinary function: urinary leakage - subjective estimation of the extent of leakage - moderate or severe leakage

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	41	177	18	164	100.0%	2.11 [1.27 , 3.52]
Total (95% CI)		**177**		**164**	**100.0%**	**2.11 [1.27 , 3.52]**
Total events:	41		18			

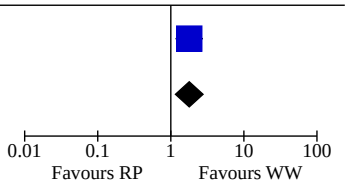
Heterogeneity: Not applicable
Test for overall effect: Z = 2.86 (P = 0.004)
Test for subgroup differences: Not applicable



Analysis 1.19. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 19: Urinary function: urinary leakage - distress from urinary leakage in daytime - moderate to great distress

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	48	174	25	162	100.0%	1.79 [1.16 , 2.76]
Total (95% CI)		**174**		**162**	**100.0%**	**1.79 [1.16 , 2.76]**
Total events:	48		25			

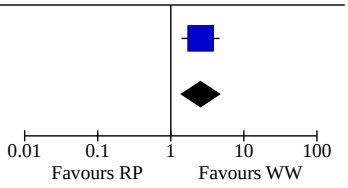
Heterogeneity: Not applicable
Test for overall effect: Z = 2.63 (P = 0.009)
Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 20: Urinary function: urinary leakage - urinary leakage at night - occurrence once a week or more

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	36	177	13	163	100.0%	2.55 [1.40 , 4.63]
Total (95% CI)		**177**		**163**	**100.0%**	**2.55 [1.40 , 4.63]**
Total events:	36		13			

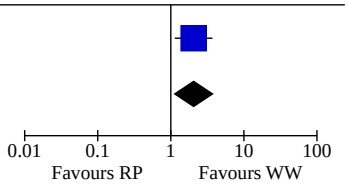
Heterogeneity: Not applicable
Test for overall effect: Z = 3.07 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 1.21. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 21: Urinary function: urinary leakage - distress from urinary leakage at night - moderate to great distress

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	31	177	14	164	100.0%	2.05 [1.13 , 3.72]
Total (95% CI)		**177**		**164**	**100.0%**	**2.05 [1.13 , 3.72]**
Total events:	31		14			

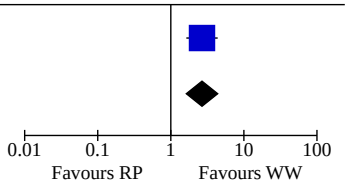
Heterogeneity: Not applicable
Test for overall effect: Z = 2.37 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 1.22. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 22: Sexual function: erectile dysfunction - adverse events requiring treatment

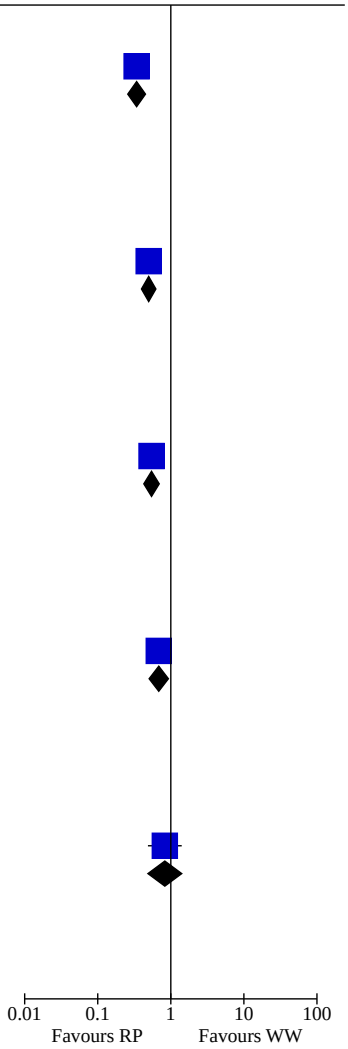
Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
PIVOT	53	364	20	367	100.0%	2.67 [1.63 , 4.38]
Total (95% CI)		**364**		**367**	**100.0%**	**2.67 [1.63 , 4.38]**
Total events:	53		20			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.90 (P < 0.0001)
Test for subgroup differences: Not applicable



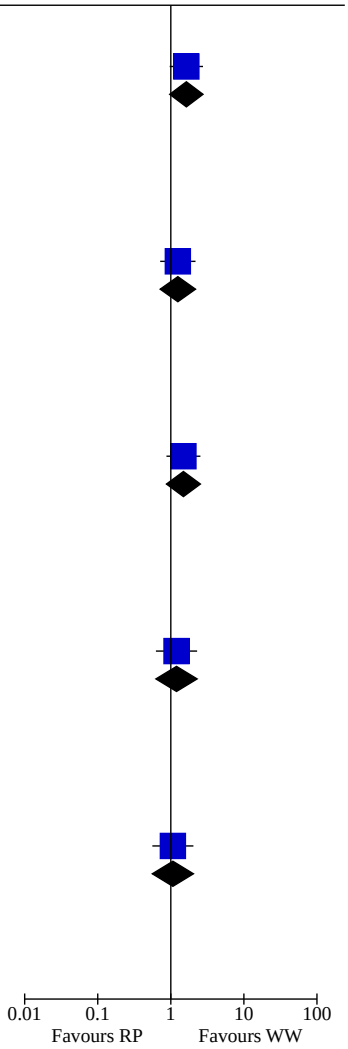
Analysis 1.23. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 23: Sexual function: men with any sexual activity or intercourse during the past month

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.23.1 6 months						
PIVOT	52	364	154	367	100.0%	0.34 [0.26 , 0.45]
Subtotal (95% CI)		**364**		**367**	**100.0%**	**0.34 [0.26 , 0.45]**
Total events:	52		154			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.57 (P < 0.00001)						
1.23.2 1 year						
PIVOT	79	364	160	367	100.0%	0.50 [0.40 , 0.62]
Subtotal (95% CI)		**364**		**367**	**100.0%**	**0.50 [0.40 , 0.62]**
Total events:	79		160			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.02 (P < 0.00001)						
1.23.3 2 years						
PIVOT	74	364	137	367	100.0%	0.54 [0.43 , 0.69]
Subtotal (95% CI)		**364**		**367**	**100.0%**	**0.54 [0.43 , 0.69]**
Total events:	74		137			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.91 (P < 0.00001)						
1.23.4 5 years						
PIVOT	57	364	84	367	100.0%	0.68 [0.51 , 0.93]
Subtotal (95% CI)		**364**		**367**	**100.0%**	**0.68 [0.51 , 0.93]**
Total events:	57		84			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.45 (P = 0.01)						
1.23.5 10 years						
PIVOT	23	364	28	367	100.0%	0.83 [0.49 , 1.41]
Subtotal (95% CI)		**364**		**367**	**100.0%**	**0.83 [0.49 , 1.41]**
Total events:	23		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Test for subgroup differences: Chi^2 = 15.17, df = 4 (P = 0.004), I^2 = 73.6%						



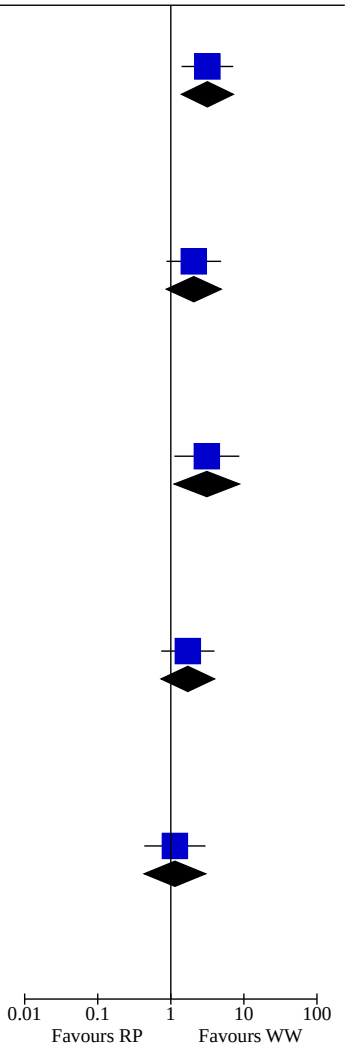
Analysis 1.24. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 24: Sexual function: level of interest in sexual activities: very low

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.24.1 6 months						
PIVOT	34	364	21	367	100.0%	1.63 [0.97 , 2.76]
Subtotal (95% CI)		**364**		**367**	**100.0%**	**1.63 [0.97 , 2.76]**
Total events:	34		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.83 (P = 0.07)						
1.24.2 1 year						
PIVOT	26	364	21	367	100.0%	1.25 [0.72 , 2.18]
Subtotal (95% CI)		**364**		**367**	**100.0%**	**1.25 [0.72 , 2.18]**
Total events:	26		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.78 (P = 0.43)						
1.24.3 2 years						
PIVOT	31	364	21	367	100.0%	1.49 [0.87 , 2.54]
Subtotal (95% CI)		**364**		**367**	**100.0%**	**1.49 [0.87 , 2.54]**
Total events:	31		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.46 (P = 0.14)						
1.24.4 5 years						
PIVOT	19	364	16	367	100.0%	1.20 [0.63 , 2.29]
Subtotal (95% CI)		**364**		**367**	**100.0%**	**1.20 [0.63 , 2.29]**
Total events:	19		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
1.24.5 10 years						
PIVOT	18	364	17	367	100.0%	1.07 [0.56 , 2.04]
Subtotal (95% CI)		**364**		**367**	**100.0%**	**1.07 [0.56 , 2.04]**
Total events:	18		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.20 (P = 0.84)						
Test for subgroup differences: Chi^2 = 1.34, df = 4 (P = 0.85), I^2 = 0%						



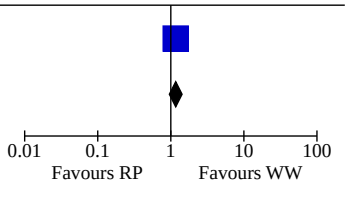
Analysis 1.25. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 25: Sexual function: physical discomfort because of anything related to prostate cancer or the effect of its treatments: a lot

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.25.1 6 months						
PIVOT	24	364	8	367	100.0%	3.17 [1.40 , 7.15]
Subtotal (95% CI)		**364**		**367**	**100.0%**	**3.17 [1.40 , 7.15]**
Total events:	24		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.78 (P = 0.005)						
1.25.2 1 year						
PIVOT	16	364	8	367	100.0%	2.06 [0.87 , 4.88]
Subtotal (95% CI)		**364**		**367**	**100.0%**	**2.06 [0.87 , 4.88]**
Total events:	16		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.65 (P = 0.10)						
1.25.3 2 years						
PIVOT	15	364	5	367	100.0%	3.11 [1.12 , 8.65]
Subtotal (95% CI)		**364**		**367**	**100.0%**	**3.11 [1.12 , 8.65]**
Total events:	15		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.18 (P = 0.03)						
1.25.4 5 years						
PIVOT	15	364	9	367	100.0%	1.71 [0.74 , 3.96]
Subtotal (95% CI)		**364**		**367**	**100.0%**	**1.71 [0.74 , 3.96]**
Total events:	15		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.25 (P = 0.21)						
1.25.5 10 years						
PIVOT	9	364	8	367	100.0%	1.14 [0.43 , 2.98]
Subtotal (95% CI)		**364**		**367**	**100.0%**	**1.14 [0.43 , 2.98]**
Total events:	9		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.79)						
Test for subgroup differences: $Chi^2 = 3.33$, df = 4 (P = 0.50), $I^2 = 0\%$						



Analysis 1.26. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 26: Sexual function: desire: sexual thoughts - occurrence more than once a month

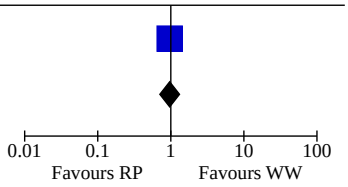
Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	101	172	79	157	100.0%	1.17 [0.96 , 1.42]
Total (95% CI)		**172**		**157**	**100.0%**	**1.17 [0.96 , 1.42]**
Total events:	101		79			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.52 (P = 0.13)						
Test for subgroup differences: Not applicable						



Analysis 1.27. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 27: Sexual function: sexuality: importance of sexuality - moderate or great importance

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	56	173	52	155	100.0%	0.96 [0.71 , 1.31]
Total (95% CI)		**173**		**155**	**100.0%**	**0.96 [0.71 , 1.31]**
Total events:	56		52			

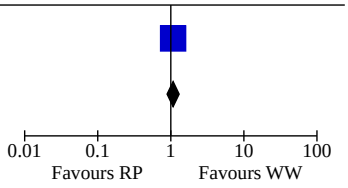
Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Not applicable



Analysis 1.28. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 28: Sexual function: sexuality: sexuality part of one's manhood - yes

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	101	170	84	152	100.0%	1.08 [0.89 , 1.30]
Total (95% CI)		**170**		**152**	**100.0%**	**1.08 [0.89 , 1.30]**
Total events:	101		84			

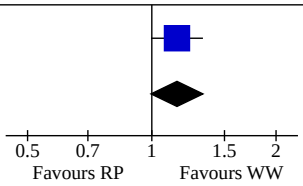
Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.45)
Test for subgroup differences: Not applicable



Analysis 1.29. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 29: Sexual function: sexuality: ability to sexually satisfy partner - seldom or never

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	105	127	74	103	100.0%	1.15 [1.00 , 1.33]
Total (95% CI)		**127**		**103**	**100.0%**	**1.15 [1.00 , 1.33]**
Total events:	105		74			

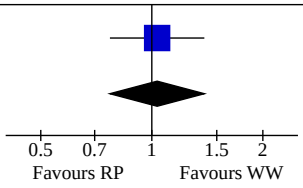
Heterogeneity: Not applicable
Test for overall effect: Z = 1.90 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 1.30. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 30: Sexual function: sexuality: distress from decreased sexual ability - moderate to great distress

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	61	167	53	150	100.0%	1.03 [0.77 , 1.39]
Total (95% CI)		**167**		**150**	**100.0%**	**1.03 [0.77 , 1.39]**
Total events:	61		53			

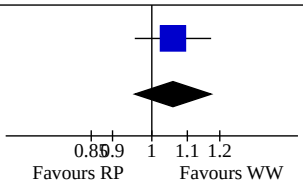
Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.83)
Test for subgroup differences: Not applicable



Analysis 1.31. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 31: Sexual function: penile stiffness: erectile function - never sufficient for intercourse

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	146	173	122	153	100.0%	1.06 [0.96 , 1.17]
Total (95% CI)		**173**		**153**	**100.0%**	**1.06 [0.96 , 1.17]**
Total events:	146		122			

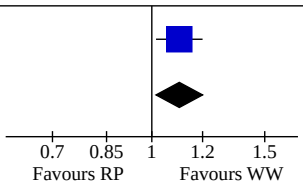
Heterogeneity: Not applicable
Test for overall effect: Z = 1.09 (P = 0.28)
Test for subgroup differences: Not applicable



Analysis 1.32. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 32: Sexual function: penile stiffness: at awakening - never sufficient for intercourse

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	158	172	129	155	100.0%	1.10 [1.02 , 1.20]
Total (95% CI)		**172**		**155**	**100.0%**	**1.10 [1.02 , 1.20]**
Total events:	158		129			

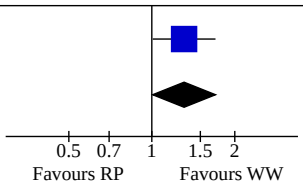
Heterogeneity: Not applicable
Test for overall effect: Z = 2.32 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 1.33. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 33: Sexual function: penile stiffness: distress from erectile dysfunction - moderate to great distress

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	80	168	56	154	100.0%	1.31 [1.01 , 1.70]
Total (95% CI)		**168**		**154**	**100.0%**	**1.31 [1.01 , 1.70]**
Total events:	80		56			

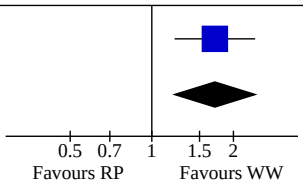
Heterogeneity: Not applicable
Test for overall effect: Z = 2.01 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 1.34. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 34: Sexual function: penile stiffness: distress on self-esteem: moderate to great distress

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	67	171	36	157	100.0%	1.71 [1.21 , 2.41]
Total (95% CI)		**171**		**157**	**100.0%**	**1.71 [1.21 , 2.41]**
Total events:	67		36			

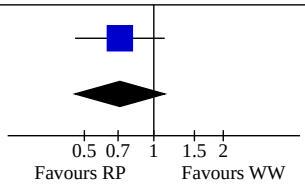
Heterogeneity: Not applicable
Test for overall effect: Z = 3.07 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 1.35. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 35: Sexual function: intercourse: frequency of intercourse - more than once in past 6 months

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	28	174	35	155	100.0%	0.71 [0.46 , 1.11]
Total (95% CI)		**174**		**155**	**100.0%**	**0.71 [0.46 , 1.11]**
Total events:	28		35			

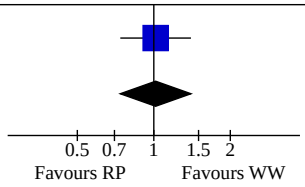
Heterogeneity: Not applicable
Test for overall effect: Z = 1.48 (P = 0.14)
Test for subgroup differences: Not applicable



Analysis 1.36. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 36: Sexual function: intercourse: distress from decreased frequency - moderate to great distress

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	54	166	48	150	100.0%	1.02 [0.74 , 1.40]
Total (95% CI)		**166**		**150**	**100.0%**	**1.02 [0.74 , 1.40]**
Total events:	54		48			

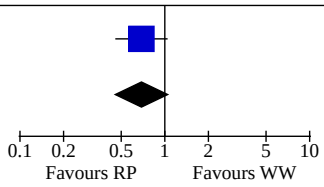
Heterogeneity: Not applicable
Test for overall effect: Z = 0.10 (P = 0.92)
Test for subgroup differences: Not applicable



Analysis 1.37. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 37: Sexual function: orgasm: frequency of orgasm - more than once in past 6 months

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	31	173	40	154	100.0%	0.69 [0.46 , 1.05]
Total (95% CI)		**173**		**154**	**100.0%**	**0.69 [0.46 , 1.05]**
Total events:	31		40			

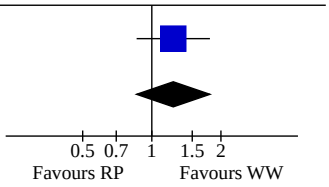
Heterogeneity: Not applicable
Test for overall effect: Z = 1.75 (P = 0.08)
Test for subgroup differences: Not applicable



Analysis 1.38. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 38: Sexual function: orgasm: distress from decreased frequency - moderate to great distress

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPCG-4	50	168	36	150	100.0%	1.24 [0.86 , 1.79]
Total (95% CI)		**168**		**150**	**100.0%**	**1.24 [0.86 , 1.79]**
Total events:	50		36			

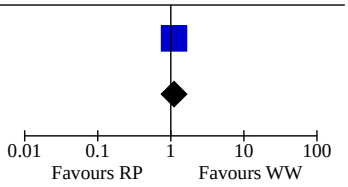
Heterogeneity: Not applicable
Test for overall effect: Z = 1.15 (P = 0.25)
Test for subgroup differences: Not applicable



Analysis 1.39. Comparison 1: Radical prostatectomy versus watchful waiting, Outcome 39: Adverse events

Study or Subgroup	Radical prostatectomy Events	Total	Watchful waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
PIVOT	45	364	41	367	100.0%	1.11 [0.74 , 1.65]
Total (95% CI)		**364**		**367**	**100.0%**	**1.11 [0.74 , 1.65]**
Total events:	45		41			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.62)
Test for subgroup differences: Not applicable



Comparison 2. Radical prostatectomy versus active monitoring

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Time to death from any cause	1	1098	Hazard Ratio (IV, Random, 95% CI)	0.93 [0.65, 1.33]
2.2 Time to death from prostate cancer	1	1098	Hazard Ratio (IV, Random, 95% CI)	0.63 [0.21, 1.89]
2.3 Time to disease progression	1	1098	Hazard Ratio (IV, Random, 95% CI)	0.39 [0.27, 0.56]
2.4 Incidence of metastatic disease	1	1098	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.21, 0.73]
2.5 Health-related quality of life: SF-12: physical health subscale	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.5.1 6 months	1	873	Mean Difference (IV, Random, 95% CI)	-2.60 [-3.82, -1.38]
2.5.2 12 months	1	900	Mean Difference (IV, Random, 95% CI)	0.00 [-1.15, 1.15]
2.5.3 24 months	1	881	Mean Difference (IV, Random, 95% CI)	0.90 [-0.25, 2.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.5.4 36 months	1	884	Mean Difference (IV, Random, 95% CI)	0.90 [-0.32, 2.12]
2.5.5 48 months	1	886	Mean Difference (IV, Random, 95% CI)	0.40 [-0.79, 1.59]
2.5.6 60 months	1	869	Mean Difference (IV, Random, 95% CI)	0.30 [-0.94, 1.54]
2.5.7 72 months	1	856	Mean Difference (IV, Random, 95% CI)	1.90 [0.58, 3.22]
2.6 Health-related quality of life: SF-12: mental health subscale	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.6.1 6 months	1	873	Mean Difference (IV, Random, 95% CI)	-0.60 [-1.77, 0.57]
2.6.2 12 months	1	900	Mean Difference (IV, Random, 95% CI)	0.10 [-0.97, 1.17]
2.6.3 24 months	1	881	Mean Difference (IV, Random, 95% CI)	0.20 [-0.92, 1.32]
2.6.4 36 months	1	884	Mean Difference (IV, Random, 95% CI)	0.70 [-0.41, 1.81]
2.6.5 48 months	1	886	Mean Difference (IV, Random, 95% CI)	0.70 [-0.37, 1.77]
2.6.6 60 months	1	869	Mean Difference (IV, Random, 95% CI)	0.90 [-0.22, 2.02]
2.6.7 72 months	1	856	Mean Difference (IV, Random, 95% CI)	0.50 [-0.65, 1.65]
2.7 Health-related quality of life: HADS: anxiety subscale scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.7.1 6 months	1	952	Mean Difference (IV, Random, 95% CI)	0.10 [-0.36, 0.56]
2.7.2 12 months	1	951	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.86, 0.06]
2.7.3 24 months	1	941	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.75, 0.15]
2.7.4 36 months	1	944	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.66, 0.26]
2.7.5 48 months	1	946	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.67, 0.27]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.7.6 60 months	1	934	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.64, 0.24]
2.7.7 72 months	1	923	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.88, 0.08]
2.8 Health-related quality of life: HADS: depression subscale scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.8.1 6 months	1	957	Mean Difference (IV, Random, 95% CI)	0.40 [0.02, 0.78]
2.8.2 12 months	1	956	Mean Difference (IV, Random, 95% CI)	0.00 [-0.36, 0.36]
2.8.3 24 months	1	952	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.46, 0.26]
2.8.4 36 months	1	947	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.58, 0.18]
2.8.5 48 months	1	947	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.49, 0.29]
2.8.6 60 months	1	937	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.58, 0.18]
2.8.7 72 months	1	923	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.82, 0.02]
2.9 Health-related quality of life: HADS: anxiety possible case score 8+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.9.1 6 months	1	952	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.68, 1.23]
2.9.2 12 months	1	951	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.54, 1.00]
2.9.3 24 months	1	941	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.59, 1.13]
2.9.4 36 months	1	944	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.54, 1.02]
2.9.5 48 months	1	946	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.70, 1.32]
2.9.6 60 months	1	934	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.52, 1.00]
2.9.7 72 months	1	923	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.72, 1.34]
2.10 Health-related quality of life: HADS: depression possible case score 8+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.10.1 6 months	1	957	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.73, 1.82]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.10.2 12 months	1	956	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.83, 2.19]
2.10.3 24 months	1	952	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.64, 1.61]
2.10.4 36 months	1	947	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.54, 1.39]
2.10.5 48 months	1	947	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.75, 1.74]
2.10.6 60 months	1	937	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.59, 1.36]
2.10.7 72 months	1	923	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.62, 1.37]
2.11 Health-related quality of life: EORTC QLQ-C30 at 5 years	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.11.1 Global health status	1	780	Mean Difference (IV, Random, 95% CI)	1.60 [-0.88, 4.08]
2.11.2 Functional scale: physical	1	778	Mean Difference (IV, Random, 95% CI)	0.70 [-1.30, 2.70]
2.11.3 Functional scale: role	1	778	Mean Difference (IV, Random, 95% CI)	0.40 [-2.32, 3.12]
2.11.4 Functional scale: emotional	1	780	Mean Difference (IV, Random, 95% CI)	0.60 [-1.74, 2.94]
2.11.5 Functional scale: cognitive	1	780	Mean Difference (IV, Random, 95% CI)	1.90 [-0.19, 3.99]
2.11.6 Functional scale: social	1	788	Mean Difference (IV, Random, 95% CI)	0.00 [-2.37, 2.37]
2.12 Urinary function: ICIQ score	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.12.1 6 months	1	935	Mean Difference (IV, Random, 95% CI)	3.50 [2.94, 4.06]
2.12.2 12 months	1	925	Mean Difference (IV, Random, 95% CI)	2.10 [1.62, 2.58]
2.12.3 24 months	1	921	Mean Difference (IV, Random, 95% CI)	1.70 [1.22, 2.18]
2.12.4 36 months	1	930	Mean Difference (IV, Random, 95% CI)	1.60 [1.10, 2.10]
2.12.5 48 months	1	925	Mean Difference (IV, Random, 95% CI)	1.60 [1.11, 2.09]
2.12.6 60 months	1	923	Mean Difference (IV, Random, 95% CI)	1.30 [0.84, 1.76]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.12.7 72 months	1	914	Mean Difference (IV, Random, 95% CI)	1.10 [0.59, 1.61]
2.13 Urinary function: EPIC urinary incontinence subscale score	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.13.1 6 months	1	706	Mean Difference (IV, Random, 95% CI)	-21.70 [-25.14, -18.26]
2.13.2 12 months	1	707	Mean Difference (IV, Random, 95% CI)	-12.60 [-15.54, -9.66]
2.13.3 24 months	1	782	Mean Difference (IV, Random, 95% CI)	-8.60 [-11.19, -6.01]
2.13.4 36 months	1	851	Mean Difference (IV, Random, 95% CI)	-8.00 [-10.61, -5.39]
2.13.5 48 months	1	891	Mean Difference (IV, Random, 95% CI)	-6.60 [-9.08, -4.12]
2.13.6 60 months	1	910	Mean Difference (IV, Random, 95% CI)	-6.60 [-9.01, -4.19]
2.13.7 72 months	1	895	Mean Difference (IV, Random, 95% CI)	-4.90 [-7.44, -2.36]
2.14 Urinary function: ICS-maleSF urinary incontinence score	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.14.1 6 months	1	955	Mean Difference (IV, Random, 95% CI)	2.30 [1.86, 2.74]
2.14.2 24 months	1	950	Mean Difference (IV, Random, 95% CI)	1.20 [0.82, 1.58]
2.14.3 12 months	1	957	Mean Difference (IV, Random, 95% CI)	1.50 [1.11, 1.89]
2.14.4 36 months	1	945	Mean Difference (IV, Random, 95% CI)	1.40 [0.99, 1.81]
2.14.5 48 months	1	950	Mean Difference (IV, Random, 95% CI)	1.20 [0.78, 1.62]
2.14.6 60 months	1	940	Mean Difference (IV, Random, 95% CI)	1.00 [0.62, 1.38]
2.14.7 72 months	1	926	Mean Difference (IV, Random, 95% CI)	0.80 [0.40, 1.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.15 Urinary incontinence: completely continent (ICIQ score 0)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.15.1 6 months	1	935	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.41, 0.56]
2.15.2 12 months	1	925	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.43, 0.60]
2.15.3 24 months	1	921	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.52, 0.70]
2.15.4 36 months	1	930	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.51, 0.70]
2.15.5 48 months	1	925	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.47, 0.65]
2.15.6 60 months	1	923	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.49, 0.68]
2.15.7 72 months	1	914	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.53, 0.74]
2.16 Urinary incontinence: 1 or more pads per day in past 4 weeks (EPIC item)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.16.1 6 months	1	708	Risk Ratio (M-H, Random, 95% CI)	10.51 [6.33, 17.47]
2.16.2 12 months	1	719	Risk Ratio (M-H, Random, 95% CI)	6.25 [3.70, 10.55]
2.16.3 24 months	1	791	Risk Ratio (M-H, Random, 95% CI)	5.24 [3.07, 8.93]
2.16.4 36 months	1	868	Risk Ratio (M-H, Random, 95% CI)	3.86 [2.46, 6.06]
2.16.5 48 months	1	906	Risk Ratio (M-H, Random, 95% CI)	2.51 [1.69, 3.72]
2.16.6 60 months	1	920	Risk Ratio (M-H, Random, 95% CI)	2.42 [1.63, 3.57]
2.16.7 72 months	1	908	Risk Ratio (M-H, Random, 95% CI)	2.13 [1.47, 3.07]
2.17 Urinary incontinence: ICIQ: moderate to large interference (score 4+).	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.17.1 6 months	1	944	Risk Ratio (M-H, Random, 95% CI)	4.99 [3.06, 8.14]
2.17.2 12 months	1	943	Risk Ratio (M-H, Random, 95% CI)	2.26 [1.44, 3.56]
2.17.3 24 months	1	927	Risk Ratio (M-H, Random, 95% CI)	2.12 [1.32, 3.42]
2.17.4 36 months	1	938	Risk Ratio (M-H, Random, 95% CI)	1.78 [1.18, 2.70]
2.17.5 48 months	1	933	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.90, 2.01]
2.17.6 60 months	1	927	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.75, 1.74]
2.17.7 72 months	1	919	Risk Ratio (M-H, Random, 95% CI)	1.50 [1.02, 2.21]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.18 Urinary function: ICS-maleSF voiding score	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.18.1 6 months	1	956	Mean Difference (IV, Random, 95% CI)	-0.60 [-1.02, -0.18]
2.18.2 12 months	1	964	Mean Difference (IV, Random, 95% CI)	-0.90 [-1.29, -0.51]
2.18.3 24 months	1	955	Mean Difference (IV, Random, 95% CI)	-1.40 [-1.79, -1.01]
2.18.4 36 months	1	956	Mean Difference (IV, Random, 95% CI)	-1.20 [-1.59, -0.81]
2.18.5 48 months	1	951	Mean Difference (IV, Random, 95% CI)	-1.20 [-1.60, -0.80]
2.18.6 60 months	1	937	Mean Difference (IV, Random, 95% CI)	-1.20 [-1.61, -0.79]
2.18.7 72 months	1	933	Mean Difference (IV, Random, 95% CI)	-1.30 [-1.72, -0.88]
2.19 Urinary function: EPIC urinary summary score	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.19.1 6 months	1	711	Mean Difference (IV, Random, 95% CI)	-10.50 [-12.54, -8.46]
2.19.2 12 months	1	718	Mean Difference (IV, Random, 95% CI)	-4.70 [-6.42, -2.98]
2.19.3 24 months	1	793	Mean Difference (IV, Random, 95% CI)	-2.20 [-3.82, -0.58]
2.19.4 36 months	1	866	Mean Difference (IV, Random, 95% CI)	-1.40 [-2.97, 0.17]
2.19.5 48 months	1	906	Mean Difference (IV, Random, 95% CI)	-0.60 [-2.19, 0.99]
2.19.6 60 months	1	921	Mean Difference (IV, Random, 95% CI)	-0.70 [-2.15, 0.75]
2.19.7 72 months	1	909	Mean Difference (IV, Random, 95% CI)	-0.30 [-1.85, 1.25]
2.20 Urinary function: EPIC urinary bother subscale score	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.20.1 6 months	1	709	Mean Difference (IV, Random, 95% CI)	-7.60 [-9.85, -5.35]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.20.2 12 months	1	719	Mean Difference (IV, Random, 95% CI)	-2.30 [-4.23, -0.37]
2.20.3 24 months	1	789	Mean Difference (IV, Random, 95% CI)	0.30 [-1.60, 2.20]
2.20.4 36 months	1	867	Mean Difference (IV, Random, 95% CI)	1.20 [-0.63, 3.03]
2.20.5 48 months	1	903	Mean Difference (IV, Random, 95% CI)	1.60 [-0.20, 3.40]
2.20.6 60 months	1	917	Mean Difference (IV, Random, 95% CI)	1.60 [-0.05, 3.25]
2.20.7 72 months	1	910	Mean Difference (IV, Random, 95% CI)	1.70 [0.02, 3.38]
2.21 Urinary function: EPIC urinary obstruction/irritative subscale score	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.21.1 6 months	1	711	Mean Difference (IV, Random, 95% CI)	-3.30 [-4.92, -1.68]
2.21.2 12 months	1	718	Mean Difference (IV, Random, 95% CI)	-0.10 [-1.43, 1.23]
2.21.3 24 months	1	794	Mean Difference (IV, Random, 95% CI)	1.70 [0.40, 3.00]
2.21.4 36 months	1	866	Mean Difference (IV, Random, 95% CI)	2.20 [0.95, 3.45]
2.21.5 48 months	1	907	Mean Difference (IV, Random, 95% CI)	2.80 [1.50, 4.10]
2.21.6 60 months	1	922	Mean Difference (IV, Random, 95% CI)	2.40 [1.27, 3.53]
2.21.7 72 months	1	908	Mean Difference (IV, Random, 95% CI)	2.20 [0.95, 3.45]
2.22 Urinary incontinence: ICSmaleSF nocturia item: twice or more per night	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.22.1 6 months	1	959	Risk Ratio (M-H, Random, 95% CI)	1.28 [1.08, 1.53]
2.22.2 12 months	1	957	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.76, 1.14]
2.22.3 24 months	1	950	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.56, 0.87]
2.22.4 36 months	1	948	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.59, 0.89]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.22.5 48 months	1	948	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.63, 0.94]
2.22.6 60 months	1	940	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.53, 0.79]
2.22.7 72 months	1	930	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.55, 0.80]
2.23 Urinary incontinence: ICSmaleSF daytime frequency: more frequent than once every 3 hours	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.23.1 6 months	1	960	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.12, 1.53]
2.23.2 12 months	1	960	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.02, 1.44]
2.23.3 24 months	1	949	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.79, 1.13]
2.23.4 36 months	1	947	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.90, 1.28]
2.23.5 48 months	1	945	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.74, 1.06]
2.23.6 60 months	1	932	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.82, 1.17]
2.23.7 72 months	1	924	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.77, 1.11]
2.24 Urinary incontinence: ICSmaleSF 'somewhat/a lot' of impact of lower urinary tract symptoms	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.24.1 6 months	1	964	Risk Ratio (M-H, Random, 95% CI)	3.01 [1.99, 4.56]
2.24.2 12 months	1	959	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.99, 2.56]
2.24.3 24 months	1	952	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.76, 1.87]
2.24.4 36 months	1	952	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.99, 2.25]
2.24.5 48 months	1	952	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.61, 1.43]
2.24.6 60 months	1	945	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.54, 1.40]
2.24.7 72 months	1	930	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.75, 1.73]
2.25 Sexual function: EPIC: erections firm enough for intercourse	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.25.1 6 months	1	734	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.19, 0.35]
2.25.2 12 months	1	696	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.23, 0.39]
2.25.3 24 months	1	769	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.32, 0.51]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.25.4 36 months	1	848	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.41, 0.63]
2.25.5 48 months	1	889	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.44, 0.68]
2.25.6 60 months	1	913	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.46, 0.72]
2.25.7 72 months	1	913	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.43, 0.71]
2.26 Sexual function: EPIC: moderate or big problem with erectile dysfunction	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.26.1 6 months	1	685	Risk Ratio (M-H, Random, 95% CI)	2.26 [1.88, 2.71]
2.26.2 12 months	1	697	Risk Ratio (M-H, Random, 95% CI)	2.13 [1.77, 2.57]
2.26.3 24 months	1	770	Risk Ratio (M-H, Random, 95% CI)	1.67 [1.42, 1.97]
2.26.4 36 months	1	835	Risk Ratio (M-H, Random, 95% CI)	1.30 [1.11, 1.52]
2.26.5 48 months	1	888	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.20, 1.63]
2.26.6 60 months	1	903	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.06, 1.45]
2.26.7 72 months	1	894	Risk Ratio (M-H, Random, 95% CI)	1.25 [1.08, 1.45]
2.27 Sexual function: EPIC sexual summary score	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.27.1 6 months	1	679	Mean Difference (IV, Random, 95% CI)	-26.20 [-30.10, -22.30]
2.27.2 12 months	1	685	Mean Difference (IV, Random, 95% CI)	-21.40 [-25.21, -17.59]
2.27.3 24 months	1	756	Mean Difference (IV, Random, 95% CI)	-14.90 [-18.54, -11.26]
2.27.4 36 months	1	826	Mean Difference (IV, Random, 95% CI)	-12.00 [-15.58, -8.42]
2.27.5 48 months	1	876	Mean Difference (IV, Random, 95% CI)	-10.20 [-13.59, -6.81]
2.27.6 60 months	1	893	Mean Difference (IV, Random, 95% CI)	-8.70 [-12.08, -5.32]
2.27.7 72 months	1	891	Mean Difference (IV, Random, 95% CI)	-8.30 [-11.59, -5.01]
2.28 Sexual function: EPIC sexual function subscale score	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.28.1 6 months	1	680	Mean Difference (IV, Random, 95% CI)	-25.20 [-28.94, -21.46]
2.28.2 12 months	1	684	Mean Difference (IV, Random, 95% CI)	-20.80 [-24.56, -17.04]
2.28.3 24 months	1	754	Mean Difference (IV, Random, 95% CI)	-14.70 [-18.29, -11.11]
2.28.4 36 months	1	838	Mean Difference (IV, Random, 95% CI)	-12.30 [-15.77, -8.83]
2.28.5 48 months	1	881	Mean Difference (IV, Random, 95% CI)	-10.10 [-13.45, -6.75]
2.28.6 60 months	1	904	Mean Difference (IV, Random, 95% CI)	-9.10 [-12.48, -5.72]
2.28.7 72 months	1	903	Mean Difference (IV, Random, 95% CI)	-8.80 [-12.06, -5.54]
2.29 Sexual function: EPIC sexual bother subscale score	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.29.1 6 months	1	678	Mean Difference (IV, Random, 95% CI)	-28.20 [-33.50, -22.90]
2.29.2 12 months	1	688	Mean Difference (IV, Random, 95% CI)	-23.30 [-28.41, -18.19]
2.29.3 24 months	1	765	Mean Difference (IV, Random, 95% CI)	-15.40 [-20.26, -10.54]
2.29.4 36 months	1	827	Mean Difference (IV, Random, 95% CI)	-11.10 [-15.95, -6.25]
2.29.5 48 months	1	876	Mean Difference (IV, Random, 95% CI)	-10.00 [-14.64, -5.36]
2.29.6 60 months	1	897	Mean Difference (IV, Random, 95% CI)	-7.50 [-12.18, -2.82]
2.29.7 72 months	1	882	Mean Difference (IV, Random, 95% CI)	-6.50 [-11.26, -1.74]
2.30 Sexual function: moderate/severe impact of sexual dysfunction on quality of life	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.30.1 6 months	1	683	Risk Ratio (M-H, Random, 95% CI)	2.29 [1.89, 2.78]
2.30.2 12 months	1	690	Risk Ratio (M-H, Random, 95% CI)	1.90 [1.56, 2.31]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.30.3 24 months	1	770	Risk Ratio (M-H, Random, 95% CI)	1.43 [1.20, 1.70]
2.30.4 36 months	1	831	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.12, 1.58]
2.30.5 48 months	1	887	Risk Ratio (M-H, Random, 95% CI)	1.30 [1.09, 1.53]
2.30.6 60 months	1	906	Risk Ratio (M-H, Random, 95% CI)	1.30 [1.10, 1.53]
2.30.7 72 months	1	895	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.94, 1.31]
2.31 Bowel function: EPIC bowel summary score	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.31.1 6 months	1	711	Mean Difference (IV, Random, 95% CI)	0.10 [-1.23, 1.43]
2.31.2 12 months	1	718	Mean Difference (IV, Random, 95% CI)	0.60 [-0.59, 1.79]
2.31.3 24 months	1	799	Mean Difference (IV, Random, 95% CI)	0.60 [-0.62, 1.82]
2.31.4 36 months	1	869	Mean Difference (IV, Random, 95% CI)	1.00 [-0.26, 2.26]
2.31.5 48 months	1	914	Mean Difference (IV, Random, 95% CI)	0.80 [-0.51, 2.11]
2.31.6 60 months	1	930	Mean Difference (IV, Random, 95% CI)	2.90 [1.73, 4.07]
2.31.7 72 months	1	920	Mean Difference (IV, Random, 95% CI)	0.20 [-1.00, 1.40]
2.32 Bowel function: EPIC bowel function subscale score	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.32.1 6 months	1	711	Mean Difference (IV, Random, 95% CI)	0.30 [-1.07, 1.67]
2.32.2 12 months	1	720	Mean Difference (IV, Random, 95% CI)	0.70 [-0.52, 1.92]
2.32.3 24 months	1	801	Mean Difference (IV, Random, 95% CI)	0.40 [-1.66, 2.46]
2.32.4 36 months	1	872	Mean Difference (IV, Random, 95% CI)	0.80 [-0.41, 2.01]
2.32.5 48 months	1	917	Mean Difference (IV, Random, 95% CI)	0.80 [-0.45, 2.05]
2.32.6 60 months	1	930	Mean Difference (IV, Random, 95% CI)	0.90 [-0.21, 2.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.32.7 72 months	1	924	Mean Difference (IV, Random, 95% CI)	0.00 [-1.18, 1.18]
2.33 Bowel function: EPIC bowel bother subscale score	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.33.1 6 months	1	711	Mean Difference (IV, Random, 95% CI)	-0.20 [-1.77, 1.37]
2.33.2 12 months	1	719	Mean Difference (IV, Random, 95% CI)	0.50 [-0.93, 1.93]
2.33.3 24 months	1	799	Mean Difference (IV, Random, 95% CI)	0.80 [-0.67, 2.27]
2.33.4 36 months	1	876	Mean Difference (IV, Random, 95% CI)	1.20 [-0.33, 2.73]
2.33.5 48 months	1	918	Mean Difference (IV, Random, 95% CI)	0.80 [-0.74, 2.34]
2.33.6 60 months	1	943	Mean Difference (IV, Random, 95% CI)	1.00 [-0.40, 2.40]
2.33.7 72 months	1	925	Mean Difference (IV, Random, 95% CI)	0.50 [-0.94, 1.94]
2.34 Bowel function: EPIC bowel bother subscale score	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.34.1 6 months	1	711	Mean Difference (IV, Random, 95% CI)	-0.20 [-1.77, 1.37]
2.34.2 12 months	1	719	Mean Difference (IV, Random, 95% CI)	0.50 [-0.93, 1.93]
2.34.3 24 months	1	799	Mean Difference (IV, Random, 95% CI)	0.80 [-0.67, 2.27]
2.34.4 36 months	1	876	Mean Difference (IV, Random, 95% CI)	1.20 [-0.33, 2.73]
2.34.5 48 months	1	918	Mean Difference (IV, Random, 95% CI)	0.80 [-0.74, 2.34]
2.34.6 60 months	1	943	Mean Difference (IV, Random, 95% CI)	1.00 [-0.40, 2.40]
2.34.7 72 months	1	925	Mean Difference (IV, Random, 95% CI)	0.50 [-0.94, 1.94]

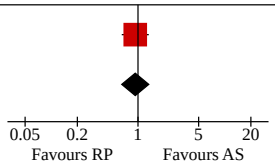
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.35 Bowel function: faecal incontinence more than once per week	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.35.1 6 months	1	715	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.18, 2.22]
2.35.2 12 months	1	719	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.17, 3.26]
2.35.3 24 months	1	801	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.31, 1.95]
2.35.4 36 months	1	873	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.32, 2.00]
2.35.5 48 months	1	919	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.28, 1.62]
2.35.6 60 months	1	935	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.20, 1.43]
2.35.7 72 months	1	930	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.31, 1.74]
2.36 Bowel function: EPIC: loose stools about half the time or more frequently	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.36.1 6 months	1	714	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.51, 0.99]
2.36.2 12 months	1	720	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.54, 1.12]
2.36.3 24 months	1	802	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.71, 1.40]
2.36.4 36 months	1	871	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.55, 1.09]
2.36.5 48 months	1	921	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.48, 0.96]
2.36.6 60 months	1	938	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.61, 1.18]
2.36.7 72 months	1	934	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.66, 1.30]
2.37 Bowel function: EPIC: bloody stools about half the time or more frequently	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.37.1 6 months	1	711	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.02, 1.11]
2.37.2 12 months	1	721	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.08, 2.01]
2.37.3 24 months	1	803	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.03, 3.10]
2.37.4 36 months	1	871	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.23, 2.23]
2.37.5 48 months	1	919	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.13, 1.27]
2.37.6 60 months	1	936	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.12, 1.25]
2.37.7 72 months	1	935	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.25, 2.68]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.38 Bowel function: EPIC: moderate/severe impact of bowel habits on quality of life	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.38.1 6 months	1	710	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.47, 2.35]
2.38.2 12 months	1	722	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.53, 4.10]
2.38.3 24 months	1	802	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.21, 1.59]
2.38.4 36 months	1	878	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.34, 1.95]
2.38.5 48 months	1	920	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.32, 1.60]
2.38.6 60 months	1	944	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.32, 1.46]
2.38.7 72 months	1	930	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.36, 1.55]

Analysis 2.1. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 1: Time to death from any cause

Study or Subgroup	log[Other]	SE	Radical prostatectomy Total	Active monitoring Total	Weight	Other IV, Random, 95% CI	Other IV, Random, 95% CI
ProtecT	-0.0726	0.1828	553	545	100.0%	0.93 [0.65 , 1.33]	
Total (95% CI)			**553**	**545**	**100.0%**	**0.93 [0.65 , 1.33]**	

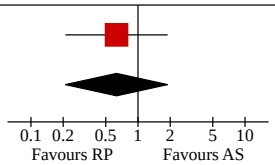
Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 2: Time to death from prostate cancer

Study or Subgroup	log[Other]	SE	Radical prostatectomy Total	Active monitoring Total	Weight	Other IV, Random, 95% CI	Other IV, Random, 95% CI
ProtecT	-0.462	0.5605	553	545	100.0%	0.63 [0.21 , 1.89]	
Total (95% CI)			**553**	**545**	**100.0%**	**0.63 [0.21 , 1.89]**	

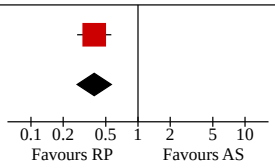
Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 3: Time to disease progression

Study or Subgroup	log[Other]	SE	Radical prostatectomy Total	Active monitoring Total	Weight	Other IV, Random, 95% CI
ProtecT	-0.9416	0.1876	553	545	100.0%	0.39 [0.27 , 0.56]
Total (95% CI)			**553**	**545**	**100.0%**	**0.39 [0.27 , 0.56]**

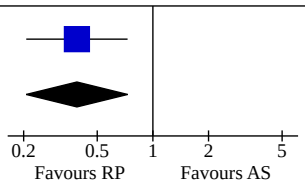
Heterogeneity: Not applicable
Test for overall effect: Z = 5.02 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 4: Incidence of metastatic disease

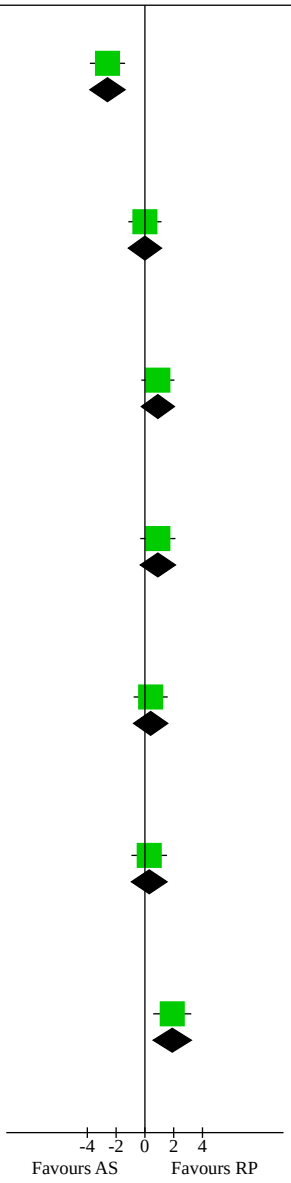
Study or Subgroup	Radical prostatectomy Events	Total	Active monitoring Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ProtecT	13	553	33	545	100.0%	0.39 [0.21 , 0.73]
Total (95% CI)		**553**		**545**	**100.0%**	**0.39 [0.21 , 0.73]**
Total events:	13		33			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.94 (P = 0.003)
Test for subgroup differences: Not applicable



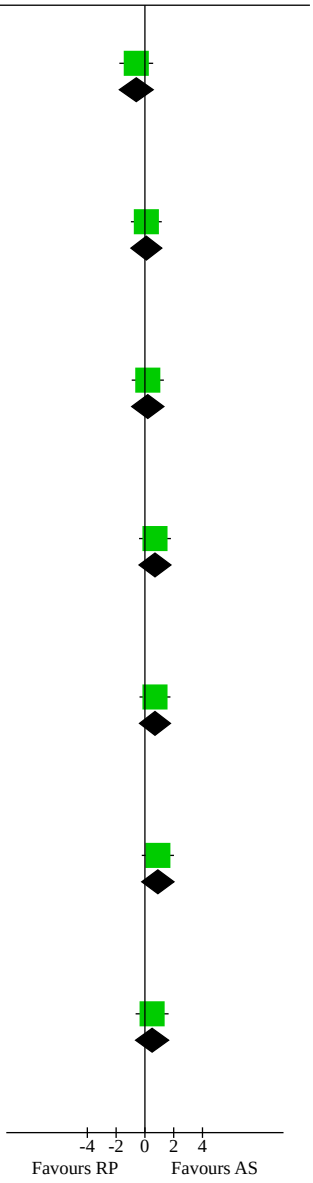
Analysis 2.5. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 5: Health-related quality of life: SF-12: physical health subscale

Study or Subgroup	Radical prostatectomy Mean	SD	Total	Active monitoring Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.5.1 6 months								
ProtecT	47.4	9.7	443	50	8.7	430	100.0%	-2.60 [-3.82 , -1.38]
Subtotal (95% CI)			**443**			**430**	**100.0%**	**-2.60 [-3.82 , -1.38]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.17 (P < 0.0001)								
2.5.2 12 months								
ProtecT	49.9	8.5	447	49.9	9.1	453	100.0%	0.00 [-1.15 , 1.15]
Subtotal (95% CI)			**447**			**453**	**100.0%**	**0.00 [-1.15 , 1.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
2.5.3 24 months								
ProtecT	50.4	8.3	437	49.5	9.1	444	100.0%	0.90 [-0.25 , 2.05]
Subtotal (95% CI)			**437**			**444**	**100.0%**	**0.90 [-0.25 , 2.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.53 (P = 0.12)								
2.5.4 36 months								
ProtecT	49.4	8.7	440	48.5	9.8	444	100.0%	0.90 [-0.32 , 2.12]
Subtotal (95% CI)			**440**			**444**	**100.0%**	**0.90 [-0.32 , 2.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.44 (P = 0.15)								
2.5.5 48 months								
ProtecT	49.1	8.7	440	48.7	9.3	446	100.0%	0.40 [-0.79 , 1.59]
Subtotal (95% CI)			**440**			**446**	**100.0%**	**0.40 [-0.79 , 1.59]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.66 (P = 0.51)								
2.5.6 60 months								
ProtecT	48.6	9.2	429	48.3	9.4	440	100.0%	0.30 [-0.94 , 1.54]
Subtotal (95% CI)			**429**			**440**	**100.0%**	**0.30 [-0.94 , 1.54]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.48 (P = 0.63)								
2.5.7 72 months								
ProtecT	48.8	9.1	428	46.9	10.6	428	100.0%	1.90 [0.58 , 3.22]
Subtotal (95% CI)			**428**			**428**	**100.0%**	**1.90 [0.58 , 3.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.81 (P = 0.005)								
Test for subgroup differences: Chi² = 29.44, df = 6 (P < 0.0001), I² = 79.6%								



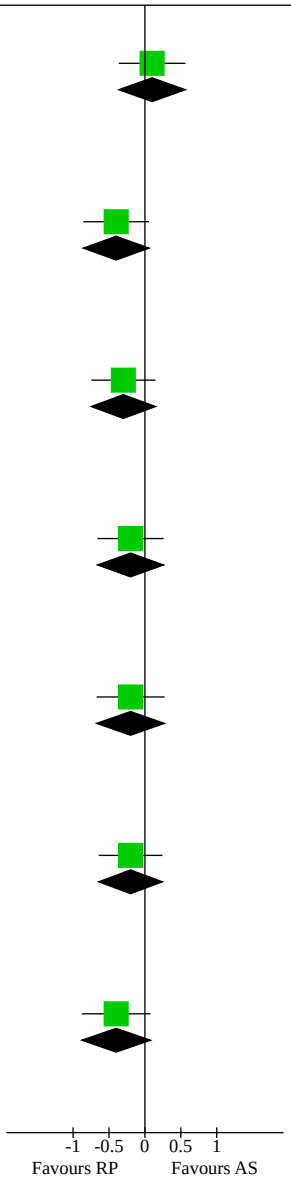
Analysis 2.6. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 6: Health-related quality of life: SF-12: mental health subscale

Study or Subgroup	Radical prostatectomy Mean	SD	Total	Active monitoring Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.6.1 6 months								
ProtecT	52.5	9.1	443	53.1	8.6	430	100.0%	-0.60 [-1.77 , 0.57]
Subtotal (95% CI)			**443**			**430**	**100.0%**	**-0.60 [-1.77 , 0.57]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.00 (P = 0.32)								
2.6.2 12 months								
ProtecT	53.7	8.3	447	53.6	8.1	453	100.0%	0.10 [-0.97 , 1.17]
Subtotal (95% CI)			**447**			**453**	**100.0%**	**0.10 [-0.97 , 1.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.18 (P = 0.85)								
2.6.3 24 months								
ProtecT	53.5	8.6	437	53.3	8.3	444	100.0%	0.20 [-0.92 , 1.32]
Subtotal (95% CI)			**437**			**444**	**100.0%**	**0.20 [-0.92 , 1.32]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.35 (P = 0.73)								
2.6.4 36 months								
ProtecT	53.8	8.3	440	53.1	8.5	444	100.0%	0.70 [-0.41 , 1.81]
Subtotal (95% CI)			**440**			**444**	**100.0%**	**0.70 [-0.41 , 1.81]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.24 (P = 0.22)								
2.6.5 48 months								
ProtecT	54.3	7.9	440	53.6	8.4	446	100.0%	0.70 [-0.37 , 1.77]
Subtotal (95% CI)			**440**			**446**	**100.0%**	**0.70 [-0.37 , 1.77]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.28 (P = 0.20)								
2.6.6 60 months								
ProtecT	53.8	7.9	429	52.9	8.9	440	100.0%	0.90 [-0.22 , 2.02]
Subtotal (95% CI)			**429**			**440**	**100.0%**	**0.90 [-0.22 , 2.02]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.58 (P = 0.11)								
2.6.7 72 months								
ProtecT	53.5	8.3	428	53	8.8	428	100.0%	0.50 [-0.65 , 1.65]
Subtotal (95% CI)			**428**			**428**	**100.0%**	**0.50 [-0.65 , 1.65]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.86 (P = 0.39)								
Test for subgroup differences: $Chi^2 = 4.57$, df = 6 (P = 0.60), $I^2 = 0\%$								



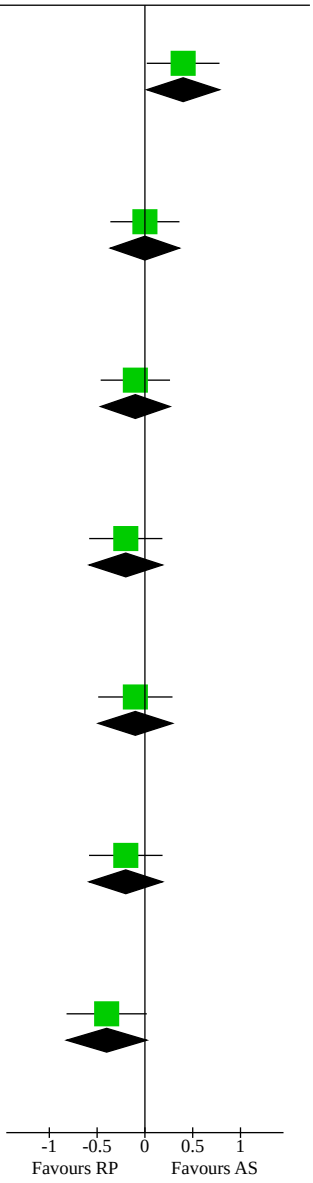
Analysis 2.7. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 7: Health-related quality of life: HADS: anxiety subscale scores

Study or Subgroup	Radical prostatectomy Mean	SD	Total	Active monitoring Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.7.1 6 months								
ProtecT	4	3.6	485	3.9	3.7	467	100.0%	0.10 [-0.36 , 0.56]
Subtotal (95% CI)			**485**			**467**	**100.0%**	**0.10 [-0.36 , 0.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.42 (P = 0.67)								
2.7.2 12 months								
ProtecT	3.6	3.6	472	4	3.6	479	100.0%	-0.40 [-0.86 , 0.06]
Subtotal (95% CI)			**472**			**479**	**100.0%**	**-0.40 [-0.86 , 0.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.71 (P = 0.09)								
2.7.3 24 months								
ProtecT	3.6	3.4	474	3.9	3.6	467	100.0%	-0.30 [-0.75 , 0.15]
Subtotal (95% CI)			**474**			**467**	**100.0%**	**-0.30 [-0.75 , 0.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.31 (P = 0.19)								
2.7.4 36 months								
ProtecT	3.7	3.4	470	3.9	3.8	474	100.0%	-0.20 [-0.66 , 0.26]
Subtotal (95% CI)			**470**			**474**	**100.0%**	**-0.20 [-0.66 , 0.26]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.85 (P = 0.39)								
2.7.5 48 months								
ProtecT	3.8	3.5	471	4	3.9	475	100.0%	-0.20 [-0.67 , 0.27]
Subtotal (95% CI)			**471**			**475**	**100.0%**	**-0.20 [-0.67 , 0.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.83 (P = 0.41)								
2.7.6 60 months								
ProtecT	3.6	3.2	470	3.8	3.7	464	100.0%	-0.20 [-0.64 , 0.24]
Subtotal (95% CI)			**470**			**464**	**100.0%**	**-0.20 [-0.64 , 0.24]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.88 (P = 0.38)								
2.7.7 72 months								
ProtecT	3.7	3.5	465	4.1	3.9	458	100.0%	-0.40 [-0.88 , 0.08]
Subtotal (95% CI)			**465**			**458**	**100.0%**	**-0.40 [-0.88 , 0.08]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.64 (P = 0.10)								
Test for subgroup differences: $Chi^2 = 3.10$, df = 6 (P = 0.80), $I^2 = 0\%$								



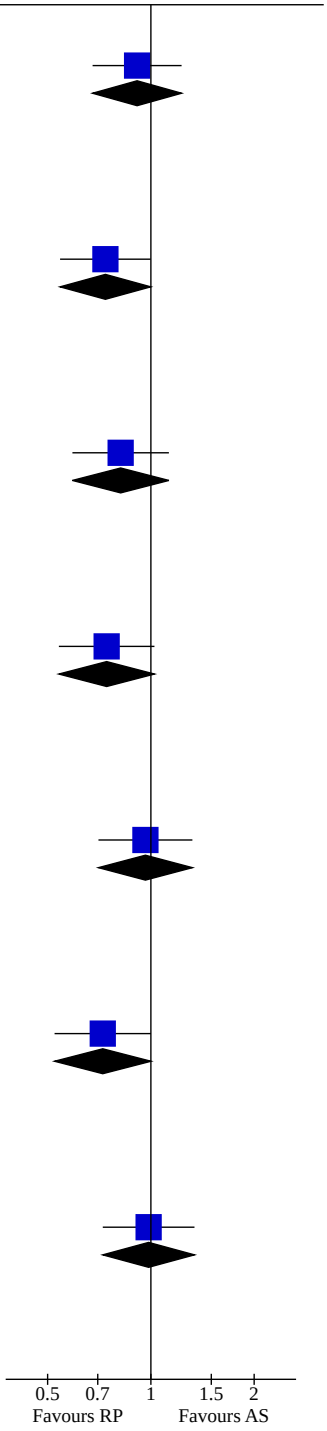
Analysis 2.8. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 8: Health-related quality of life: HADS: depression subscale scores

Study or Subgroup	Radical prostatectomy Mean	SD	Total	Active monitoring Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.8.1 6 months								
ProtecT	2.8	3	487	2.4	3	470	100.0%	0.40 [0.02 , 0.78]
Subtotal (95% CI)			**487**			**470**	**100.0%**	**0.40 [0.02 , 0.78]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.06 (P = 0.04)								
2.8.2 12 months								
ProtecT	2.4	2.9	475	2.4	2.8	481	100.0%	0.00 [-0.36 , 0.36]
Subtotal (95% CI)			**475**			**481**	**100.0%**	**0.00 [-0.36 , 0.36]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
2.8.3 24 months								
ProtecT	2.5	2.7	480	2.6	3	472	100.0%	-0.10 [-0.46 , 0.26]
Subtotal (95% CI)			**480**			**472**	**100.0%**	**-0.10 [-0.46 , 0.26]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.54 (P = 0.59)								
2.8.4 36 months								
ProtecT	2.5	2.8	471	2.7	3.2	476	100.0%	-0.20 [-0.58 , 0.18]
Subtotal (95% CI)			**471**			**476**	**100.0%**	**-0.20 [-0.58 , 0.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.02 (P = 0.31)								
2.8.5 48 months								
ProtecT	2.6	3	471	2.7	3.1	476	100.0%	-0.10 [-0.49 , 0.29]
Subtotal (95% CI)			**471**			**476**	**100.0%**	**-0.10 [-0.49 , 0.29]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.50 (P = 0.61)								
2.8.6 60 months								
ProtecT	2.6	2.9	471	2.8	3.1	466	100.0%	-0.20 [-0.58 , 0.18]
Subtotal (95% CI)			**471**			**466**	**100.0%**	**-0.20 [-0.58 , 0.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.02 (P = 0.31)								
2.8.7 72 months								
ProtecT	2.7	3.1	459	3.1	3.4	464	100.0%	-0.40 [-0.82 , 0.02]
Subtotal (95% CI)			**459**			**464**	**100.0%**	**-0.40 [-0.82 , 0.02]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.87 (P = 0.06)								
Test for subgroup differences: $Chi^2 = 9.31$, df = 6 (P = 0.16), $I^2 = 35.6\%$								



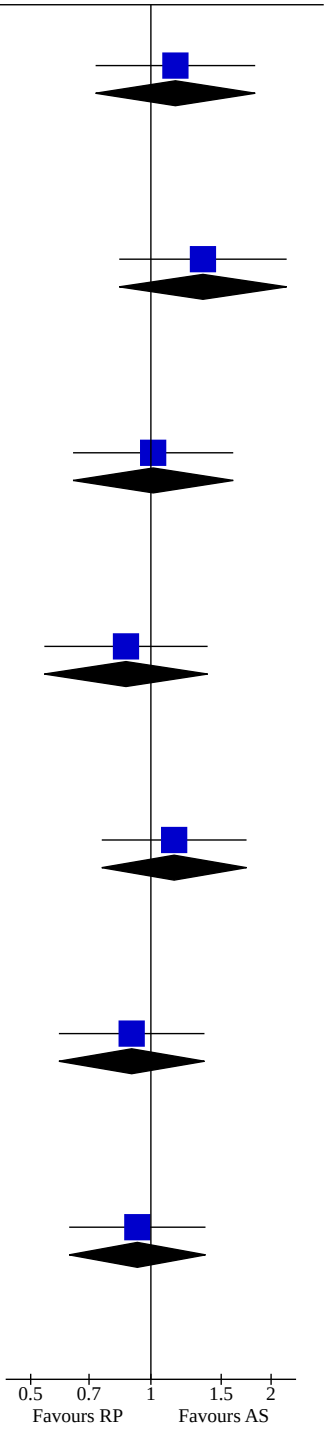
Analysis 2.9. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 9: Health-related quality of life: HADS: anxiety possible case score 8+

Study or Subgroup	Radical prostatectomy Events	Total	Active monitoring Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.9.1 6 months						
ProtecT	71	485	75	467	100.0%	0.91 [0.68 , 1.23]
Subtotal (95% CI)		**485**		**467**	**100.0%**	**0.91 [0.68 , 1.23]**
Total events:	71		75			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
2.9.2 12 months						
ProtecT	61	472	84	479	100.0%	0.74 [0.54 , 1.00]
Subtotal (95% CI)		**472**		**479**	**100.0%**	**0.74 [0.54 , 1.00]**
Total events:	61		84			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.97 (P = 0.05)						
2.9.3 24 months						
ProtecT	58	474	70	467	100.0%	0.82 [0.59 , 1.13]
Subtotal (95% CI)		**474**		**467**	**100.0%**	**0.82 [0.59 , 1.13]**
Total events:	58		70			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.23 (P = 0.22)						
2.9.4 36 months						
ProtecT	56	470	76	474	100.0%	0.74 [0.54 , 1.02]
Subtotal (95% CI)		**470**		**474**	**100.0%**	**0.74 [0.54 , 1.02]**
Total events:	56		76			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.81 (P = 0.07)						
2.9.5 48 months						
ProtecT	65	471	68	475	100.0%	0.96 [0.70 , 1.32]
Subtotal (95% CI)		**471**		**475**	**100.0%**	**0.96 [0.70 , 1.32]**
Total events:	65		68			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.23 (P = 0.82)						
2.9.6 60 months						
ProtecT	55	470	75	464	100.0%	0.72 [0.52 , 1.00]
Subtotal (95% CI)		**470**		**464**	**100.0%**	**0.72 [0.52 , 1.00]**
Total events:	55		75			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.96 (P = 0.05)						
2.9.7 72 months						
ProtecT	69	465	69	458	100.0%	0.98 [0.72 , 1.34]
Subtotal (95% CI)		**465**		**458**	**100.0%**	**0.98 [0.72 , 1.34]**
Total events:	69		69			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						
Test for subgroup differences: $Chi^2 = 4.16$, df = 6 (P = 0.66), $I^2 = 0\%$						



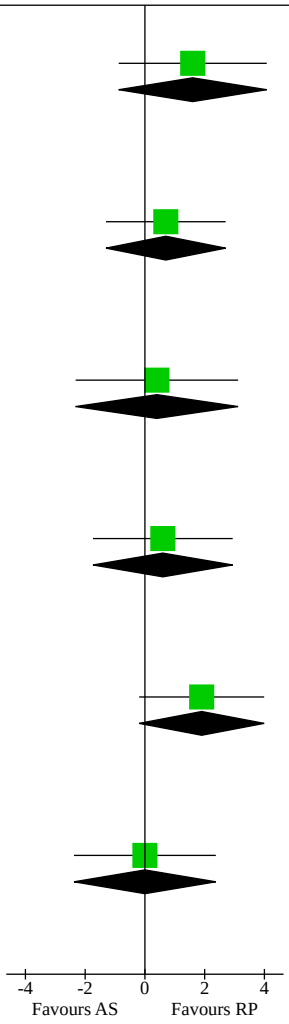
Analysis 2.10. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 10: Health-related quality of life: HADS: depression possible case score 8+

Study or Subgroup	Radical prostatectomy Events	Total	Active monitoring Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.10.1 6 months						
ProtecT	37	487	31	470	100.0%	1.15 [0.73 , 1.82]
Subtotal (95% CI)		**487**		**470**	**100.0%**	**1.15 [0.73 , 1.82]**
Total events:	37		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
2.10.2 12 months						
ProtecT	36	475	27	481	100.0%	1.35 [0.83 , 2.19]
Subtotal (95% CI)		**475**		**481**	**100.0%**	**1.35 [0.83 , 2.19]**
Total events:	36		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.22 (P = 0.22)						
2.10.3 24 months						
ProtecT	34	480	33	472	100.0%	1.01 [0.64 , 1.61]
Subtotal (95% CI)		**480**		**472**	**100.0%**	**1.01 [0.64 , 1.61]**
Total events:	34		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.96)						
2.10.4 36 months						
ProtecT	30	471	35	476	100.0%	0.87 [0.54 , 1.39]
Subtotal (95% CI)		**471**		**476**	**100.0%**	**0.87 [0.54 , 1.39]**
Total events:	30		35			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
2.10.5 48 months						
ProtecT	43	471	38	476	100.0%	1.14 [0.75 , 1.74]
Subtotal (95% CI)		**471**		**476**	**100.0%**	**1.14 [0.75 , 1.74]**
Total events:	43		38			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
2.10.6 60 months						
ProtecT	38	471	42	466	100.0%	0.90 [0.59 , 1.36]
Subtotal (95% CI)		**471**		**466**	**100.0%**	**0.90 [0.59 , 1.36]**
Total events:	38		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.52 (P = 0.61)						
2.10.7 72 months						
ProtecT	43	459	47	464	100.0%	0.92 [0.62 , 1.37]
Subtotal (95% CI)		**459**		**464**	**100.0%**	**0.92 [0.62 , 1.37]**
Total events:	43		47			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
Test for subgroup differences: Chi^2 = 2.92, df = 6 (P = 0.82), I^2 = 0%						



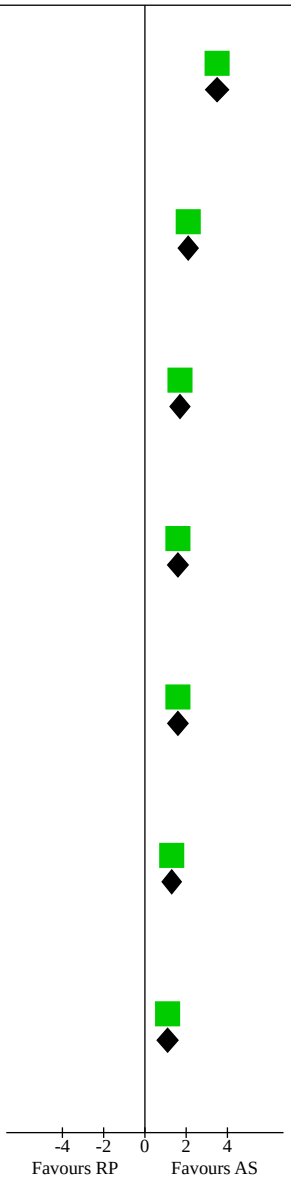
Analysis 2.11. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 11: Health-related quality of life: EORTC QLQ-C30 at 5 years

Study or Subgroup	Radical prostatectomy Mean	SD	Total	Active monitoring Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.11.1 Global health status								
ProtecT	78.4	17.7	386	76.8	17.6	394	100.0%	1.60 [-0.88 , 4.08]
Subtotal (95% CI)			**386**			**394**	**100.0%**	**1.60 [-0.88 , 4.08]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.27 (P = 0.21)								
2.11.2 Functional scale: physical								
ProtecT	91.6	13.8	383	90.9	14.7	395	100.0%	0.70 [-1.30 , 2.70]
Subtotal (95% CI)			**383**			**395**	**100.0%**	**0.70 [-1.30 , 2.70]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.68 (P = 0.49)								
2.11.3 Functional scale: role								
ProtecT	90.9	19	383	90.5	19.7	395	100.0%	0.40 [-2.32 , 3.12]
Subtotal (95% CI)			**383**			**395**	**100.0%**	**0.40 [-2.32 , 3.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.29 (P = 0.77)								
2.11.4 Functional scale: emotional								
ProtecT	87.9	16	386	87.3	17.3	394	100.0%	0.60 [-1.74 , 2.94]
Subtotal (95% CI)			**386**			**394**	**100.0%**	**0.60 [-1.74 , 2.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.50 (P = 0.61)								
2.11.5 Functional scale: cognitive								
ProtecT	87.9	14.4	386	86	15.4	394	100.0%	1.90 [-0.19 , 3.99]
Subtotal (95% CI)			**386**			**394**	**100.0%**	**1.90 [-0.19 , 3.99]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.78 (P = 0.08)								
2.11.6 Functional scale: social								
ProtecT	91.3	16.8	394	91.3	17.2	394	100.0%	0.00 [-2.37 , 2.37]
Subtotal (95% CI)			**394**			**394**	**100.0%**	**0.00 [-2.37 , 2.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Test for subgroup differences: $Chi^2 = 1.97$, df = 5 (P = 0.85), $I^2 = 0\%$								



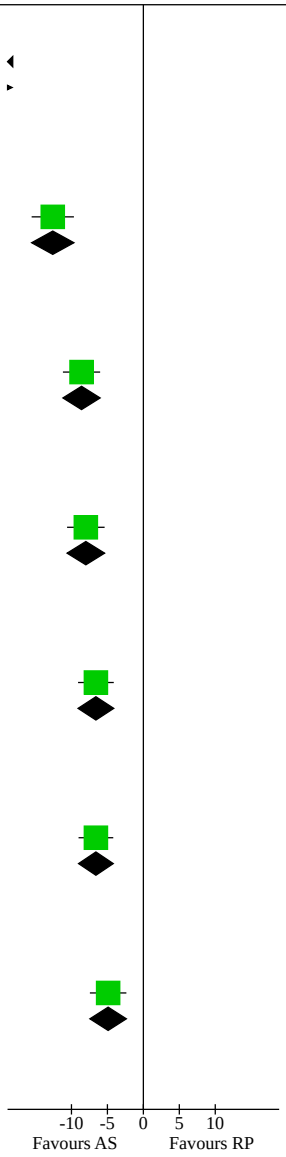
Analysis 2.12. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 12: Urinary function: ICIQ score

Study or Subgroup	Radical prostatectomy Mean	SD	Total	Active monitoring Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.12.1 6 months								
ProtecT	5.5	5.2	476	2	3.3	459	100.0%	3.50 [2.94 , 4.06]
Subtotal (95% CI)			**476**			**459**	**100.0%**	**3.50 [2.94 , 4.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 12.33 (P < 0.00001)								
2.12.2 12 months								
ProtecT	4.3	4.2	460	2.2	3.2	465	100.0%	2.10 [1.62 , 2.58]
Subtotal (95% CI)			**460**			**465**	**100.0%**	**2.10 [1.62 , 2.58]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 8.55 (P < 0.00001)								
2.12.3 24 months								
ProtecT	3.9	4.1	468	2.2	3.3	453	100.0%	1.70 [1.22 , 2.18]
Subtotal (95% CI)			**468**			**453**	**100.0%**	**1.70 [1.22 , 2.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.94 (P < 0.00001)								
2.12.4 36 months								
ProtecT	4	4.3	461	2.4	3.4	469	100.0%	1.60 [1.10 , 2.10]
Subtotal (95% CI)			**461**			**469**	**100.0%**	**1.60 [1.10 , 2.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.29 (P < 0.00001)								
2.12.5 48 months								
ProtecT	4.2	4.1	462	2.6	3.5	463	100.0%	1.60 [1.11 , 2.09]
Subtotal (95% CI)			**462**			**463**	**100.0%**	**1.60 [1.11 , 2.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.38 (P < 0.00001)								
2.12.6 60 months								
ProtecT	3.8	3.7	465	2.5	3.5	458	100.0%	1.30 [0.84 , 1.76]
Subtotal (95% CI)			**465**			**458**	**100.0%**	**1.30 [0.84 , 1.76]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.48 (P < 0.00001)								
2.12.7 72 months								
ProtecT	4	4	463	2.9	3.8	451	100.0%	1.10 [0.59 , 1.61]
Subtotal (95% CI)			**463**			**451**	**100.0%**	**1.10 [0.59 , 1.61]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.26 (P < 0.0001)								
Test for subgroup differences: Chi² = 50.59, df = 6 (P < 0.00001), I² = 88.1%								



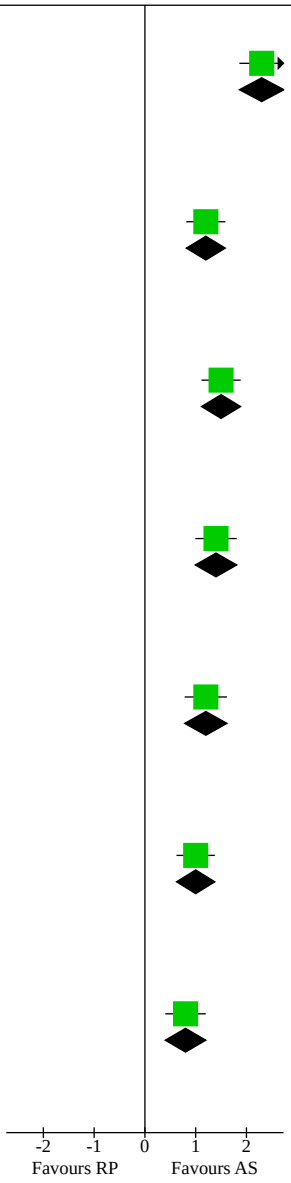
Analysis 2.13. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 13: Urinary function: EPIC urinary incontinence subscale score

Study or Subgroup	Radical prostatectomy Mean	SD	Total	Active monitoring Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.13.1 6 months								
ProtecT	67.4	29.1	361	89.1	16	345	100.0%	-21.70 [-25.14 , -18.26]
Subtotal (95% CI)			**361**			**345**	**100.0%**	**-21.70 [-25.14 , -18.26]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 12.35 (P < 0.00001)								
2.13.2 12 months								
ProtecT	76.5	23.7	354	89.1	15.3	353	100.0%	-12.60 [-15.54 , -9.66]
Subtotal (95% CI)			**354**			**353**	**100.0%**	**-12.60 [-15.54 , -9.66]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 8.40 (P < 0.00001)								
2.13.3 24 months								
ProtecT	80.3	21.4	393	88.9	15	389	100.0%	-8.60 [-11.19 , -6.01]
Subtotal (95% CI)			**393**			**389**	**100.0%**	**-8.60 [-11.19 , -6.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.51 (P < 0.00001)								
2.13.4 36 months								
ProtecT	79.3	21.8	425	87.3	16.7	426	100.0%	-8.00 [-10.61 , -5.39]
Subtotal (95% CI)			**425**			**426**	**100.0%**	**-8.00 [-10.61 , -5.39]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.01 (P < 0.00001)								
2.13.5 48 months								
ProtecT	80.2	20.3	445	86.8	17.4	446	100.0%	-6.60 [-9.08 , -4.12]
Subtotal (95% CI)			**445**			**446**	**100.0%**	**-6.60 [-9.08 , -4.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.21 (P < 0.00001)								
2.13.6 60 months								
ProtecT	80.6	20.2	455	87.2	16.8	455	100.0%	-6.60 [-9.01 , -4.19]
Subtotal (95% CI)			**455**			**455**	**100.0%**	**-6.60 [-9.01 , -4.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.36 (P < 0.00001)								
2.13.7 72 months								
ProtecT	80.9	20.2	449	85.8	18.5	446	100.0%	-4.90 [-7.44 , -2.36]
Subtotal (95% CI)			**449**			**446**	**100.0%**	**-4.90 [-7.44 , -2.36]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.78 (P = 0.0002)								
Test for subgroup differences: Chi² = 75.97, df = 6 (P < 0.00001), I² = 92.1%								



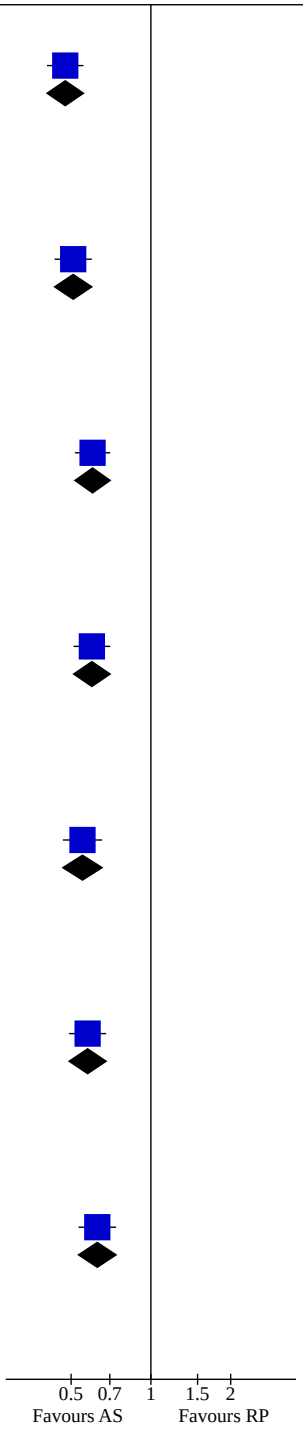
Analysis 2.14. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 14: Urinary function: ICSmaleSF urinary incontinence score

Study or Subgroup	Radical prostatectomy Mean	SD	Total	Active monitoring Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.14.1 6 months								
ProtecT	4.6	4.1	485	2.3	2.7	470	100.0%	2.30 [1.86 , 2.74]
Subtotal (95% CI)			**485**			**470**	**100.0%**	**2.30 [1.86 , 2.74]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 10.27 (P < 0.00001)								
2.14.2 24 months								
ProtecT	3.7	3.4	480	2.5	2.6	470	100.0%	1.20 [0.82 , 1.58]
Subtotal (95% CI)			**480**			**470**	**100.0%**	**1.20 [0.82 , 1.58]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.12 (P < 0.00001)								
2.14.3 12 months								
ProtecT	3.8	3.5	474	2.3	2.5	483	100.0%	1.50 [1.11 , 1.89]
Subtotal (95% CI)			**474**			**483**	**100.0%**	**1.50 [1.11 , 1.89]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 7.62 (P < 0.00001)								
2.14.4 36 months								
ProtecT	4	3.7	467	2.6	2.6	478	100.0%	1.40 [0.99 , 1.81]
Subtotal (95% CI)			**467**			**478**	**100.0%**	**1.40 [0.99 , 1.81]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.72 (P < 0.00001)								
2.14.5 48 months								
ProtecT	4	3.6	470	2.8	2.9	480	100.0%	1.20 [0.78 , 1.62]
Subtotal (95% CI)			**470**			**480**	**100.0%**	**1.20 [0.78 , 1.62]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.65 (P < 0.00001)								
2.14.6 60 months								
ProtecT	3.8	3.1	473	2.8	2.8	467	100.0%	1.00 [0.62 , 1.38]
Subtotal (95% CI)			**473**			**467**	**100.0%**	**1.00 [0.62 , 1.38]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.19 (P < 0.00001)								
2.14.7 72 months								
ProtecT	3.8	3.1	465	3	3.1	461	100.0%	0.80 [0.40 , 1.20]
Subtotal (95% CI)			**465**			**461**	**100.0%**	**0.80 [0.40 , 1.20]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.93 (P < 0.0001)								
Test for subgroup differences: Chi² = 30.09, df = 6 (P < 0.0001), I² = 80.1%								



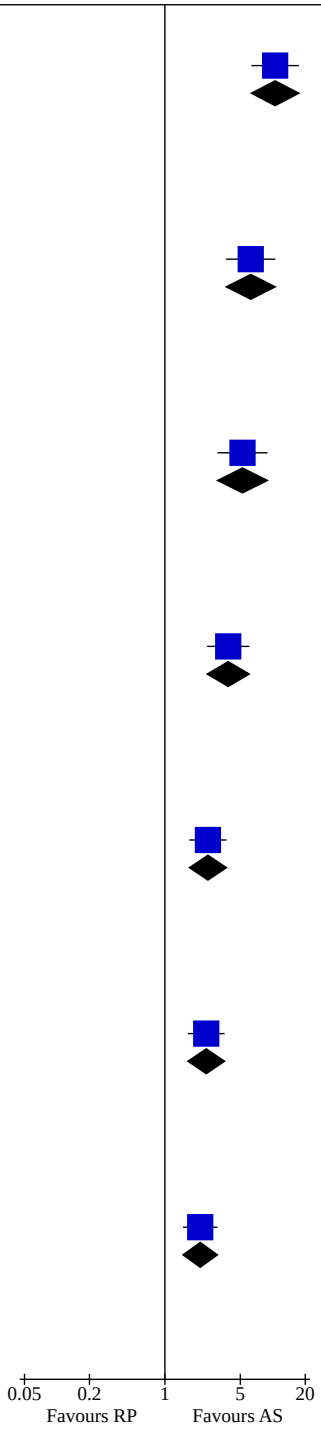
Analysis 2.15. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 15: Urinary incontinence: completely continent (ICIQ score 0)

Study or Subgroup	Radical prostatectomy Events	Total	Active monitoring Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.15.1 6 months						
ProtecT	138	476	280	459	100.0%	0.48 [0.41 , 0.56]
Subtotal (95% CI)		**476**		**459**	**100.0%**	**0.48 [0.41 , 0.56]**
Total events:	138		280			
Heterogeneity: Not applicable						
Test for overall effect: Z = 9.20 (P < 0.00001)						
2.15.2 12 months						
ProtecT	135	460	268	465	100.0%	0.51 [0.43 , 0.60]
Subtotal (95% CI)		**460**		**465**	**100.0%**	**0.51 [0.43 , 0.60]**
Total events:	135		268			
Heterogeneity: Not applicable						
Test for overall effect: Z = 8.18 (P < 0.00001)						
2.15.3 24 months						
ProtecT	155	468	249	453	100.0%	0.60 [0.52 , 0.70]
Subtotal (95% CI)		**468**		**453**	**100.0%**	**0.60 [0.52 , 0.70]**
Total events:	155		249			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.47 (P < 0.00001)						
2.15.4 36 months						
ProtecT	146	461	248	469	100.0%	0.60 [0.51 , 0.70]
Subtotal (95% CI)		**461**		**469**	**100.0%**	**0.60 [0.51 , 0.70]**
Total events:	146		248			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.32 (P < 0.00001)						
2.15.5 48 months						
ProtecT	130	462	236	463	100.0%	0.55 [0.47 , 0.65]
Subtotal (95% CI)		**462**		**463**	**100.0%**	**0.55 [0.47 , 0.65]**
Total events:	130		236			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.81 (P < 0.00001)						
2.15.6 60 months						
ProtecT	143	465	244	458	100.0%	0.58 [0.49 , 0.68]
Subtotal (95% CI)		**465**		**458**	**100.0%**	**0.58 [0.49 , 0.68]**
Total events:	143		244			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.68 (P < 0.00001)						
2.15.7 72 months						
ProtecT	145	463	225	451	100.0%	0.63 [0.53 , 0.74]
Subtotal (95% CI)		**463**		**451**	**100.0%**	**0.63 [0.53 , 0.74]**
Total events:	145		225			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.58 (P < 0.00001)						
Test for subgroup differences: Chi^2 = 9.04, df = 6 (P = 0.17), I^2 = 33.6%						



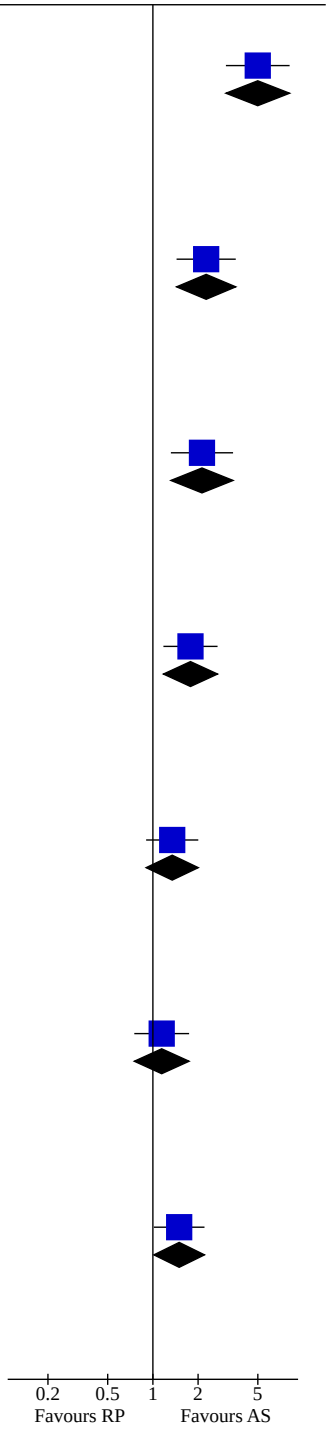
Analysis 2.16. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 16: Urinary incontinence: 1 or more pads per day in past 4 weeks (EPIC item)

Study or Subgroup	Radical prostatectomy Events	Total	Active monitoring Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.16.1 6 months						
ProtecT	165	362	15	346	100.0%	10.51 [6.33 , 17.47]
Subtotal (95% CI)		**362**		**346**	**100.0%**	**10.51 [6.33 , 17.47]**
Total events:	165		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 9.08 (P < 0.00001)						
2.16.2 12 months						
ProtecT	95	362	15	357	100.0%	6.25 [3.70 , 10.55]
Subtotal (95% CI)		**362**		**357**	**100.0%**	**6.25 [3.70 , 10.55]**
Total events:	95		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.84 (P < 0.00001)						
2.16.3 24 months						
ProtecT	80	399	15	392	100.0%	5.24 [3.07 , 8.93]
Subtotal (95% CI)		**399**		**392**	**100.0%**	**5.24 [3.07 , 8.93]**
Total events:	80		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.08 (P < 0.00001)						
2.16.4 36 months						
ProtecT	85	434	22	434	100.0%	3.86 [2.46 , 6.06]
Subtotal (95% CI)		**434**		**434**	**100.0%**	**3.86 [2.46 , 6.06]**
Total events:	85		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.89 (P < 0.00001)						
2.16.5 48 months						
ProtecT	77	451	31	455	100.0%	2.51 [1.69 , 3.72]
Subtotal (95% CI)		**451**		**455**	**100.0%**	**2.51 [1.69 , 3.72]**
Total events:	77		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.55 (P < 0.00001)						
2.16.6 60 months						
ProtecT	77	459	32	461	100.0%	2.42 [1.63 , 3.57]
Subtotal (95% CI)		**459**		**461**	**100.0%**	**2.42 [1.63 , 3.57]**
Total events:	77		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.42 (P < 0.00001)						
2.16.7 72 months						
ProtecT	79	455	37	453	100.0%	2.13 [1.47 , 3.07]
Subtotal (95% CI)		**455**		**453**	**100.0%**	**2.13 [1.47 , 3.07]**
Total events:	79		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.01 (P < 0.0001)						
Test for subgroup differences: Chi² = 38.32, df = 6 (P < 0.00001), I² = 84.3%						



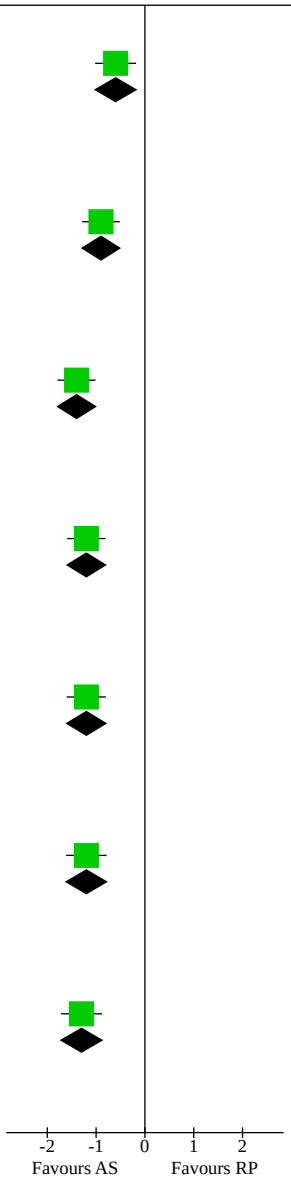
Analysis 2.17. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 17: Urinary incontinence: ICIQ: moderate to large interference (score 4+).

Study or Subgroup	Radical prostatectomy Events	Total	Active monitoring Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.17.1 6 months						
ProtecT	93	480	18	464	100.0%	4.99 [3.06 , 8.14]
Subtotal (95% CI)		**480**		**464**	**100.0%**	**4.99 [3.06 , 8.14]**
Total events:	93		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.46 (P < 0.00001)						
2.17.2 12 months						
ProtecT	56	469	25	474	100.0%	2.26 [1.44 , 3.56]
Subtotal (95% CI)		**469**		**474**	**100.0%**	**2.26 [1.44 , 3.56]**
Total events:	56		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.53 (P = 0.0004)						
2.17.3 24 months						
ProtecT	50	469	23	458	100.0%	2.12 [1.32 , 3.42]
Subtotal (95% CI)		**469**		**458**	**100.0%**	**2.12 [1.32 , 3.42]**
Total events:	50		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.09 (P = 0.002)						
2.17.4 36 months						
ProtecT	56	465	32	473	100.0%	1.78 [1.18 , 2.70]
Subtotal (95% CI)		**465**		**473**	**100.0%**	**1.78 [1.18 , 2.70]**
Total events:	56		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.72 (P = 0.006)						
2.17.5 48 months						
ProtecT	51	466	38	467	100.0%	1.34 [0.90 , 2.01]
Subtotal (95% CI)		**466**		**467**	**100.0%**	**1.34 [0.90 , 2.01]**
Total events:	51		38			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.45 (P = 0.15)						
2.17.6 60 months						
ProtecT	43	467	37	460	100.0%	1.14 [0.75 , 1.74]
Subtotal (95% CI)		**467**		**460**	**100.0%**	**1.14 [0.75 , 1.74]**
Total events:	43		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
2.17.7 72 months						
ProtecT	58	464	38	455	100.0%	1.50 [1.02 , 2.21]
Subtotal (95% CI)		**464**		**455**	**100.0%**	**1.50 [1.02 , 2.21]**
Total events:	58		38			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.04 (P = 0.04)						
Test for subgroup differences: Chi^2 = 25.57, df = 6 (P = 0.0003), I^2 = 76.5%						



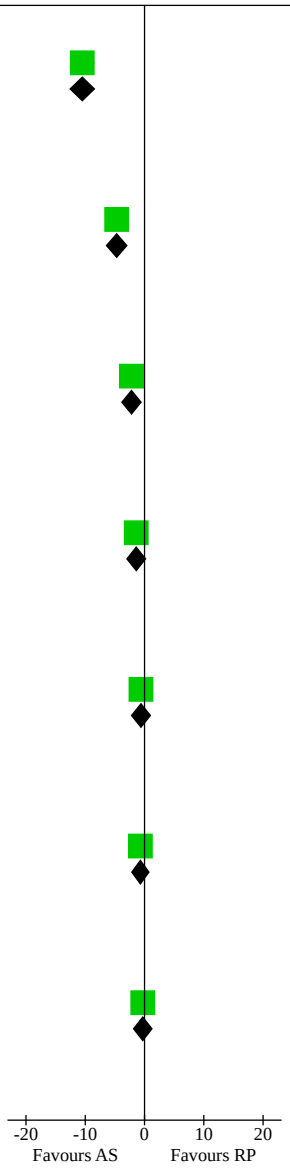
Analysis 2.18. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 18: Urinary function: ICSmaleSF voiding score

Study or Subgroup	Radical prostatectomy Mean	SD	Total	Active monitoring Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.18.1 6 months								
ProtecT	3.2	3.2	483	3.8	3.4	473	100.0%	-0.60 [-1.02 , -0.18]
Subtotal (95% CI)			**483**			**473**	**100.0%**	**-0.60 [-1.02 , -0.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.81 (P = 0.005)								
2.18.2 12 months								
ProtecT	2.8	2.9	480	3.7	3.2	484	100.0%	-0.90 [-1.29 , -0.51]
Subtotal (95% CI)			**480**			**484**	**100.0%**	**-0.90 [-1.29 , -0.51]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.58 (P < 0.00001)								
2.18.3 24 months								
ProtecT	2.5	2.7	481	3.9	3.4	474	100.0%	-1.40 [-1.79 , -1.01]
Subtotal (95% CI)			**481**			**474**	**100.0%**	**-1.40 [-1.79 , -1.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 7.04 (P < 0.00001)								
2.18.4 36 months								
ProtecT	2.8	2.9	475	4	3.3	481	100.0%	-1.20 [-1.59 , -0.81]
Subtotal (95% CI)			**475**			**481**	**100.0%**	**-1.20 [-1.59 , -0.81]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.97 (P < 0.00001)								
2.18.5 48 months								
ProtecT	2.8	2.9	470	4	3.4	481	100.0%	-1.20 [-1.60 , -0.80]
Subtotal (95% CI)			**470**			**481**	**100.0%**	**-1.20 [-1.60 , -0.80]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.86 (P < 0.00001)								
2.18.6 60 months								
ProtecT	2.9	2.8	476	4.1	3.6	461	100.0%	-1.20 [-1.61 , -0.79]
Subtotal (95% CI)			**476**			**461**	**100.0%**	**-1.20 [-1.61 , -0.79]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.68 (P < 0.00001)								
2.18.7 72 months								
ProtecT	2.9	2.9	469	4.2	3.6	464	100.0%	-1.30 [-1.72 , -0.88]
Subtotal (95% CI)			**469**			**464**	**100.0%**	**-1.30 [-1.72 , -0.88]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.07 (P < 0.00001)								
Test for subgroup differences: Chi^2 = 10.32, df = 6 (P = 0.11), I^2 = 41.9%								



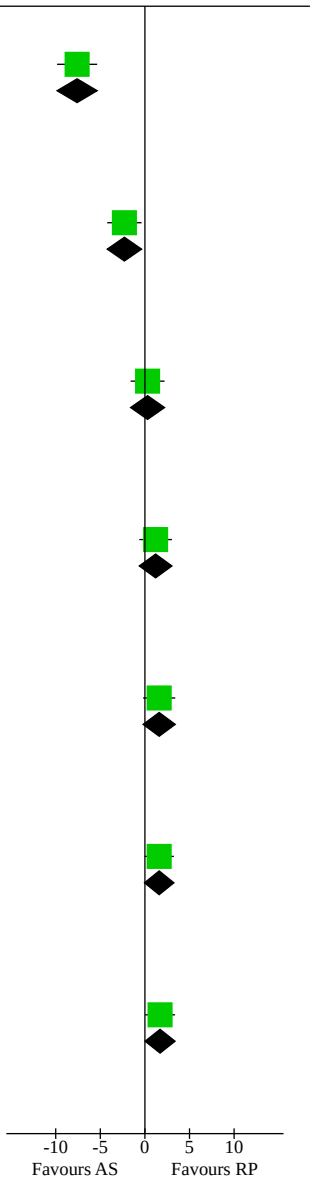
Analysis 2.19. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 19: Urinary function: EPIC urinary summary score

Study or Subgroup	Radical prostatectomy Mean	SD	Total	Active monitoring Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.19.1 6 months								
ProtecT	80.1	16.6	364	90.6	10.7	347	100.0%	-10.50 [-12.54 , -8.46]
Subtotal (95% CI)			**364**			**347**	**100.0%**	**-10.50 [-12.54 , -8.46]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 10.07 (P < 0.00001)								
2.19.2 12 months								
ProtecT	86.5	13.2	364	91.2	10.1	354	100.0%	-4.70 [-6.42 , -2.98]
Subtotal (95% CI)			**364**			**354**	**100.0%**	**-4.70 [-6.42 , -2.98]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.37 (P < 0.00001)								
2.19.3 24 months								
ProtecT	88.1	12.3	401	90.3	10.9	392	100.0%	-2.20 [-3.82 , -0.58]
Subtotal (95% CI)			**401**			**392**	**100.0%**	**-2.20 [-3.82 , -0.58]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.67 (P = 0.008)								
2.19.4 36 months								
ProtecT	87.9	12.1	433	89.3	11.5	433	100.0%	-1.40 [-2.97 , 0.17]
Subtotal (95% CI)			**433**			**433**	**100.0%**	**-1.40 [-2.97 , 0.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.75 (P = 0.08)								
2.19.5 48 months								
ProtecT	88.6	11.9	451	89.2	12.5	455	100.0%	-0.60 [-2.19 , 0.99]
Subtotal (95% CI)			**451**			**455**	**100.0%**	**-0.60 [-2.19 , 0.99]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.74 (P = 0.46)								
2.19.6 60 months								
ProtecT	88.9	11.1	460	89.6	11.3	461	100.0%	-0.70 [-2.15 , 0.75]
Subtotal (95% CI)			**460**			**461**	**100.0%**	**-0.70 [-2.15 , 0.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.95 (P = 0.34)								
2.19.7 72 months								
ProtecT	88.7	11.3	455	89	12.5	454	100.0%	-0.30 [-1.85 , 1.25]
Subtotal (95% CI)			**455**			**454**	**100.0%**	**-0.30 [-1.85 , 1.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.38 (P = 0.70)								
Test for subgroup differences: Chi^2 = 86.13, df = 6 (P < 0.00001), I^2 = 93.0%								



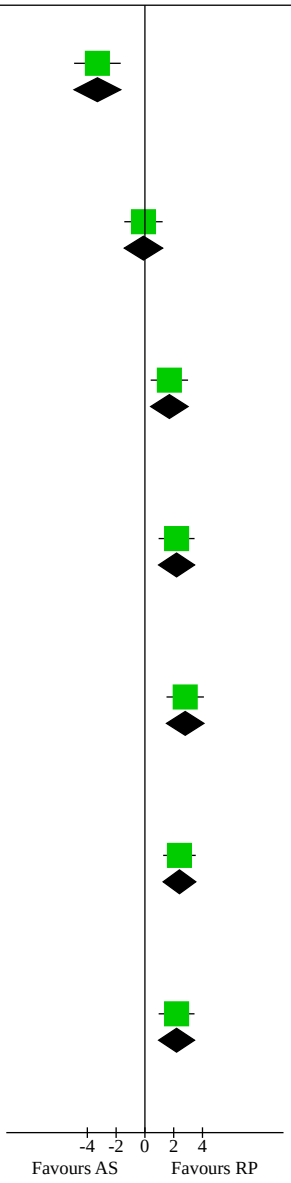
Analysis 2.20. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 20: Urinary function: EPIC urinary bother subscale score

Study or Subgroup	Radical prostatectomy Mean	SD	Total	Active monitoring Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.20.1 6 months								
ProtecT	81.4	17.4	364	89	12.9	345	100.0%	-7.60 [-9.85 , -5.35]
Subtotal (95% CI)			**364**			**345**	**100.0%**	**-7.60 [-9.85 , -5.35]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.63 (P < 0.00001)								
2.20.2 12 months								
ProtecT	87.7	14.1	365	90	12.2	354	100.0%	-2.30 [-4.23 , -0.37]
Subtotal (95% CI)			**365**			**354**	**100.0%**	**-2.30 [-4.23 , -0.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.34 (P = 0.02)								
2.20.3 24 months								
ProtecT	88.9	13.8	399	88.6	13.5	390	100.0%	0.30 [-1.60 , 2.20]
Subtotal (95% CI)			**399**			**390**	**100.0%**	**0.30 [-1.60 , 2.20]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.31 (P = 0.76)								
2.20.4 36 months								
ProtecT	88.7	13.4	434	87.5	14.1	433	100.0%	1.20 [-0.63 , 3.03]
Subtotal (95% CI)			**434**			**433**	**100.0%**	**1.20 [-0.63 , 3.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.28 (P = 0.20)								
2.20.5 48 months								
ProtecT	89.5	13	445	87.9	14.6	458	100.0%	1.60 [-0.20 , 3.40]
Subtotal (95% CI)			**445**			**458**	**100.0%**	**1.60 [-0.20 , 3.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.74 (P = 0.08)								
2.20.6 60 months								
ProtecT	89.9	11.9	457	88.3	13.5	460	100.0%	1.60 [-0.05 , 3.25]
Subtotal (95% CI)			**457**			**460**	**100.0%**	**1.60 [-0.05 , 3.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.90 (P = 0.06)								
2.20.7 72 months								
ProtecT	89.7	11.9	453	88	13.9	457	100.0%	1.70 [0.02 , 3.38]
Subtotal (95% CI)			**453**			**457**	**100.0%**	**1.70 [0.02 , 3.38]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.98 (P = 0.05)								
Test for subgroup differences: Chi^2 = 61.76, df = 6 (P < 0.00001), I^2 = 90.3%								



Analysis 2.21. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 21: Urinary function: EPIC urinary obstruction/irritative subscale score

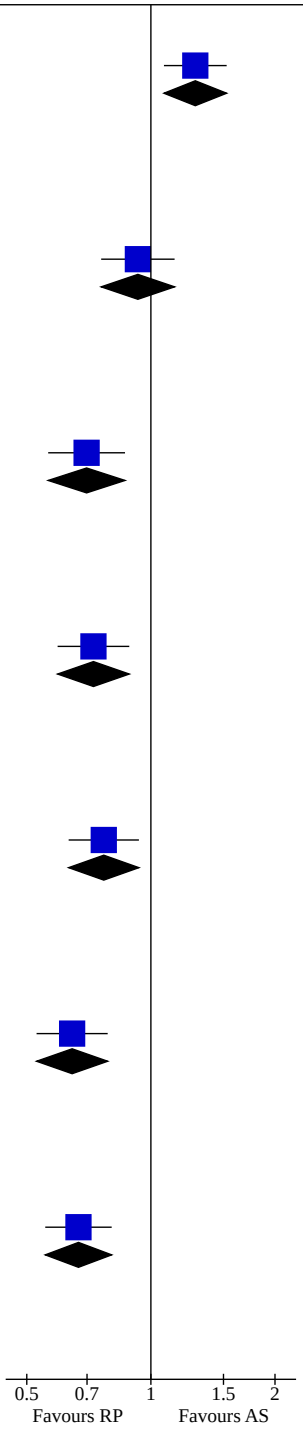
Study or Subgroup	Radical prostatectomy Mean	SD	Total	Active monitoring Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.21.1 6 months								
ProtecT	88.7	12.3	364	92	9.6	347	100.0%	-3.30 [-4.92 , -1.68]
Subtotal (95% CI)			**364**			**347**	**100.0%**	**-3.30 [-4.92 , -1.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.00 (P < 0.0001)								
2.21.2 12 months								
ProtecT	92.8	9.2	364	92.9	9	354	100.0%	-0.10 [-1.43 , 1.23]
Subtotal (95% CI)			**364**			**354**	**100.0%**	**-0.10 [-1.43 , 1.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.15 (P = 0.88)								
2.21.3 24 months								
ProtecT	93.4	8.7	402	91.7	9.9	392	100.0%	1.70 [0.40 , 3.00]
Subtotal (95% CI)			**402**			**392**	**100.0%**	**1.70 [0.40 , 3.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.57 (P = 0.01)								
2.21.4 36 months								
ProtecT	93.3	8.7	433	91.1	10	433	100.0%	2.20 [0.95 , 3.45]
Subtotal (95% CI)			**433**			**433**	**100.0%**	**2.20 [0.95 , 3.45]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.45 (P = 0.0006)								
2.21.5 48 months								
ProtecT	94.1	8.6	451	91.3	11.2	456	100.0%	2.80 [1.50 , 4.10]
Subtotal (95% CI)			**451**			**456**	**100.0%**	**2.80 [1.50 , 4.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.23 (P < 0.0001)								
2.21.6 60 months								
ProtecT	94.1	7.6	461	91.7	9.8	461	100.0%	2.40 [1.27 , 3.53]
Subtotal (95% CI)			**461**			**461**	**100.0%**	**2.40 [1.27 , 3.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.16 (P < 0.0001)								
2.21.7 72 months								
ProtecT	93.7	7.9	454	91.5	11	454	100.0%	2.20 [0.95 , 3.45]
Subtotal (95% CI)			**454**			**454**	**100.0%**	**2.20 [0.95 , 3.45]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.46 (P = 0.0005)								
Test for subgroup differences: Chi^2 = 48.10, df = 6 (P < 0.00001), I^2 = 87.5%								



Analysis 2.22. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 22: Urinary incontinence: ICSmaleSF nocturia item: twice or more per night

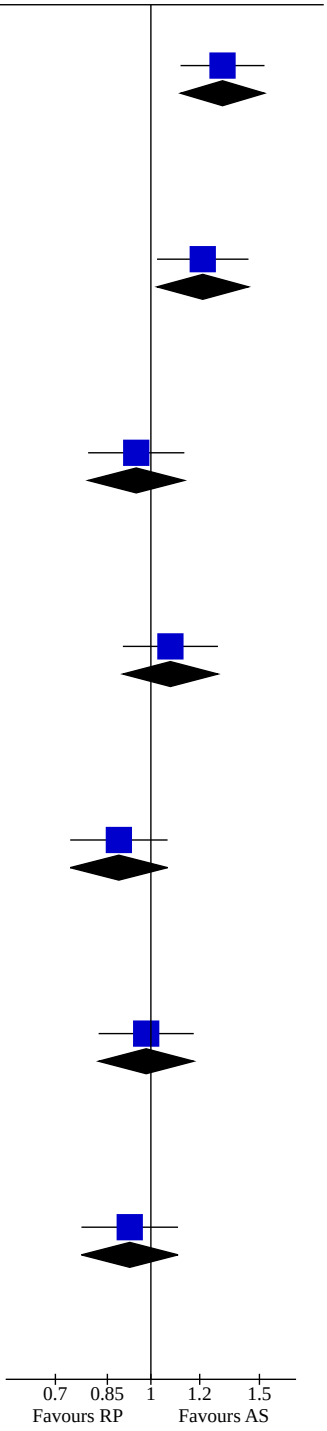
Study or Subgroup	Radical prostatectomy Events	Total	Active monitoring Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.22.1 6 months						
ProtecT	192	489	144	470	100.0%	1.28 [1.08 , 1.53]
Subtotal (95% CI)		**489**		**470**	**100.0%**	**1.28 [1.08 , 1.53]**
Total events:	192		144			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.78 (P = 0.005)						
2.22.2 12 months						
ProtecT	127	476	138	481	100.0%	0.93 [0.76 , 1.14]
Subtotal (95% CI)		**476**		**481**	**100.0%**	**0.93 [0.76 , 1.14]**
Total events:	127		138			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
2.22.3 24 months						
ProtecT	106	481	148	469	100.0%	0.70 [0.56 , 0.87]
Subtotal (95% CI)		**481**		**469**	**100.0%**	**0.70 [0.56 , 0.87]**
Total events:	106		148			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.28 (P = 0.001)						
2.22.4 36 months						
ProtecT	117	470	164	478	100.0%	0.73 [0.59 , 0.89]
Subtotal (95% CI)		**470**		**478**	**100.0%**	**0.73 [0.59 , 0.89]**
Total events:	117		164			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.14 (P = 0.002)						
2.22.5 48 months						
ProtecT	124	473	162	475	100.0%	0.77 [0.63 , 0.94]
Subtotal (95% CI)		**473**		**475**	**100.0%**	**0.77 [0.63 , 0.94]**
Total events:	124		162			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.63 (P = 0.009)						
2.22.6 60 months						
ProtecT	114	474	174	466	100.0%	0.64 [0.53 , 0.79]
Subtotal (95% CI)		**474**		**466**	**100.0%**	**0.64 [0.53 , 0.79]**
Total events:	114		174			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.34 (P < 0.0001)						
2.22.7 72 months						
ProtecT	126	466	188	464	100.0%	0.67 [0.55 , 0.80]
Subtotal (95% CI)		**466**		**464**	**100.0%**	**0.67 [0.55 , 0.80]**
Total events:	126		188			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.27 (P < 0.0001)						

Test for subgroup differences: $Chi^2 = 40.69$, df = 6 (P < 0.00001), $I^2 = 85.3\%$



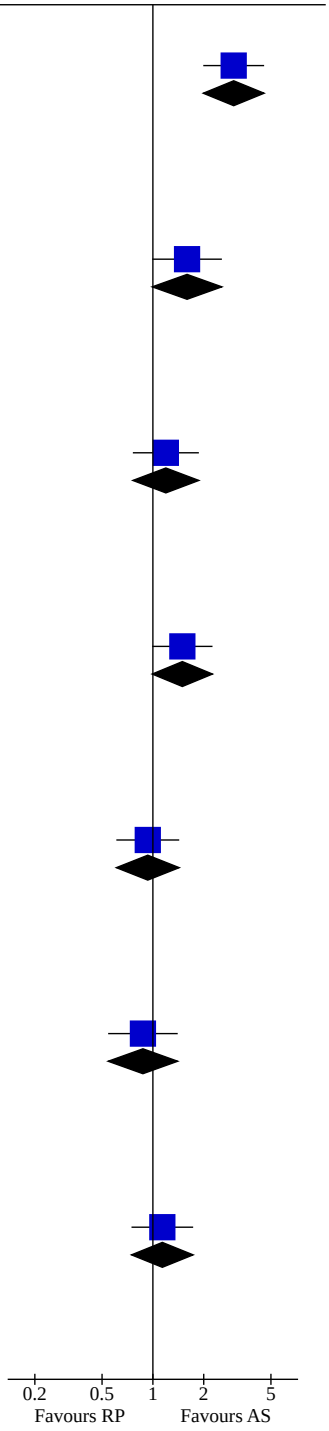
Analysis 2.23. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 23: Urinary incontinence: ICSmaleSF daytime frequency: more frequent than once every 3 hours

Study or Subgroup	Radical prostatectomy Events	Total	Active monitoring Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.23.1 6 months						
ProtecT	222	487	165	473	100.0%	1.31 [1.12 , 1.53]
Subtotal (95% CI)		**487**		**473**	**100.0%**	**1.31 [1.12 , 1.53]**
Total events:	222		165			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.35 (P = 0.0008)						
2.23.2 12 months						
ProtecT	187	477	156	483	100.0%	1.21 [1.02 , 1.44]
Subtotal (95% CI)		**477**		**483**	**100.0%**	**1.21 [1.02 , 1.44]**
Total events:	187		156			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.22 (P = 0.03)						
2.23.3 24 months						
ProtecT	156	480	161	469	100.0%	0.95 [0.79 , 1.13]
Subtotal (95% CI)		**480**		**469**	**100.0%**	**0.95 [0.79 , 1.13]**
Total events:	156		161			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
2.23.4 36 months						
ProtecT	165	468	157	479	100.0%	1.08 [0.90 , 1.28]
Subtotal (95% CI)		**468**		**479**	**100.0%**	**1.08 [0.90 , 1.28]**
Total events:	165		157			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.81 (P = 0.42)						
2.23.5 48 months						
ProtecT	146	469	167	476	100.0%	0.89 [0.74 , 1.06]
Subtotal (95% CI)		**469**		**476**	**100.0%**	**0.89 [0.74 , 1.06]**
Total events:	146		167			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						
2.23.6 60 months						
ProtecT	161	473	159	459	100.0%	0.98 [0.82 , 1.17]
Subtotal (95% CI)		**473**		**459**	**100.0%**	**0.98 [0.82 , 1.17]**
Total events:	161		159			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.19 (P = 0.85)						
2.23.7 72 months						
ProtecT	151	464	162	460	100.0%	0.92 [0.77 , 1.11]
Subtotal (95% CI)		**464**		**460**	**100.0%**	**0.92 [0.77 , 1.11]**
Total events:	151		162			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.86 (P = 0.39)						
Test for subgroup differences: Chi^2 = 17.35, df = 6 (P = 0.008), I^2 = 65.4%						



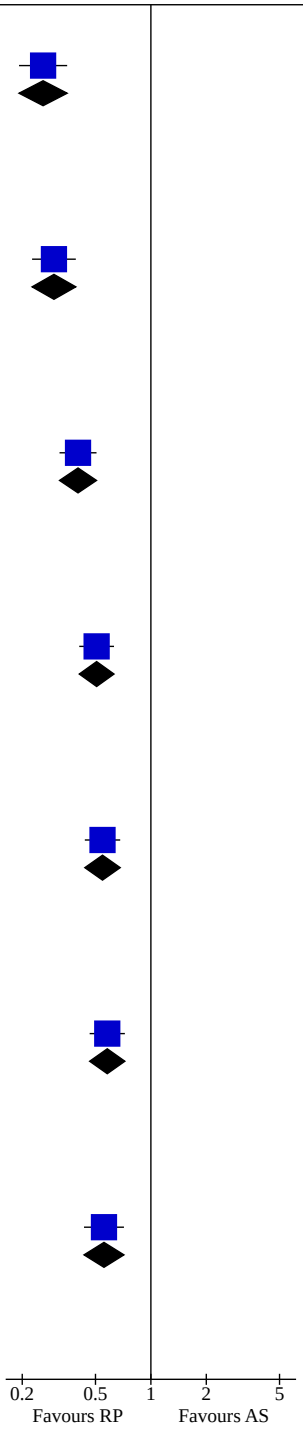
Analysis 2.24. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 24: Urinary incontinence: ICSmaleSF 'somewhat/a lot' of impact of lower urinary tract symptoms

Study or Subgroup	Radical prostatectomy Events	Total	Active monitoring Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.24.1 6 months						
ProtecT	84	490	27	474	100.0%	3.01 [1.99 , 4.56]
Subtotal (95% CI)		**490**		**474**	**100.0%**	**3.01 [1.99 , 4.56]**
Total events:	84		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.21 (P < 0.00001)						
2.24.2 12 months						
ProtecT	41	477	26	482	100.0%	1.59 [0.99 , 2.56]
Subtotal (95% CI)		**477**		**482**	**100.0%**	**1.59 [0.99 , 2.56]**
Total events:	41		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.92 (P = 0.05)						
2.24.3 24 months						
ProtecT	39	481	32	471	100.0%	1.19 [0.76 , 1.87]
Subtotal (95% CI)		**481**		**471**	**100.0%**	**1.19 [0.76 , 1.87]**
Total events:	39		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						
2.24.4 36 months						
ProtecT	51	470	35	482	100.0%	1.49 [0.99 , 2.25]
Subtotal (95% CI)		**470**		**482**	**100.0%**	**1.49 [0.99 , 2.25]**
Total events:	51		35			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.92 (P = 0.06)						
2.24.5 48 months						
ProtecT	37	474	40	478	100.0%	0.93 [0.61 , 1.43]
Subtotal (95% CI)		**474**		**478**	**100.0%**	**0.93 [0.61 , 1.43]**
Total events:	37		40			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
2.24.6 60 months						
ProtecT	30	475	34	470	100.0%	0.87 [0.54 , 1.40]
Subtotal (95% CI)		**475**		**470**	**100.0%**	**0.87 [0.54 , 1.40]**
Total events:	30		34			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.57)						
2.24.7 72 months						
ProtecT	43	470	37	460	100.0%	1.14 [0.75 , 1.73]
Subtotal (95% CI)		**470**		**460**	**100.0%**	**1.14 [0.75 , 1.73]**
Total events:	43		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
Test for subgroup differences: Chi² = 22.06, df = 6 (P = 0.001), I² = 72.8%						



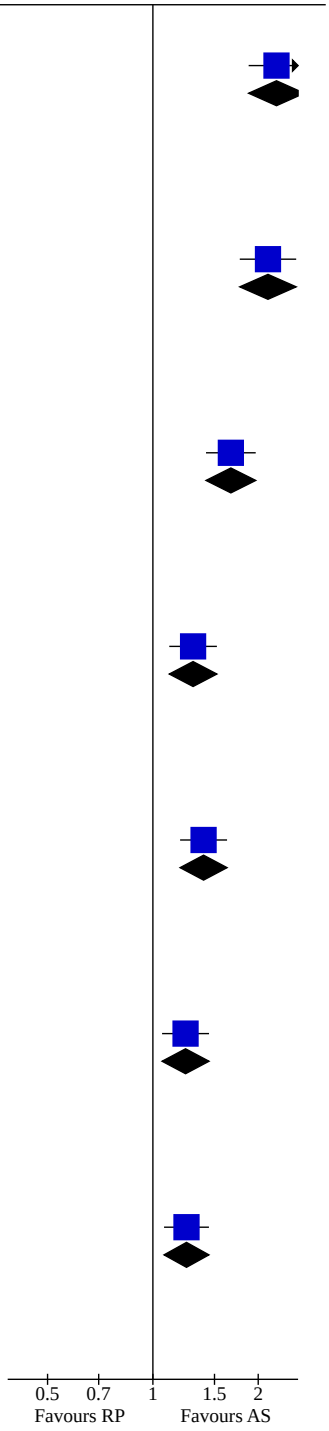
Analysis 2.25. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 25: Sexual function: EPIC: erections firm enough for intercourse

Study or Subgroup	Radical prostatectomy Events	Total	Active monitoring Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.25.1 6 months						
ProtecT	43	359	173	375	100.0%	0.26 [0.19 , 0.35]
Subtotal (95% CI)		**359**		**375**	**100.0%**	**0.26 [0.19 , 0.35]**
Total events:	43		173			
Heterogeneity: Not applicable						
Test for overall effect: Z = 8.78 (P < 0.00001)						
2.25.2 12 months						
ProtecT	52	356	167	340	100.0%	0.30 [0.23 , 0.39]
Subtotal (95% CI)		**356**		**340**	**100.0%**	**0.30 [0.23 , 0.39]**
Total events:	52		167			
Heterogeneity: Not applicable						
Test for overall effect: Z = 8.69 (P < 0.00001)						
2.25.3 24 months						
ProtecT	74	391	178	378	100.0%	0.40 [0.32 , 0.51]
Subtotal (95% CI)		**391**		**378**	**100.0%**	**0.40 [0.32 , 0.51]**
Total events:	74		178			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.72 (P < 0.00001)						
2.25.4 36 months						
ProtecT	89	427	173	421	100.0%	0.51 [0.41 , 0.63]
Subtotal (95% CI)		**427**		**421**	**100.0%**	**0.51 [0.41 , 0.63]**
Total events:	89		173			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.12 (P < 0.00001)						
2.25.5 48 months						
ProtecT	90	447	163	442	100.0%	0.55 [0.44 , 0.68]
Subtotal (95% CI)		**447**		**442**	**100.0%**	**0.55 [0.44 , 0.68]**
Total events:	90		163			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.36 (P < 0.00001)						
2.25.6 60 months						
ProtecT	94	464	157	449	100.0%	0.58 [0.46 , 0.72]
Subtotal (95% CI)		**464**		**449**	**100.0%**	**0.58 [0.46 , 0.72]**
Total events:	94		157			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.86 (P < 0.00001)						
2.25.7 72 months						
ProtecT	76	461	134	452	100.0%	0.56 [0.43 , 0.71]
Subtotal (95% CI)		**461**		**452**	**100.0%**	**0.56 [0.43 , 0.71]**
Total events:	76		134			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.60 (P < 0.00001)						
Test for subgroup differences: Chi² = 34.41, df = 6 (P < 0.00001), I² = 82.6%						

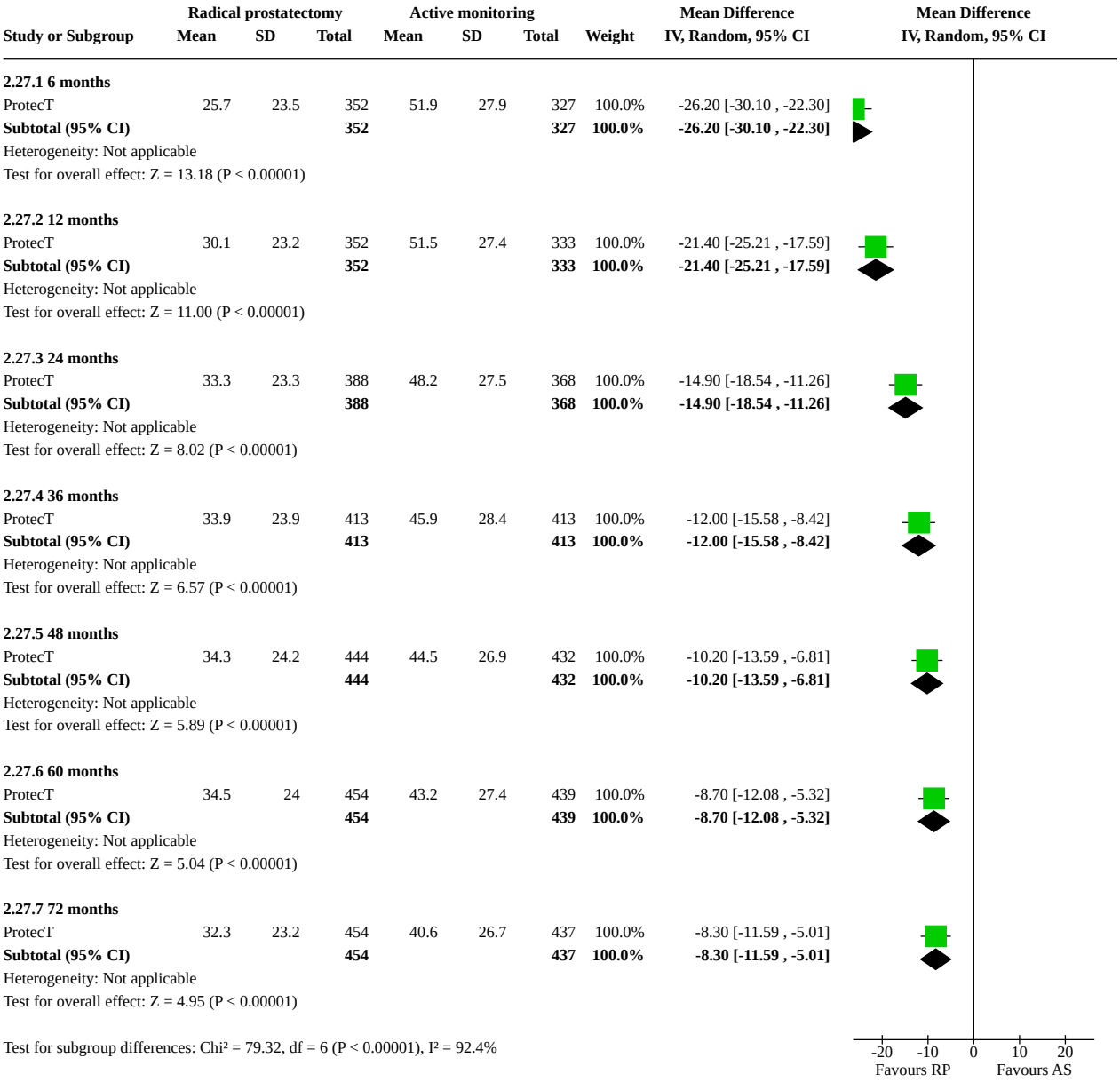


Analysis 2.26. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 26: Sexual function: EPIC: moderate or big problem with erectile dysfunction

Study or Subgroup	Radical prostatectomy Events	Total	Active monitoring Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.26.1 6 months						
ProtecT	234	354	97	331	100.0%	2.26 [1.88 , 2.71]
Subtotal (95% CI)		**354**		**331**	**100.0%**	**2.26 [1.88 , 2.71]**
Total events:	234		97			
Heterogeneity: Not applicable						
Test for overall effect: Z = 8.70 (P < 0.00001)						
2.26.2 12 months						
ProtecT	222	359	98	338	100.0%	2.13 [1.77 , 2.57]
Subtotal (95% CI)		**359**		**338**	**100.0%**	**2.13 [1.77 , 2.57]**
Total events:	222		98			
Heterogeneity: Not applicable						
Test for overall effect: Z = 8.00 (P < 0.00001)						
2.26.3 24 months						
ProtecT	227	395	129	375	100.0%	1.67 [1.42 , 1.97]
Subtotal (95% CI)		**395**		**375**	**100.0%**	**1.67 [1.42 , 1.97]**
Total events:	227		129			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.15 (P < 0.00001)						
2.26.4 36 months						
ProtecT	208	421	157	414	100.0%	1.30 [1.11 , 1.52]
Subtotal (95% CI)		**421**		**414**	**100.0%**	**1.30 [1.11 , 1.52]**
Total events:	208		157			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.31 (P = 0.0009)						
2.26.5 48 months						
ProtecT	226	448	159	440	100.0%	1.40 [1.20 , 1.63]
Subtotal (95% CI)		**448**		**440**	**100.0%**	**1.40 [1.20 , 1.63]**
Total events:	226		159			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.23 (P < 0.0001)						
2.26.6 60 months						
ProtecT	215	460	167	443	100.0%	1.24 [1.06 , 1.45]
Subtotal (95% CI)		**460**		**443**	**100.0%**	**1.24 [1.06 , 1.45]**
Total events:	215		167			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.73 (P = 0.006)						
2.26.7 72 months						
ProtecT	227	457	174	437	100.0%	1.25 [1.08 , 1.45]
Subtotal (95% CI)		**457**		**437**	**100.0%**	**1.25 [1.08 , 1.45]**
Total events:	227		174			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.94 (P = 0.003)						
Test for subgroup differences: Chi² = 50.29, df = 6 (P < 0.00001), I² = 88.1%						

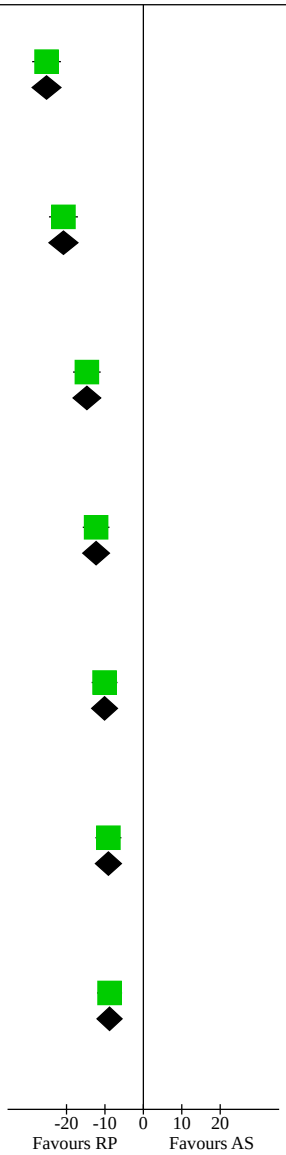


Analysis 2.27. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 27: Sexual function: EPIC sexual summary score



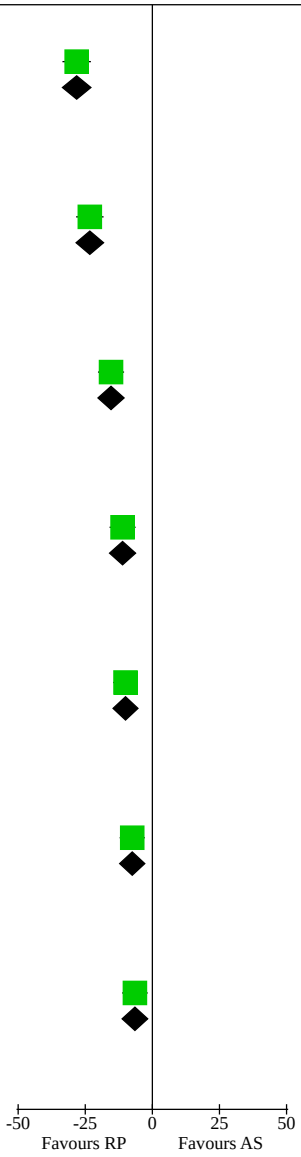
Analysis 2.28. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 28: Sexual function: EPIC sexual function subscale score

Study or Subgroup	Radical prostatectomy Mean	SD	Total	Active monitoring Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.28.1 6 months								
ProtecT	19.9	22.4	351	45.1	27	329	100.0%	-25.20 [-28.94 , -21.46]
Subtotal (95% CI)			**351**			**329**	**100.0%**	**-25.20 [-28.94 , -21.46]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 13.20 (P < 0.00001)								
2.28.2 12 months								
ProtecT	23.6	22.8	352	44.4	27.1	332	100.0%	-20.80 [-24.56 , -17.04]
Subtotal (95% CI)			**352**			**332**	**100.0%**	**-20.80 [-24.56 , -17.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 10.83 (P < 0.00001)								
2.28.3 24 months								
ProtecT	27.2	23.4	387	41.9	26.7	367	100.0%	-14.70 [-18.29 , -11.11]
Subtotal (95% CI)			**387**			**367**	**100.0%**	**-14.70 [-18.29 , -11.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 8.02 (P < 0.00001)								
2.28.4 36 months								
ProtecT	26.9	23.7	420	39.2	27.4	418	100.0%	-12.30 [-15.77 , -8.83]
Subtotal (95% CI)			**420**			**418**	**100.0%**	**-12.30 [-15.77 , -8.83]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.95 (P < 0.00001)								
2.28.5 48 months								
ProtecT	27.1	24.2	444	37.2	26.5	437	100.0%	-10.10 [-13.45 , -6.75]
Subtotal (95% CI)			**444**			**437**	**100.0%**	**-10.10 [-13.45 , -6.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.90 (P < 0.00001)								
2.28.6 60 months								
ProtecT	26.5	24.4	457	35.6	27.3	447	100.0%	-9.10 [-12.48 , -5.72]
Subtotal (95% CI)			**457**			**447**	**100.0%**	**-9.10 [-12.48 , -5.72]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.28 (P < 0.00001)								
2.28.7 72 months								
ProtecT	23.7	23.4	459	32.5	26.4	444	100.0%	-8.80 [-12.06 , -5.54]
Subtotal (95% CI)			**459**			**444**	**100.0%**	**-8.80 [-12.06 , -5.54]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.29 (P < 0.00001)								
Test for subgroup differences: Chi^2 = 71.05, df = 6 (P < 0.00001), I^2 = 91.6%								



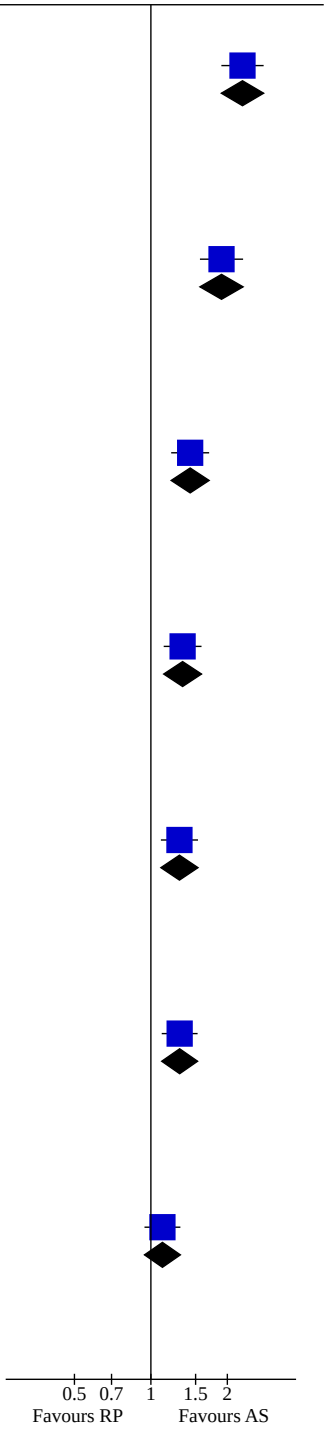
Analysis 2.29. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 29: Sexual function: EPIC sexual bother subscale score

Study or Subgroup	Radical prostatectomy Mean	SD	Total	Active monitoring Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.29.1 6 months								
ProtecT	38.7	35	351	66.9	35.3	327	100.0%	-28.20 [-33.50 , -22.90]
Subtotal (95% CI)			**351**			**327**	**100.0%**	**-28.20 [-33.50 , -22.90]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 10.44 (P < 0.00001)								
2.29.2 12 months								
ProtecT	44.5	34.1	353	67.8	34.3	335	100.0%	-23.30 [-28.41 , -18.19]
Subtotal (95% CI)			**353**			**335**	**100.0%**	**-23.30 [-28.41 , -18.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 8.93 (P < 0.00001)								
2.29.3 24 months								
ProtecT	46.8	33.1	392	62.2	35.4	373	100.0%	-15.40 [-20.26 , -10.54]
Subtotal (95% CI)			**392**			**373**	**100.0%**	**-15.40 [-20.26 , -10.54]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.21 (P < 0.00001)								
2.29.4 36 months								
ProtecT	49.6	34.8	413	60.7	36.3	414	100.0%	-11.10 [-15.95 , -6.25]
Subtotal (95% CI)			**413**			**414**	**100.0%**	**-11.10 [-15.95 , -6.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.49 (P < 0.00001)								
2.29.5 48 months								
ProtecT	50.4	34.2	443	60.4	35.8	433	100.0%	-10.00 [-14.64 , -5.36]
Subtotal (95% CI)			**443**			**433**	**100.0%**	**-10.00 [-14.64 , -5.36]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.23 (P < 0.0001)								
2.29.6 60 months								
ProtecT	52.6	35.1	456	60.1	36.3	441	100.0%	-7.50 [-12.18 , -2.82]
Subtotal (95% CI)			**456**			**441**	**100.0%**	**-7.50 [-12.18 , -2.82]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.14 (P = 0.002)								
2.29.7 72 months								
ProtecT	51.4	35.5	448	57.9	36.6	434	100.0%	-6.50 [-11.26 , -1.74]
Subtotal (95% CI)			**448**			**434**	**100.0%**	**-6.50 [-11.26 , -1.74]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.68 (P = 0.007)								
Test for subgroup differences: Chi^2 = 61.83, df = 6 (P < 0.00001), I^2 = 90.3%								



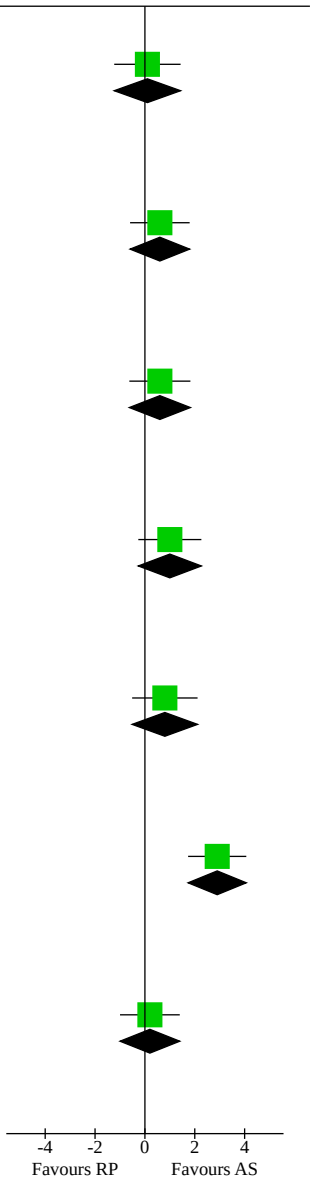
Analysis 2.30. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 30: Sexual function: moderate/severe impact of sexual dysfunction on quality of life

Study or Subgroup	Radical prostatectomy Events	Total	Active monitoring Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.30.1 6 months						
ProtecT	226	355	91	328	100.0%	2.29 [1.89 , 2.78]
Subtotal (95% CI)		**355**		**328**	**100.0%**	**2.29 [1.89 , 2.78]**
Total events:	226		91			
Heterogeneity: Not applicable						
Test for overall effect: Z = 8.50 (P < 0.00001)						
2.30.2 12 months						
ProtecT	191	355	95	335	100.0%	1.90 [1.56 , 2.31]
Subtotal (95% CI)		**355**		**335**	**100.0%**	**1.90 [1.56 , 2.31]**
Total events:	191		95			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.42 (P < 0.00001)						
2.30.3 24 months						
ProtecT	194	395	129	375	100.0%	1.43 [1.20 , 1.70]
Subtotal (95% CI)		**395**		**375**	**100.0%**	**1.43 [1.20 , 1.70]**
Total events:	194		129			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.06 (P < 0.0001)						
2.30.4 36 months						
ProtecT	188	417	140	414	100.0%	1.33 [1.12 , 1.58]
Subtotal (95% CI)		**417**		**414**	**100.0%**	**1.33 [1.12 , 1.58]**
Total events:	188		140			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.29 (P = 0.001)						
2.30.5 48 months						
ProtecT	197	451	147	436	100.0%	1.30 [1.09 , 1.53]
Subtotal (95% CI)		**451**		**436**	**100.0%**	**1.30 [1.09 , 1.53]**
Total events:	197		147			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.02 (P = 0.003)						
2.30.6 60 months						
ProtecT	208	462	154	444	100.0%	1.30 [1.10 , 1.53]
Subtotal (95% CI)		**462**		**444**	**100.0%**	**1.30 [1.10 , 1.53]**
Total events:	208		154			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.14 (P = 0.002)						
2.30.7 72 months						
ProtecT	190	457	164	438	100.0%	1.11 [0.94 , 1.31]
Subtotal (95% CI)		**457**		**438**	**100.0%**	**1.11 [0.94 , 1.31]**
Total events:	190		164			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.26 (P = 0.21)						
Test for subgroup differences: Chi^2 = 44.04, df = 6 (P < 0.00001), I^2 = 86.4%						



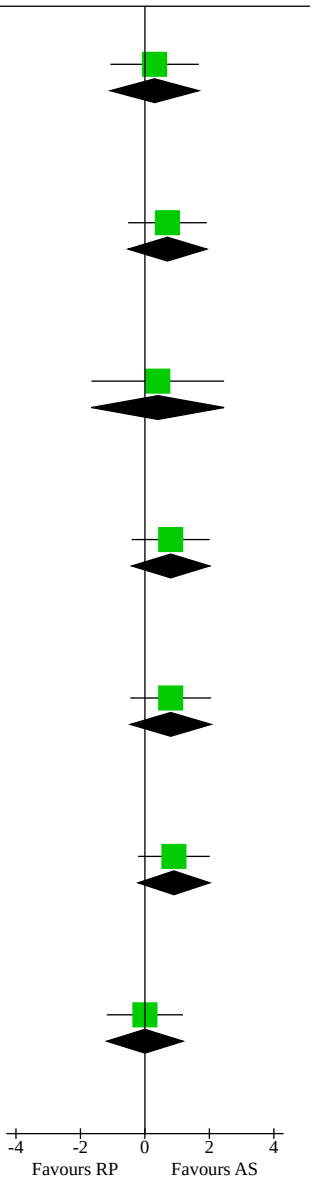
Analysis 2.31. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 31: Bowel function: EPIC bowel summary score

Study or Subgroup	Radical prostatectomy Mean	SD	Total	Active monitoring Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.31.1 6 months								
ProtecT	92.9	9	363	92.8	9.1	348	100.0%	0.10 [-1.23 , 1.43]
Subtotal (95% CI)			**363**			**348**	**100.0%**	**0.10 [-1.23 , 1.43]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.15 (P = 0.88)								
2.31.2 12 months								
ProtecT	94	7.7	362	93.4	8.6	356	100.0%	0.60 [-0.59 , 1.79]
Subtotal (95% CI)			**362**			**356**	**100.0%**	**0.60 [-0.59 , 1.79]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.98 (P = 0.32)								
2.31.3 24 months								
ProtecT	93.8	8.2	405	93.2	9.4	394	100.0%	0.60 [-0.62 , 1.82]
Subtotal (95% CI)			**405**			**394**	**100.0%**	**0.60 [-0.62 , 1.82]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.96 (P = 0.34)								
2.31.4 36 months								
ProtecT	93.8	8	436	92.8	10.8	433	100.0%	1.00 [-0.26 , 2.26]
Subtotal (95% CI)			**436**			**433**	**100.0%**	**1.00 [-0.26 , 2.26]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.55 (P = 0.12)								
2.31.5 48 months								
ProtecT	93.7	8.9	458	92.9	11.2	456	100.0%	0.80 [-0.51 , 2.11]
Subtotal (95% CI)			**458**			**456**	**100.0%**	**0.80 [-0.51 , 2.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.20 (P = 0.23)								
2.31.6 60 months								
ProtecT	94	7.9	469	91.1	10.1	461	100.0%	2.90 [1.73 , 4.07]
Subtotal (95% CI)			**469**			**461**	**100.0%**	**2.90 [1.73 , 4.07]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.87 (P < 0.00001)								
2.31.7 72 months								
ProtecT	93.2	8.7	463	93	9.8	457	100.0%	0.20 [-1.00 , 1.40]
Subtotal (95% CI)			**463**			**457**	**100.0%**	**0.20 [-1.00 , 1.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.33 (P = 0.74)								
Test for subgroup differences: Chi² = 14.49, df = 6 (P = 0.02), I² = 58.6%								



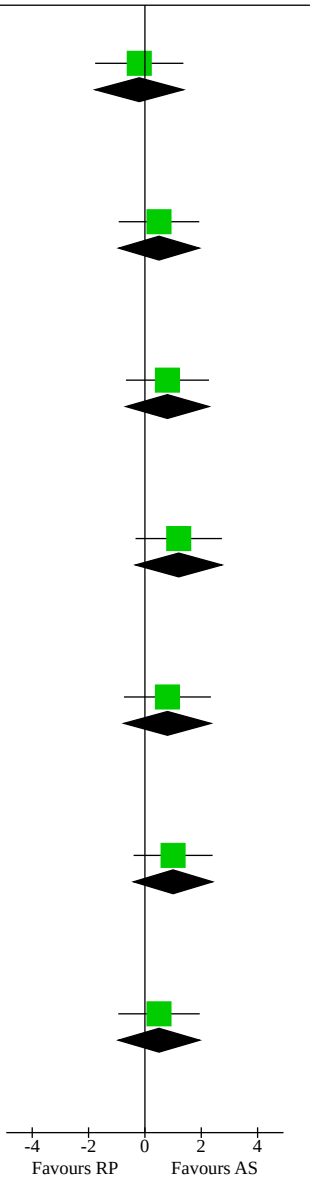
Analysis 2.32. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 32: Bowel function: EPIC bowel function subscale score

Study or Subgroup	Radical prostatectomy Mean	SD	Total	Active monitoring Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.32.1 6 months								
ProtecT	91.7	8.8	363	91.4	9.8	348	100.0%	0.30 [-1.07 , 1.67]
Subtotal (95% CI)			**363**			**348**	**100.0%**	**0.30 [-1.07 , 1.67]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.43 (P = 0.67)								
2.32.2 12 months								
ProtecT	92.8	8.1	363	92.1	8.6	357	100.0%	0.70 [-0.52 , 1.92]
Subtotal (95% CI)			**363**			**357**	**100.0%**	**0.70 [-0.52 , 1.92]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.12 (P = 0.26)								
2.32.3 24 months								
ProtecT	92.6	8.5	406	92.2	19.1	395	100.0%	0.40 [-1.66 , 2.46]
Subtotal (95% CI)			**406**			**395**	**100.0%**	**0.40 [-1.66 , 2.46]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.38 (P = 0.70)								
2.32.4 36 months								
ProtecT	92.7	8.1	437	91.9	10	435	100.0%	0.80 [-0.41 , 2.01]
Subtotal (95% CI)			**437**			**435**	**100.0%**	**0.80 [-0.41 , 2.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.30 (P = 0.19)								
2.32.5 48 months								
ProtecT	93	8.4	458	92.2	10.8	459	100.0%	0.80 [-0.45 , 2.05]
Subtotal (95% CI)			**458**			**459**	**100.0%**	**0.80 [-0.45 , 2.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.25 (P = 0.21)								
2.32.6 60 months								
ProtecT	92.9	7.7	469	92	9.5	461	100.0%	0.90 [-0.21 , 2.01]
Subtotal (95% CI)			**469**			**461**	**100.0%**	**0.90 [-0.21 , 2.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.59 (P = 0.11)								
2.32.7 72 months								
ProtecT	92.3	8.6	463	92.3	9.7	461	100.0%	0.00 [-1.18 , 1.18]
Subtotal (95% CI)			**463**			**461**	**100.0%**	**0.00 [-1.18 , 1.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Test for subgroup differences: Chi² = 1.71, df = 6 (P = 0.94), I² = 0%								



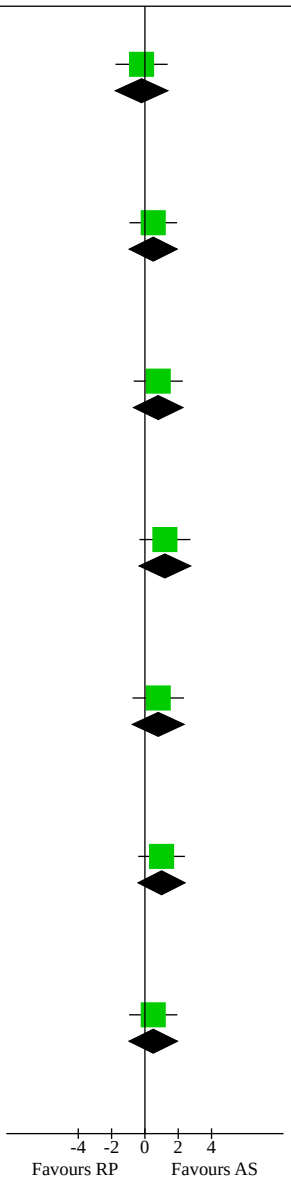
Analysis 2.33. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 33: Bowel function: EPIC bowel bother subscale score

Study or Subgroup	Radical prostatectomy Mean	SD	Total	Active monitoring Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.33.1 6 months								
ProtecT	94	10.7	363	94.2	10.6	348	100.0%	-0.20 [-1.77 , 1.37]
Subtotal (95% CI)			**363**			**348**	**100.0%**	**-0.20 [-1.77 , 1.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.25 (P = 0.80)								
2.33.2 12 months								
ProtecT	95.2	9.1	363	94.7	10.4	356	100.0%	0.50 [-0.93 , 1.93]
Subtotal (95% CI)			**363**			**356**	**100.0%**	**0.50 [-0.93 , 1.93]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.69 (P = 0.49)								
2.33.3 24 months								
ProtecT	95	9.4	405	94.2	11.7	394	100.0%	0.80 [-0.67 , 2.27]
Subtotal (95% CI)			**405**			**394**	**100.0%**	**0.80 [-0.67 , 2.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.06 (P = 0.29)								
2.33.4 36 months								
ProtecT	94.9	9.8	439	93.7	13.1	437	100.0%	1.20 [-0.33 , 2.73]
Subtotal (95% CI)			**439**			**437**	**100.0%**	**1.20 [-0.33 , 2.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.53 (P = 0.12)								
2.33.5 48 months								
ProtecT	94.6	11.1	459	93.8	12.7	459	100.0%	0.80 [-0.74 , 2.34]
Subtotal (95% CI)			**459**			**459**	**100.0%**	**0.80 [-0.74 , 2.34]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.02 (P = 0.31)								
2.33.6 60 months								
ProtecT	95.1	9.6	473	94.1	12.2	470	100.0%	1.00 [-0.40 , 2.40]
Subtotal (95% CI)			**473**			**470**	**100.0%**	**1.00 [-0.40 , 2.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.40 (P = 0.16)								
2.33.7 72 months								
ProtecT	94.2	10.8	465	93.7	11.6	460	100.0%	0.50 [-0.94 , 1.94]
Subtotal (95% CI)			**465**			**460**	**100.0%**	**0.50 [-0.94 , 1.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.68 (P = 0.50)								
Test for subgroup differences: Chi² = 2.02, df = 6 (P = 0.92), I² = 0%								



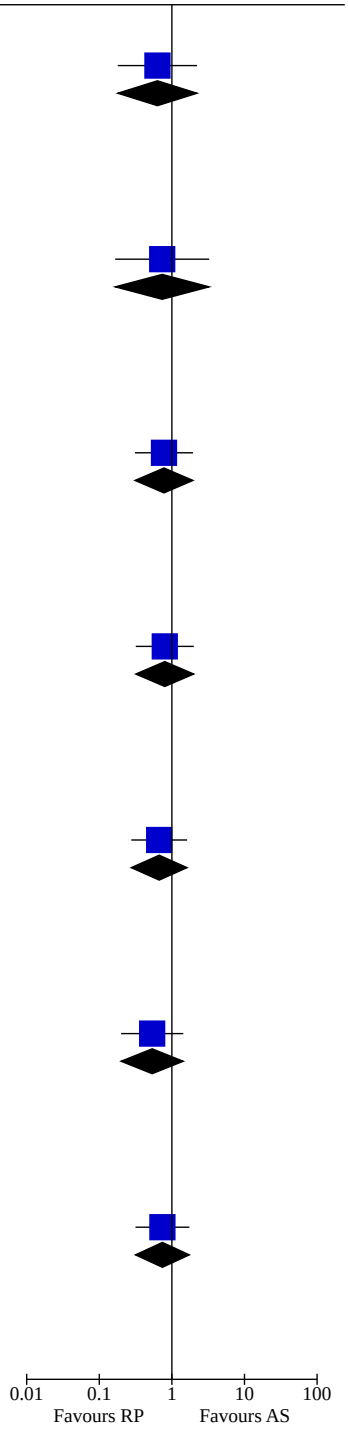
Analysis 2.34. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 34: Bowel function: EPIC bowel bother subscale score

Study or Subgroup	Radical prostatectomy Mean	SD	Total	Active monitoring Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.34.1 6 months								
ProtecT	94	10.7	363	94.2	10.6	348	100.0%	-0.20 [-1.77 , 1.37]
Subtotal (95% CI)			**363**			**348**	**100.0%**	**-0.20 [-1.77 , 1.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.25 (P = 0.80)								
2.34.2 12 months								
ProtecT	95.2	9.1	363	94.7	10.4	356	100.0%	0.50 [-0.93 , 1.93]
Subtotal (95% CI)			**363**			**356**	**100.0%**	**0.50 [-0.93 , 1.93]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.69 (P = 0.49)								
2.34.3 24 months								
ProtecT	95	9.4	405	94.2	11.7	394	100.0%	0.80 [-0.67 , 2.27]
Subtotal (95% CI)			**405**			**394**	**100.0%**	**0.80 [-0.67 , 2.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.06 (P = 0.29)								
2.34.4 36 months								
ProtecT	94.9	9.8	439	93.7	13.1	437	100.0%	1.20 [-0.33 , 2.73]
Subtotal (95% CI)			**439**			**437**	**100.0%**	**1.20 [-0.33 , 2.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.53 (P = 0.12)								
2.34.5 48 months								
ProtecT	94.6	11.1	459	93.8	12.7	459	100.0%	0.80 [-0.74 , 2.34]
Subtotal (95% CI)			**459**			**459**	**100.0%**	**0.80 [-0.74 , 2.34]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.02 (P = 0.31)								
2.34.6 60 months								
ProtecT	95.1	9.6	473	94.1	12.2	470	100.0%	1.00 [-0.40 , 2.40]
Subtotal (95% CI)			**473**			**470**	**100.0%**	**1.00 [-0.40 , 2.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.40 (P = 0.16)								
2.34.7 72 months								
ProtecT	94.2	10.8	465	93.7	11.6	460	100.0%	0.50 [-0.94 , 1.94]
Subtotal (95% CI)			**465**			**460**	**100.0%**	**0.50 [-0.94 , 1.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.68 (P = 0.50)								
Test for subgroup differences: $Chi^2 = 2.02$, df = 6 (P = 0.92), $I^2 = 0\%$								



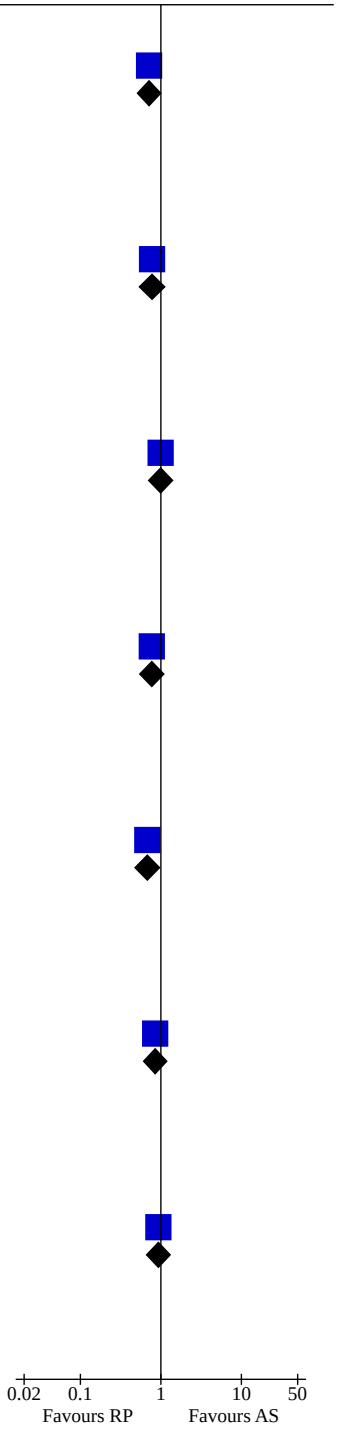
Analysis 2.35. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 35: Bowel function: faecal incontinence more than once per week

Study or Subgroup	Radical prostatectomy Events	Total	Active monitoring Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.35.1 6 months						
ProtecT	4	367	6	348	100.0%	0.63 [0.18 , 2.22]
Subtotal (95% CI)		**367**		**348**	**100.0%**	**0.63 [0.18 , 2.22]**
Total events:	4		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
2.35.2 12 months						
ProtecT	3	363	4	356	100.0%	0.74 [0.17 , 3.26]
Subtotal (95% CI)		**363**		**356**	**100.0%**	**0.74 [0.17 , 3.26]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
2.35.3 24 months						
ProtecT	8	406	10	395	100.0%	0.78 [0.31 , 1.95]
Subtotal (95% CI)		**406**		**395**	**100.0%**	**0.78 [0.31 , 1.95]**
Total events:	8		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.59)						
2.35.4 36 months						
ProtecT	8	437	10	436	100.0%	0.80 [0.32 , 2.00]
Subtotal (95% CI)		**437**		**436**	**100.0%**	**0.80 [0.32 , 2.00]**
Total events:	8		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
2.35.5 48 months						
ProtecT	8	459	12	460	100.0%	0.67 [0.28 , 1.62]
Subtotal (95% CI)		**459**		**460**	**100.0%**	**0.67 [0.28 , 1.62]**
Total events:	8		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.89 (P = 0.37)						
2.35.6 60 months						
ProtecT	6	472	11	463	100.0%	0.54 [0.20 , 1.43]
Subtotal (95% CI)		**472**		**463**	**100.0%**	**0.54 [0.20 , 1.43]**
Total events:	6		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.24 (P = 0.21)						
2.35.7 72 months						
ProtecT	9	468	12	462	100.0%	0.74 [0.31 , 1.74]
Subtotal (95% CI)		**468**		**462**	**100.0%**	**0.74 [0.31 , 1.74]**
Total events:	9		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Test for subgroup differences: Chi^2 = 0.47, df = 6 (P = 1.00), I^2 = 0%						



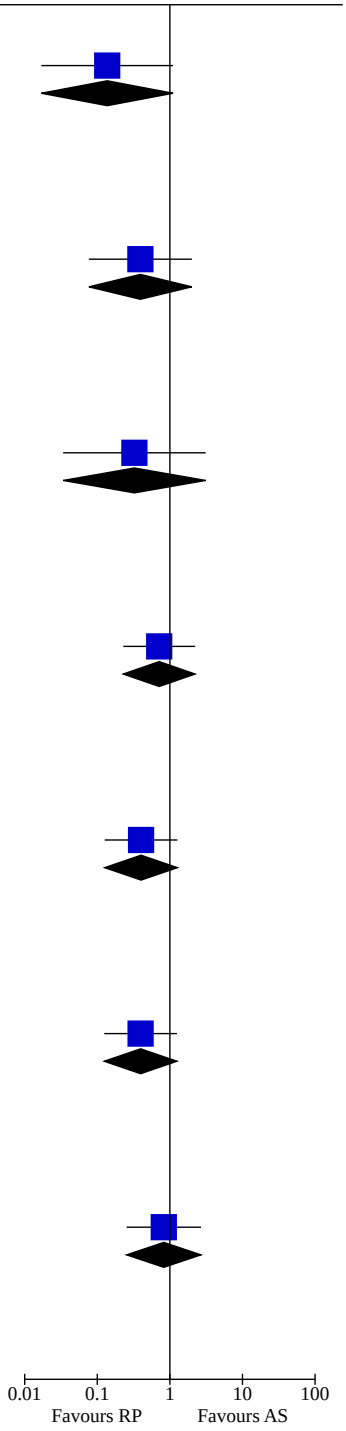
Analysis 2.36. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 36: Bowel function: EPIC: loose stools about half the time or more frequently

Study or Subgroup	Radical prostatectomy Events	Total	Active monitoring Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.36.1 6 months						
ProtecT	51	366	68	348	100.0%	0.71 [0.51 , 0.99]
Subtotal (95% CI)		**366**		**348**	**100.0%**	**0.71 [0.51 , 0.99]**
Total events:	51		68			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.00 (P = 0.05)						
2.36.2 12 months						
ProtecT	45	363	57	357	100.0%	0.78 [0.54 , 1.12]
Subtotal (95% CI)		**363**		**357**	**100.0%**	**0.78 [0.54 , 1.12]**
Total events:	45		57			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.37 (P = 0.17)						
2.36.3 24 months						
ProtecT	57	406	56	396	100.0%	0.99 [0.71 , 1.40]
Subtotal (95% CI)		**406**		**396**	**100.0%**	**0.99 [0.71 , 1.40]**
Total events:	57		56			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.04 (P = 0.97)						
2.36.4 36 months						
ProtecT	50	435	65	436	100.0%	0.77 [0.55 , 1.09]
Subtotal (95% CI)		**435**		**436**	**100.0%**	**0.77 [0.55 , 1.09]**
Total events:	50		65			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.48 (P = 0.14)						
2.36.5 48 months						
ProtecT	46	460	68	461	100.0%	0.68 [0.48 , 0.96]
Subtotal (95% CI)		**460**		**461**	**100.0%**	**0.68 [0.48 , 0.96]**
Total events:	46		68			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.17 (P = 0.03)						
2.36.6 60 months						
ProtecT	57	473	66	465	100.0%	0.85 [0.61 , 1.18]
Subtotal (95% CI)		**473**		**465**	**100.0%**	**0.85 [0.61 , 1.18]**
Total events:	57		66			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
2.36.7 72 months						
ProtecT	57	468	61	466	100.0%	0.93 [0.66 , 1.30]
Subtotal (95% CI)		**468**		**466**	**100.0%**	**0.93 [0.66 , 1.30]**
Total events:	57		61			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.42 (P = 0.68)						
Test for subgroup differences: $Chi^2 = 3.77$, df = 6 (P = 0.71), $I^2 = 0\%$						



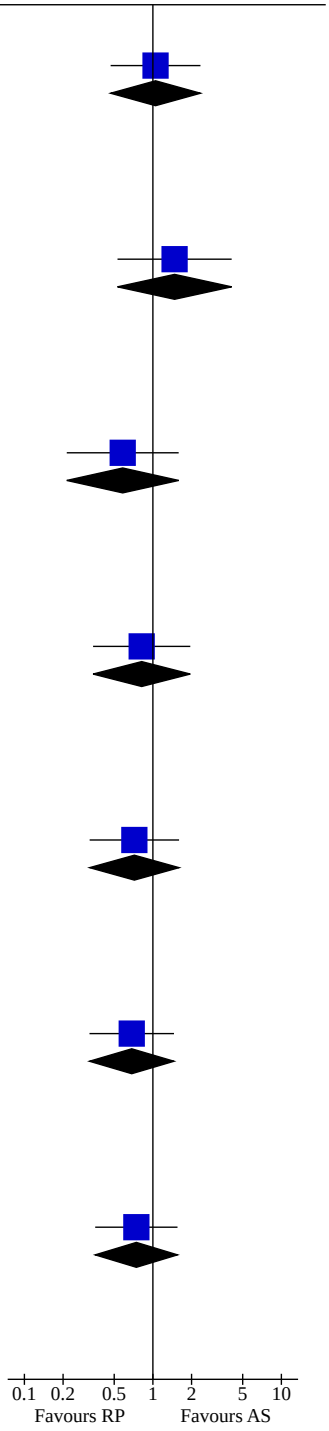
Analysis 2.37. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 37: Bowel function: EPIC: bloody stools about half the time or more frequently

Study or Subgroup	Radical prostatectomy Events	Total	Active monitoring Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.37.1 6 months						
ProtecT	1	363	7	348	100.0%	0.14 [0.02 , 1.11]
Subtotal (95% CI)		**363**		**348**	**100.0%**	**0.14 [0.02 , 1.11]**
Total events:	1		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						
2.37.2 12 months						
ProtecT	2	364	5	357	100.0%	0.39 [0.08 , 2.01]
Subtotal (95% CI)		**364**		**357**	**100.0%**	**0.39 [0.08 , 2.01]**
Total events:	2		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						
2.37.3 24 months						
ProtecT	1	407	3	396	100.0%	0.32 [0.03 , 3.10]
Subtotal (95% CI)		**407**		**396**	**100.0%**	**0.32 [0.03 , 3.10]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						
2.37.4 36 months						
ProtecT	5	436	7	435	100.0%	0.71 [0.23 , 2.23]
Subtotal (95% CI)		**436**		**435**	**100.0%**	**0.71 [0.23 , 2.23]**
Total events:	5		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
2.37.5 48 months						
ProtecT	4	459	10	460	100.0%	0.40 [0.13 , 1.27]
Subtotal (95% CI)		**459**		**460**	**100.0%**	**0.40 [0.13 , 1.27]**
Total events:	4		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						
2.37.6 60 months						
ProtecT	4	471	10	465	100.0%	0.39 [0.12 , 1.25]
Subtotal (95% CI)		**471**		**465**	**100.0%**	**0.39 [0.12 , 1.25]**
Total events:	4		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.58 (P = 0.11)						
2.37.7 72 months						
ProtecT	5	470	6	465	100.0%	0.82 [0.25 , 2.68]
Subtotal (95% CI)		**470**		**465**	**100.0%**	**0.82 [0.25 , 2.68]**
Total events:	5		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
Test for subgroup differences: Chi^2 = 3.03, df = 6 (P = 0.81), I^2 = 0%						



Analysis 2.38. Comparison 2: Radical prostatectomy versus active monitoring, Outcome 38: Bowel function: EPIC: moderate/severe impact of bowel habits on quality of life

Study or Subgroup	Radical prostatectomy Events	Total	Active monitoring Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.38.1 6 months						
ProtecT	12	362	11	348	100.0%	1.05 [0.47 , 2.35]
Subtotal (95% CI)		**362**		**348**	**100.0%**	**1.05 [0.47 , 2.35]**
Total events:	12		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.12 (P = 0.91)						
2.38.2 12 months						
ProtecT	9	364	6	358	100.0%	1.48 [0.53 , 4.10]
Subtotal (95% CI)		**364**		**358**	**100.0%**	**1.48 [0.53 , 4.10]**
Total events:	9		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.75 (P = 0.46)						
2.38.3 24 months						
ProtecT	6	407	10	395	100.0%	0.58 [0.21 , 1.59]
Subtotal (95% CI)		**407**		**395**	**100.0%**	**0.58 [0.21 , 1.59]**
Total events:	6		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
2.38.4 36 months						
ProtecT	9	439	11	439	100.0%	0.82 [0.34 , 1.95]
Subtotal (95% CI)		**439**		**439**	**100.0%**	**0.82 [0.34 , 1.95]**
Total events:	9		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						
2.38.5 48 months						
ProtecT	10	459	14	461	100.0%	0.72 [0.32 , 1.60]
Subtotal (95% CI)		**459**		**461**	**100.0%**	**0.72 [0.32 , 1.60]**
Total events:	10		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.81 (P = 0.42)						
2.38.6 60 months						
ProtecT	11	473	16	471	100.0%	0.68 [0.32 , 1.46]
Subtotal (95% CI)		**473**		**471**	**100.0%**	**0.68 [0.32 , 1.46]**
Total events:	11		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						
2.38.7 72 months						
ProtecT	12	467	16	463	100.0%	0.74 [0.36 , 1.55]
Subtotal (95% CI)		**467**		**463**	**100.0%**	**0.74 [0.36 , 1.55]**
Total events:	12		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.79 (P = 0.43)						
Test for subgroup differences: Chi^2 = 2.46, df = 6 (P = 0.87), I^2 = 0%						

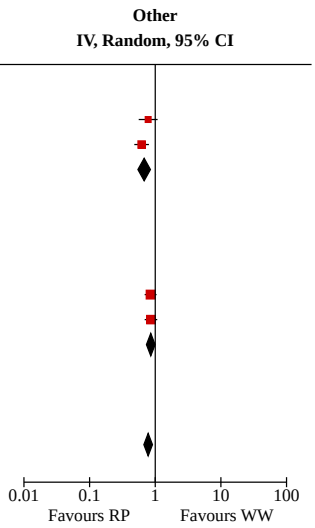


Comparison 3. Subgroup analyses 1 - younger than 65 years versus 65 years or older: radical prostatectomy versus watchful waiting

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Time to death from any cause	2	1426	Hazard Ratio (IV, Random, 95% CI)	0.78 [0.67, 0.91]
3.1.1 Younger than 65 years	2	576	Hazard Ratio (IV, Random, 95% CI)	0.68 [0.54, 0.84]
3.1.2 65 years or older	2	850	Hazard Ratio (IV, Random, 95% CI)	0.85 [0.73, 0.99]
3.2 Time to death from prostate cancer	2	1426	Hazard Ratio (IV, Random, 95% CI)	0.57 [0.45, 0.73]
3.2.1 Younger than 65 years	2	576	Hazard Ratio (IV, Random, 95% CI)	0.52 [0.37, 0.74]
3.2.2 65 years or older	2	850	Hazard Ratio (IV, Random, 95% CI)	0.63 [0.44, 0.90]
3.3 Time to disease progression	1	695	Hazard Ratio (IV, Random, 95% CI)	0.48 [0.32, 0.74]
3.3.1 Younger than 65 years	1	323	Hazard Ratio (IV, Random, 95% CI)	0.39 [0.29, 0.52]
3.3.2 65 years or older	1	372	Hazard Ratio (IV, Random, 95% CI)	0.60 [0.45, 0.80]
3.4 Time to metastatic disease	1	695	Hazard Ratio (IV, Random, 95% CI)	0.54 [0.42, 0.70]
3.4.1 Younger than 65 years	1	323	Hazard Ratio (IV, Random, 95% CI)	0.49 [0.34, 0.71]
3.4.2 65 years or older	1	372	Hazard Ratio (IV, Random, 95% CI)	0.59 [0.41, 0.85]

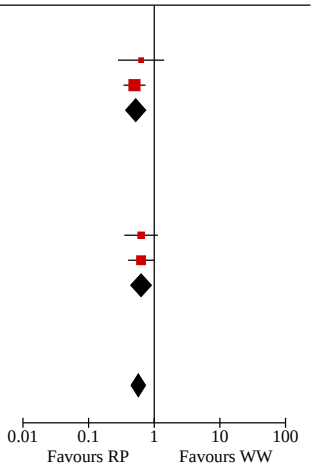
Analysis 3.1. Comparison 3: Subgroup analyses 1 - younger than 65 years versus 65 years or older: radical prostatectomy versus watchful waiting, Outcome 1: Time to death from any cause

Study or Subgroup	log[Other]	SE	Radical prostatectomy Total	Watchful waiting Total	Weight	Other IV, Random, 95% CI
3.1.1 Younger than 65 years						
PIVOT	-0.2485	0.1691	122	131	16.3%	0.78 [0.56 , 1.09]
SPCG-4	-0.478	0.1306	157	166	23.8%	0.62 [0.48 , 0.80]
Subtotal (95% CI)			**279**	**297**	**40.1%**	**0.68 [0.54 , 0.84]**
Heterogeneity: Tau² = 0.00; Chi² = 1.15, df = 1 (P = 0.28); I² = 13%						
Test for overall effect: Z = 3.47 (P = 0.0005)						
3.1.2 65 years or older						
PIVOT	-0.1625	0.1064	242	236	30.9%	0.85 [0.69 , 1.05]
SPCG-4	-0.1508	0.1124	190	182	29.0%	0.86 [0.69 , 1.07]
Subtotal (95% CI)			**432**	**418**	**59.9%**	**0.85 [0.73 , 0.99]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%						
Test for overall effect: Z = 2.03 (P = 0.04)						
Total (95% CI)			**711**	**715**	**100.0%**	**0.78 [0.67 , 0.91]**
Heterogeneity: Tau² = 0.01; Chi² = 4.48, df = 3 (P = 0.21); I² = 33%						
Test for overall effect: Z = 3.22 (P = 0.001)						
Test for subgroup differences: Chi² = 2.89, df = 1 (P = 0.09), I² = 65.4%						



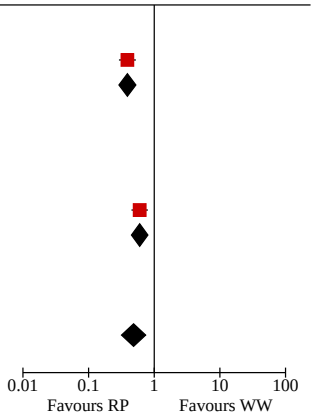
Analysis 3.2. Comparison 3: Subgroup analyses 1 - younger than 65 years versus 65 years or older: radical prostatectomy versus watchful waiting, Outcome 2: Time to death from prostate cancer

Study or Subgroup	log[Other]	SE	Radical prostatectomy Total	Watchful waiting Total	Weight	Other IV, Random, 95% CI
3.2.1 Younger than 65 years						
PIVOT	-0.462	0.4137	122	131	9.5%	0.63 [0.28 , 1.42]
SPCG-4	-0.6931	0.1968	157	166	42.1%	0.50 [0.34 , 0.74]
Subtotal (95% CI)			**279**	**297**	**51.6%**	**0.52 [0.37 , 0.74]**
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.61); I² = 0%						
Test for overall effect: Z = 3.66 (P = 0.0003)						
3.2.2 65 years or older						
PIVOT	-0.462	0.2999	242	236	18.1%	0.63 [0.35 , 1.13]
SPCG-4	-0.462	0.2318	190	182	30.3%	0.63 [0.40 , 0.99]
Subtotal (95% CI)			**432**	**418**	**48.4%**	**0.63 [0.44 , 0.90]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 2.52 (P = 0.01)						
Total (95% CI)			**711**	**715**	**100.0%**	**0.57 [0.45 , 0.73]**
Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 3 (P = 0.85); I² = 0%						
Test for overall effect: Z = 4.38 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.54, df = 1 (P = 0.46), I² = 0%						

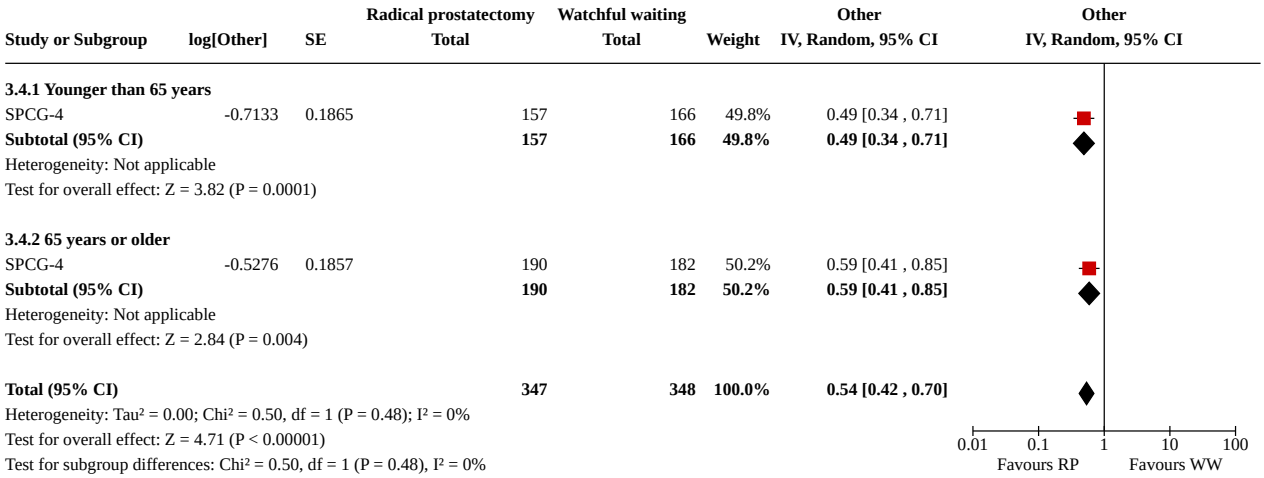


Analysis 3.3. Comparison 3: Subgroup analyses 1 - younger than 65 years versus 65 years or older: radical prostatectomy versus watchful waiting, Outcome 3: Time to disease progression

Study or Subgroup	log[Other]	SE	Radical prostatectomy Total	Watchful waiting Total	Weight	Other IV, Random, 95% CI
3.3.1 Younger than 65 years						
SPCG-4	-0.9416	0.1512	157	166	49.6%	0.39 [0.29 , 0.52]
Subtotal (95% CI)			**157**	**166**	**49.6%**	**0.39 [0.29 , 0.52]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.23 (P < 0.00001)						
3.3.2 65 years or older						
SPCG-4	-0.5108	0.1468	190	182	50.4%	0.60 [0.45 , 0.80]
Subtotal (95% CI)			**190**	**182**	**50.4%**	**0.60 [0.45 , 0.80]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.48 (P = 0.0005)						
Total (95% CI)			**347**	**348**	**100.0%**	**0.48 [0.32 , 0.74]**
Heterogeneity: Tau² = 0.07; Chi² = 4.18, df = 1 (P = 0.04); I² = 76%						
Test for overall effect: Z = 3.36 (P = 0.0008)						
Test for subgroup differences: Chi² = 4.18, df = 1 (P = 0.04), I² = 76.1%						



Analysis 3.4. Comparison 3: Subgroup analyses 1 - younger than 65 years versus 65 years or older: radical prostatectomy versus watchful waiting, Outcome 4: Time to metastatic disease

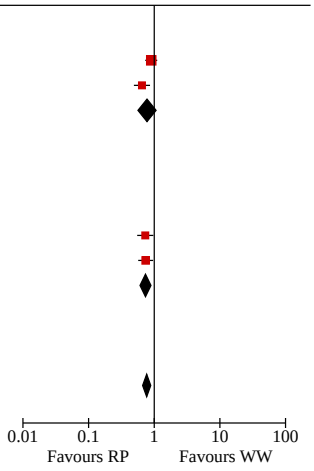


Comparison 4. Subgroup analyses 2 - PSA 10 ng/mL or lower versus more than 10 ng/mL: radical prostatectomy versus watchful waiting

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Time to death from any cause	2	1415	Hazard Ratio (IV, Random, 95% CI)	0.77 [0.67, 0.88]
4.1.1 PSA 10 ng/mL or lower	2	840	Hazard Ratio (IV, Random, 95% CI)	0.78 [0.56, 1.07]
4.1.2 PSA more than 10 ng/mL	2	575	Hazard Ratio (IV, Random, 95% CI)	0.74 [0.61, 0.89]
4.2 Time to death from prostate cancer	2	1415	Hazard Ratio (IV, Random, 95% CI)	0.57 [0.44, 0.75]
4.2.1 PSA 10 ng/mL or lower	2	840	Hazard Ratio (IV, Random, 95% CI)	0.55 [0.37, 0.82]
4.2.2 PSA more than 10 ng/mL	2	575	Hazard Ratio (IV, Random, 95% CI)	0.59 [0.42, 0.84]
4.3 Time to metastatic disease	1	685	Hazard Ratio (IV, Random, 95% CI)	0.56 [0.43, 0.74]
4.3.1 PSA 10 ng/mL or lower	1	361	Hazard Ratio (IV, Random, 95% CI)	0.48 [0.31, 0.74]
4.3.2 PSA more than 10 ng/mL	1	324	Hazard Ratio (IV, Random, 95% CI)	0.62 [0.44, 0.87]

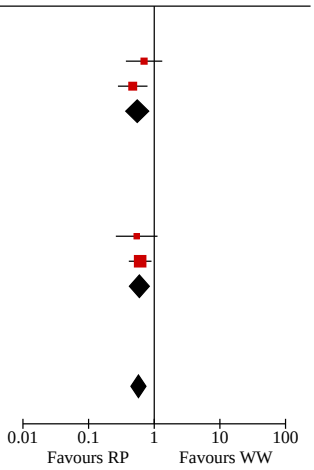
Analysis 4.1. Comparison 4: Subgroup analyses 2 - PSA 10 ng/mL or lower versus more than 10 ng/mL: radical prostatectomy versus watchful waiting, Outcome 1: Time to death from any cause

Study or Subgroup	log[Other]	SE	Radical prostatectomy Total	Watchful waiting Total	Weight	Other IV, Random, 95% CI
4.1.1 PSA 10 ng/mL or lower						
PIVOT	-0.1054	0.1068	238	241	33.8%	0.90 [0.73 , 1.11]
SPCG-4	-0.4308	0.1442	171	190	21.1%	0.65 [0.49 , 0.86]
Subtotal (95% CI)			**409**	**431**	**54.9%**	**0.78 [0.56 , 1.07]**
Heterogeneity: Tau² = 0.04; Chi² = 3.29, df = 1 (P = 0.07); I² = 70%						
Test for overall effect: Z = 1.57 (P = 0.12)						
4.1.2 PSA more than 10 ng/mL						
PIVOT	-0.3147	0.1445	126	125	21.0%	0.73 [0.55 , 0.97]
SPCG-4	-0.3011	0.1332	169	155	24.0%	0.74 [0.57 , 0.96]
Subtotal (95% CI)			**295**	**280**	**45.1%**	**0.74 [0.61 , 0.89]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.94); I² = 0%						
Test for overall effect: Z = 3.14 (P = 0.002)						
Total (95% CI)			**704**	**711**	**100.0%**	**0.77 [0.67 , 0.88]**
Heterogeneity: Tau² = 0.00; Chi² = 3.74, df = 3 (P = 0.29); I² = 20%						
Test for overall effect: Z = 3.65 (P = 0.0003)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%						

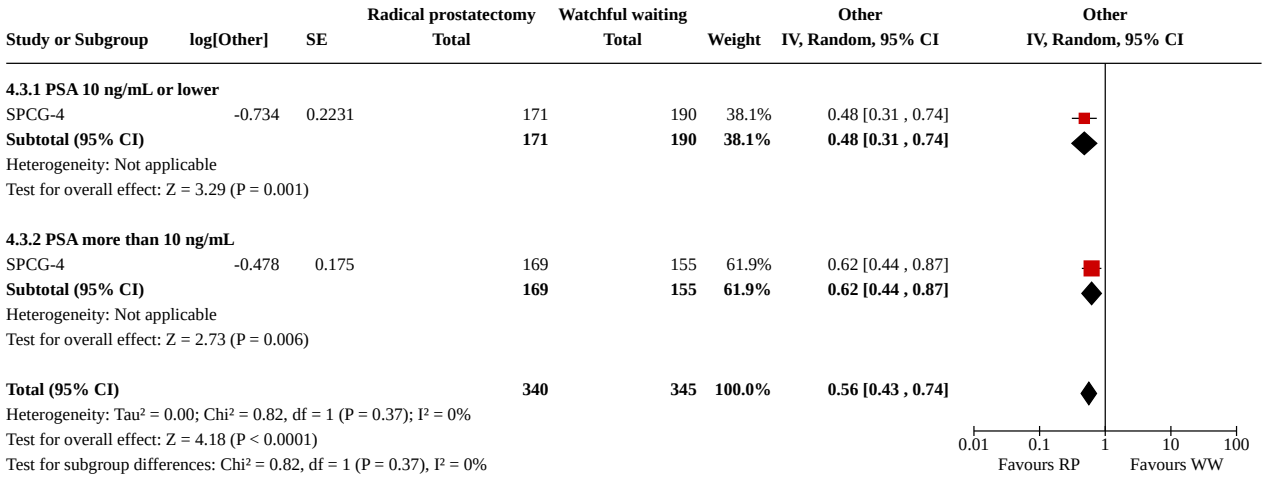


Analysis 4.2. Comparison 4: Subgroup analyses 2 - PSA 10 ng/mL or lower versus more than 10 ng/mL: radical prostatectomy versus watchful waiting, Outcome 2: Time to death from prostate cancer

Study or Subgroup	log[Other]	SE	Radical prostatectomy Total	Watchful waiting Total	Weight	Other IV, Random, 95% CI
4.2.1 PSA 10 ng/mL or lower						
PIVOT	-0.3567	0.3253	238	241	17.1%	0.70 [0.37 , 1.32]
SPCG-4	-0.755	0.2643	171	190	25.9%	0.47 [0.28 , 0.79]
Subtotal (95% CI)			**409**	**431**	**43.0%**	**0.55 [0.37 , 0.82]**
Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 1 (P = 0.34); I² = 0%						
Test for overall effect: Z = 2.91 (P = 0.004)						
4.2.2 PSA more than 10 ng/mL						
PIVOT	-0.6162	0.3729	126	125	13.0%	0.54 [0.26 , 1.12]
SPCG-4	-0.4943	0.2027	169	155	44.0%	0.61 [0.41 , 0.91]
Subtotal (95% CI)			**295**	**280**	**57.0%**	**0.59 [0.42 , 0.84]**
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.77); I² = 0%						
Test for overall effect: Z = 2.93 (P = 0.003)						
Total (95% CI)			**704**	**711**	**100.0%**	**0.57 [0.44 , 0.75]**
Heterogeneity: Tau² = 0.00; Chi² = 1.06, df = 3 (P = 0.79); I² = 0%						
Test for overall effect: Z = 4.12 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%						



Analysis 4.3. Comparison 4: Subgroup analyses 2 - PSA 10 ng/mL or lower versus more than 10 ng/mL: radical prostatectomy versus watchful waiting, Outcome 3: Time to metastatic disease

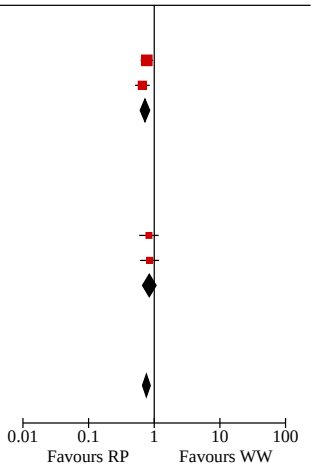


Comparison 5. Subgroup analyses 3 - Gleason score lower than 7 versus Gleason score 7 or higher: radical prostatectomy versus watchful waiting

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Time to death from any cause	2	1312	Hazard Ratio (IV, Random, 95% CI)	0.76 [0.66, 0.87]
5.1.1 Gleason score lower than 7	2	934	Hazard Ratio (IV, Random, 95% CI)	0.72 [0.61, 0.85]
5.1.2 Gleason score 7 or higher	2	378	Hazard Ratio (IV, Random, 95% CI)	0.84 [0.66, 1.07]
5.2 Time to death from prostate cancer	2	1312	Hazard Ratio (IV, Random, 95% CI)	0.65 [0.50, 0.84]
5.2.1 Gleason score lower than 7	2	934	Hazard Ratio (IV, Random, 95% CI)	0.51 [0.34, 0.76]
5.2.2 Gleason score 7 or higher	2	378	Hazard Ratio (IV, Random, 95% CI)	0.75 [0.57, 1.00]
5.3 Time to metastatic disease	1	613	Hazard Ratio (IV, Random, 95% CI)	0.54 [0.35, 0.85]
5.3.1 Gleason score lower than 7	1	419	Hazard Ratio (IV, Random, 95% CI)	0.43 [0.28, 0.66]
5.3.2 Gleason score 7 or higher	1	194	Hazard Ratio (IV, Random, 95% CI)	0.68 [0.45, 1.03]

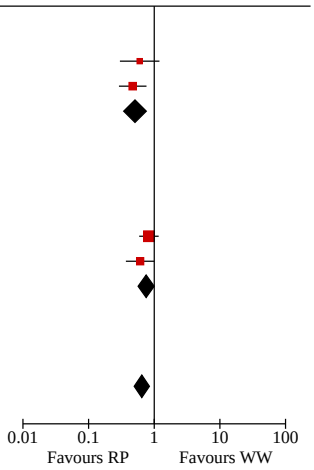
Analysis 5.1. Comparison 5: Subgroup analyses 3 - Gleason score lower than 7 versus Gleason score 7 or higher: radical prostatectomy versus watchful waiting, Outcome 1: Time to death from any cause

Study or Subgroup	log[Other]	SE	Radical prostatectomy Total	Watchful waiting Total	Weight	Other IV, Random, 95% CI
5.1.1 Gleason score lower than 7						
PIVOT	-0.2614	0.1105	254	261	39.4%	0.77 [0.62 , 0.96]
SPCG-4	-0.4155	0.1315	210	209	27.9%	0.66 [0.51 , 0.85]
Subtotal (95% CI)			**464**	**470**	**67.3%**	**0.72 [0.61 , 0.85]**
Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 1 (P = 0.37); I² = 0%						
Test for overall effect: Z = 3.84 (P = 0.0001)						
5.1.2 Gleason score 7 or higher						
PIVOT	-0.1863	0.1741	98	86	15.9%	0.83 [0.59 , 1.17]
SPCG-4	-0.1625	0.1693	91	103	16.8%	0.85 [0.61 , 1.18]
Subtotal (95% CI)			**189**	**189**	**32.7%**	**0.84 [0.66 , 1.07]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 1.43 (P = 0.15)						
Total (95% CI)			**653**	**659**	**100.0%**	**0.76 [0.66 , 0.87]**
Heterogeneity: Tau² = 0.00; Chi² = 1.86, df = 3 (P = 0.60); I² = 0%						
Test for overall effect: Z = 3.97 (P < 0.0001)						
Test for subgroup differences: Chi² = 1.04, df = 1 (P = 0.31), I² = 4.1%						

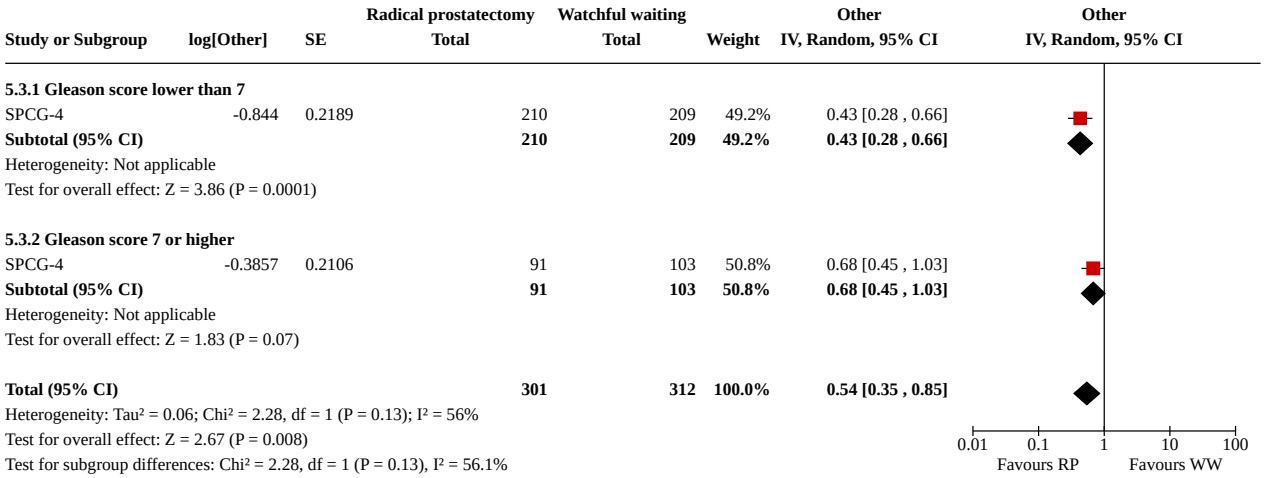


Analysis 5.2. Comparison 5: Subgroup analyses 3 - Gleason score lower than 7 versus Gleason score 7 or higher: radical prostatectomy versus watchful waiting, Outcome 2: Time to death from prostate cancer

Study or Subgroup	log[Other]	SE	Radical prostatectomy Total	Watchful waiting Total	Weight	Other IV, Random, 95% CI
5.2.1 Gleason score lower than 7						
PIVOT	-0.5108	0.3537	254	261	13.1%	0.60 [0.30 , 1.20]
SPCG-4	-0.755	0.2464	210	209	24.1%	0.47 [0.29 , 0.76]
Subtotal (95% CI)			**464**	**470**	**37.2%**	**0.51 [0.34 , 0.76]**
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%						
Test for overall effect: Z = 3.34 (P = 0.0008)						
5.2.2 Gleason score 7 or higher						
PIVOT	-0.1863	0.1741	98	86	40.0%	0.83 [0.59 , 1.17]
SPCG-4	-0.4943	0.2551	91	103	22.8%	0.61 [0.37 , 1.01]
Subtotal (95% CI)			**189**	**189**	**62.8%**	**0.75 [0.57 , 1.00]**
Heterogeneity: Tau² = 0.00; Chi² = 0.99, df = 1 (P = 0.32); I² = 0%						
Test for overall effect: Z = 1.98 (P = 0.05)						
Total (95% CI)			**653**	**659**	**100.0%**	**0.65 [0.50 , 0.84]**
Heterogeneity: Tau² = 0.02; Chi² = 3.80, df = 3 (P = 0.28); I² = 21%						
Test for overall effect: Z = 3.21 (P = 0.001)						
Test for subgroup differences: Chi² = 2.48, df = 1 (P = 0.11), I² = 59.7%						



Analysis 5.3. Comparison 5: Subgroup analyses 3 - Gleason score lower than 7 versus Gleason score 7 or higher: radical prostatectomy versus watchful waiting, Outcome 3: Time to metastatic disease

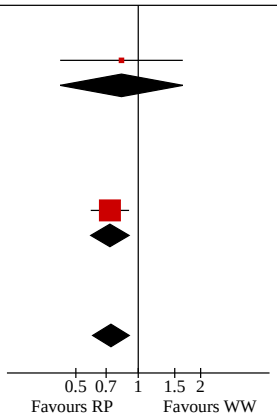


Comparison 6. Subgroup analyses 4 - clinical stage T1c versus clinical stage T2: radical prostatectomy versus watchful waiting

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Time to death from any cause	1	613	Hazard Ratio (IV, Random, 95% CI)	0.74 [0.60, 0.90]
6.1.1 Clinical stage T1c	1	419	Hazard Ratio (IV, Random, 95% CI)	0.83 [0.42, 1.64]
6.1.2 Clinical stage T2	1	194	Hazard Ratio (IV, Random, 95% CI)	0.73 [0.59, 0.90]
6.2 Time to death from prostate cancer	1	613	Hazard Ratio (IV, Random, 95% CI)	0.72 [0.59, 0.89]
6.2.1 Clinical stage T1c	1	419	Hazard Ratio (IV, Random, 95% CI)	0.39 [0.07, 2.17]
6.2.2 Clinical stage T2	1	194	Hazard Ratio (IV, Random, 95% CI)	0.73 [0.59, 0.90]
6.3 Time to metastatic disease	1	693	Hazard Ratio (IV, Random, 95% CI)	0.58 [0.45, 0.76]
6.3.1 Clinical stage T1c	1	164	Hazard Ratio (IV, Random, 95% CI)	0.43 [0.11, 1.68]
6.3.2 Clinical stage T2	1	529	Hazard Ratio (IV, Random, 95% CI)	0.59 [0.45, 0.77]

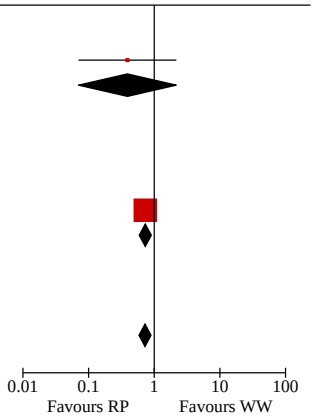
Analysis 6.1. Comparison 6: Subgroup analyses 4 - clinical stage T1c versus clinical stage T2: radical prostatectomy versus watchful waiting, Outcome 1: Time to death from any cause

Study or Subgroup	log[Other]	SE	Radical prostatectomy Total	Watchful waiting Total	Weight	Other IV, Random, 95% CI
6.1.1 Clinical stage T1c						
SPCG-4	-0.1863	0.3475	210	209	8.9%	0.83 [0.42 , 1.64]
Subtotal (95% CI)			**210**	**209**	**8.9%**	**0.83 [0.42 , 1.64]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
6.1.2 Clinical stage T2						
SPCG-4	-0.3147	0.1086	91	103	91.1%	0.73 [0.59 , 0.90]
Subtotal (95% CI)			**91**	**103**	**91.1%**	**0.73 [0.59 , 0.90]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.90 (P = 0.004)						
Total (95% CI)			**301**	**312**	**100.0%**	**0.74 [0.60 , 0.90]**
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.72); I² = 0%						
Test for overall effect: Z = 2.93 (P = 0.003)						
Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.72), I² = 0%						

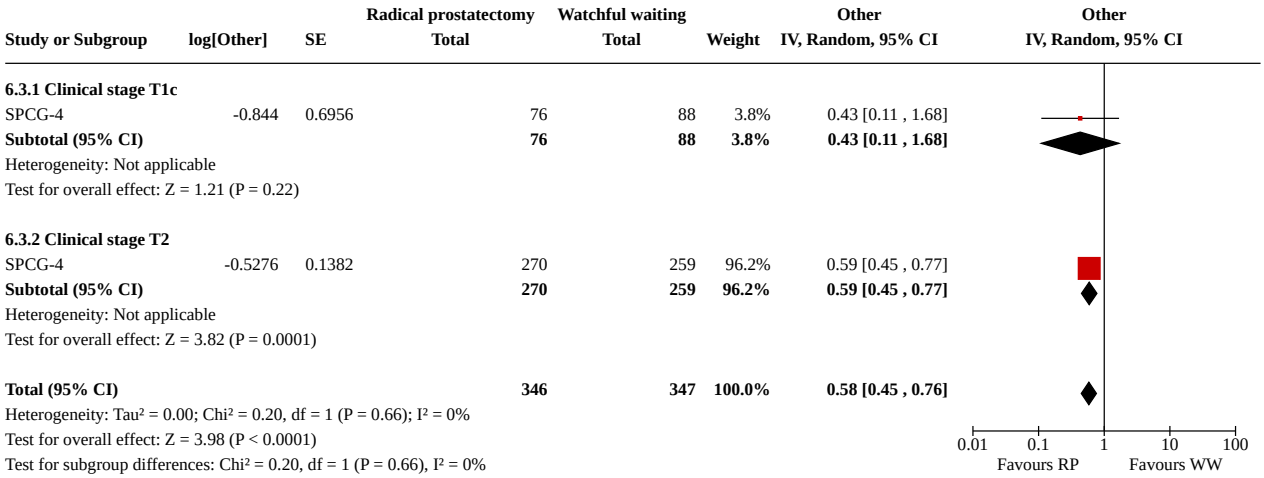


Analysis 6.2. Comparison 6: Subgroup analyses 4 - clinical stage T1c versus clinical stage T2: radical prostatectomy versus watchful waiting, Outcome 2: Time to death from prostate cancer

Study or Subgroup	log[Other]	SE	Radical prostatectomy Total	Watchful waiting Total	Weight	Other IV, Random, 95% CI
6.2.1 Clinical stage T1c						
SPCG-4	-0.9416	0.8764	210	209	1.5%	0.39 [0.07 , 2.17]
Subtotal (95% CI)			**210**	**209**	**1.5%**	**0.39 [0.07 , 2.17]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.28)						
6.2.2 Clinical stage T2						
SPCG-4	-0.3147	0.1086	91	103	98.5%	0.73 [0.59 , 0.90]
Subtotal (95% CI)			**91**	**103**	**98.5%**	**0.73 [0.59 , 0.90]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.90 (P = 0.004)						
Total (95% CI)			**301**	**312**	**100.0%**	**0.72 [0.59 , 0.89]**
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%						
Test for overall effect: Z = 3.01 (P = 0.003)						
Test for subgroup differences: Chi² = 0.50, df = 1 (P = 0.48), I² = 0%						



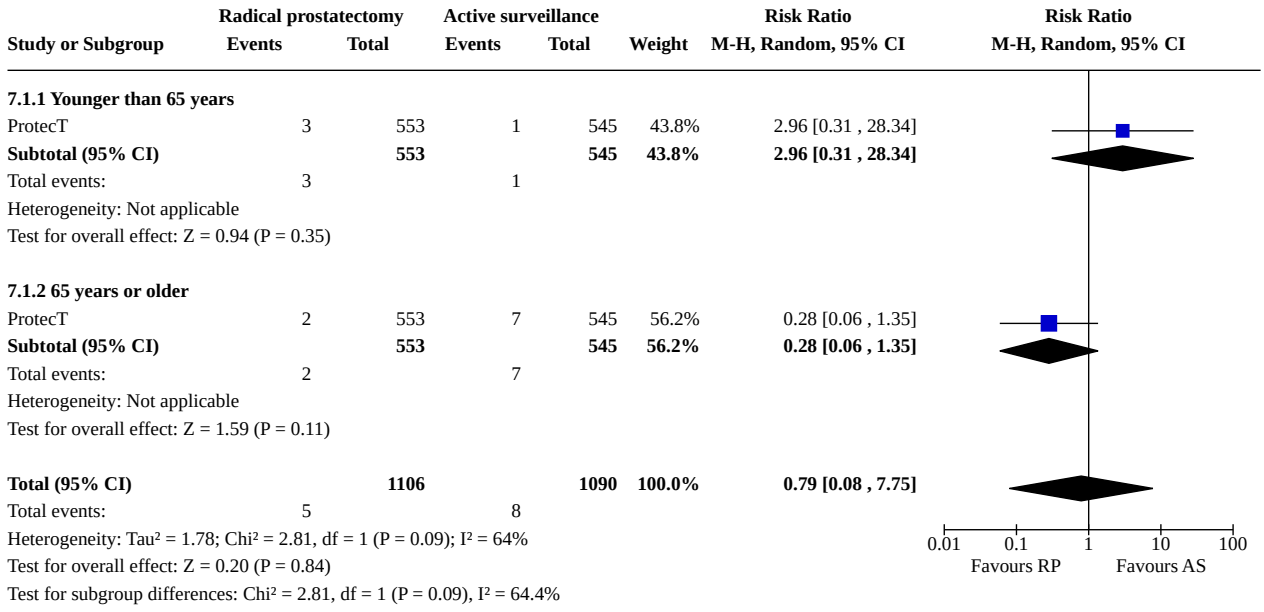
Analysis 6.3. Comparison 6: Subgroup analyses 4 - clinical stage T1c versus clinical stage T2: radical prostatectomy versus watchful waiting, Outcome 3: Time to metastatic disease



Comparison 7. Subgroup analyses 5 - younger than 65 years versus 65 years or older: radical prostatectomy versus active monitoring

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Time to death from prostate cancer	1	2196	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.08, 7.75]
7.1.1 Younger than 65 years	1	1098	Risk Ratio (M-H, Random, 95% CI)	2.96 [0.31, 28.34]
7.1.2 65 years or older	1	1098	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.06, 1.35]

Analysis 7.1. Comparison 7: Subgroup analyses 5 - younger than 65 years versus 65 years or older: radical prostatectomy versus active monitoring, Outcome 1: Time to death from prostate cancer

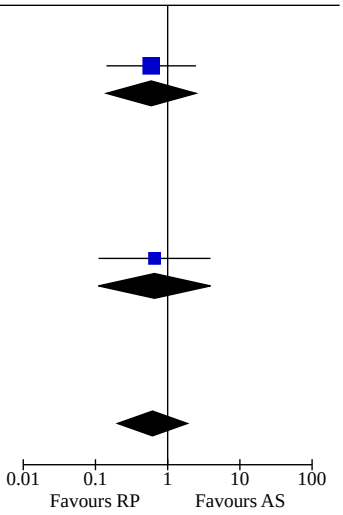


Comparison 8. Subgroup analyses 6 - PSA 6 ng/mL or lower versus more than 6 ng/mL: radical prostatectomy versus active monitoring

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Time to death from prostate cancer	1	2196	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.20, 1.88]
8.1.1 PSA 6 ng/mL or lower	1	1098	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.14, 2.46]
8.1.2 PSA more than 6 ng/mL	1	1098	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.11, 3.92]

Analysis 8.1. Comparison 8: Subgroup analyses 6 - PSA 6 ng/mL or lower versus more than 6 ng/mL: radical prostatectomy versus active monitoring, Outcome 1: Time to death from prostate cancer

Study or Subgroup	Radical prostatectomy Events	Total	Active surveillance Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
8.1.1 PSA 6 ng/mL or lower						
ProtecT	3	553	5	545	61.0%	0.59 [0.14 , 2.46]
Subtotal (95% CI)		**553**		**545**	**61.0%**	**0.59 [0.14 , 2.46]**
Total events:	3		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
8.1.2 PSA more than 6 ng/mL						
ProtecT	2	553	3	545	39.0%	0.66 [0.11 , 3.92]
Subtotal (95% CI)		**553**		**545**	**39.0%**	**0.66 [0.11 , 3.92]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.64)						
Total (95% CI)		**1106**		**1090**	**100.0%**	**0.62 [0.20 , 1.88]**
Total events:	5		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.85 (P = 0.39)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%						

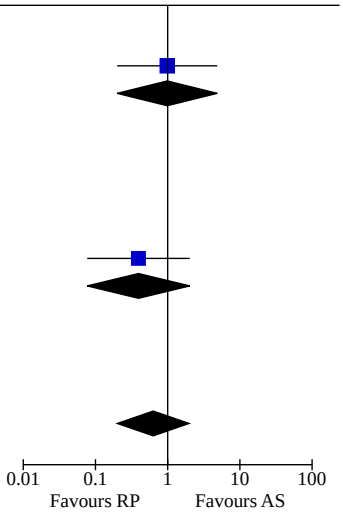


Comparison 9. Subgroup analyses 7 - Gleason score 6 versus Gleason score 7 or higher: radical prostatectomy versus active monitoring

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Time to death from prostate cancer	1	2196	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.20, 1.98]
9.1.1 Gleason score 6	1	1098	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.20, 4.86]
9.1.2 Gleason score 7 or higher	1	1098	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.08, 2.02]

Analysis 9.1. Comparison 9: Subgroup analyses 7 - Gleason score 6 versus Gleason score 7 or higher: radical prostatectomy versus active monitoring, Outcome 1: Time to death from prostate cancer

Study or Subgroup	Radical prostatectomy Events	Total	Active surveillance Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
9.1.1 Gleason score 6						
ProtecT	3	553	3	545	51.2%	0.99 [0.20 , 4.86]
Subtotal (95% CI)		**553**		**545**	**51.2%**	**0.99 [0.20 , 4.86]**
Total events:	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.99)						
9.1.2 Gleason score 7 or higher						
ProtecT	2	553	5	545	48.8%	0.39 [0.08 , 2.02]
Subtotal (95% CI)		**553**		**545**	**48.8%**	**0.39 [0.08 , 2.02]**
Total events:	2		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						
Total (95% CI)		**1106**		**1090**	**100.0%**	**0.63 [0.20 , 1.98]**
Total events:	5		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.79 (P = 0.43)						
Test for subgroup differences: Chi² = 0.62, df = 1 (P = 0.43), I² = 0%						

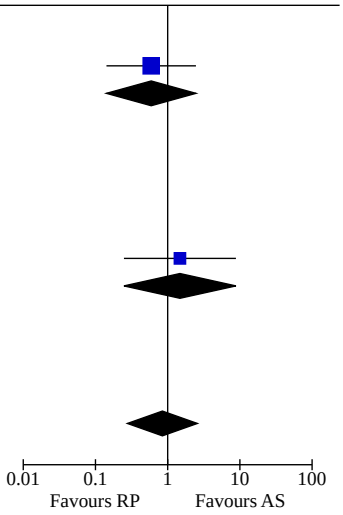


Comparison 10. Subgroup analyses 8 - clinical stage T1c versus clinical stage T2: radical prostatectomy versus active monitoring

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Time to death from prostate cancer	1	2196	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.28, 2.58]
10.1.1 Clinical stage T1c	1	1098	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.14, 2.46]
10.1.2 Clinical stage T2	1	1098	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.25, 8.81]

Analysis 10.1. Comparison 10: Subgroup analyses 8 - clinical stage T1c versus clinical stage T2: radical prostatectomy versus active monitoring, Outcome 1: Time to death from prostate cancer

Study or Subgroup	Radical prostatectomy Events	Total	Active surveillance Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
10.1.1 Clinical stage T1c						
ProtecT	3	553	5	545	61.0%	0.59 [0.14 , 2.46]
Subtotal (95% CI)		**553**		**545**	**61.0%**	**0.59 [0.14 , 2.46]**
Total events:	3		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
10.1.2 Clinical stage T2						
ProtecT	3	553	2	545	39.0%	1.48 [0.25 , 8.81]
Subtotal (95% CI)		**553**		**545**	**39.0%**	**1.48 [0.25 , 8.81]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.67)						
Total (95% CI)		**1106**		**1090**	**100.0%**	**0.85 [0.28 , 2.58]**
Total events:	6		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.30 (P = 0.77)						
Test for subgroup differences: Chi² = 0.62, df = 1 (P = 0.43), I² = 0%						

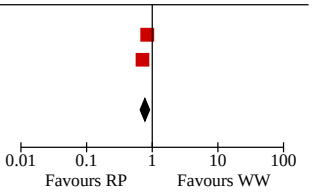


Comparison 11. Sensitivity analyses 1 - risk of bias: radical prostatectomy versus watchful waiting

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Time to death from any cause	2	1426	Hazard Ratio (IV, Random, 95% CI)	0.77 [0.66, 0.91]

Analysis 11.1. Comparison 11: Sensitivity analyses 1 - risk of bias: radical prostatectomy versus watchful waiting, Outcome 1: Time to death from any cause

Study or Subgroup	log[Other]	SE	Radical prostatectomy Total	Watchful waiting Total	Weight	Other IV, Random, 95% CI
PIVOT	-0.1744	0.093	364	367	50.5%	0.84 [0.70 , 1.01]
SPCG-4	-0.3425	0.0945	347	348	49.5%	0.71 [0.59 , 0.85]
Total (95% CI)			**711**	**715**	**100.0%**	**0.77 [0.66 , 0.91]**
Heterogeneity: Tau² = 0.01; Chi² = 1.61, df = 1 (P = 0.20); I² = 38%						
Test for overall effect: Z = 3.07 (P = 0.002)						
Test for subgroup differences: Not applicable						



APPENDICES

Appendix 1. Electronic search strategies

MEDLINE, MEDLINE-in-Process and Epub ahead of print (OVIDSP)

1. exp Prostatic Neoplasms/

2. exp Prostatic Intraepithelial Neoplasia/

3. (prostat* adj3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or adeno* or intraepithelial)).tw.

4. exp prostate/

5. or/1-4

6. exp Prostatectomy/

7. prostatectom*.tw.

8. (prostat* adj3 (remov* or resect*)).tw.

9. or/6-8

10. exp Watchful Waiting/

11. (watch* adj2 wait*).tw.

12. ((careful* or prostat*) adj2 monitor*).tw.

13. "active surveillance".tw.

14. ((defer* or delay* or expectant*) adj2 (treatment* or management*)).tw.

15. ((observ* or surveillance) adj3 prostat*).tw.

16. or/10-15

17. 5 and 9 and 16

18. randomized controlled trial.pt.

19. controlled clinical trial.pt.

20. randomized.ab.

21. placebo.ab.

22. drug therapy.fs.

23. randomly.ab.

24. trial.ab.

25. groups.ab.

26. or/18-25

27. exp animals/ not humans/

28. 26 not 27

29. 17 and 28

Embase (OVIDSP)

1. exp prostate tumor/

2. (prostat* adj3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or adeno* or intraepithelial)).tw.

3. exp prostate/

4. or/1-3

5. exp prostate surgery/

6. prostatectom*.tw.

7. (prostat* adj3 (remov* or resect*)).tw.

8. or/5-7

9. exp watchful waiting/

10. (watch* adj2 wait*).tw.

11. ((careful* or prostat*) adj2 monitor*).tw.

12. "active surveillance".tw.

13. ((defer* or delay* or expectant*) adj2 (treatment* or management*)).tw.

14. ((observ* or surveillance) adj3 prostat*).tw.

15. or/9-14

16. 4 and 8 and 15

17. crossover procedure/

18. double blind procedure/

19. randomized controlled trial/

20. single blind procedure/

21. (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or assign* or allocate* or volunteer*).mp.

22. ((doubl* or singl*) adj blind*).mp.

23. or/17-22

24. 16 and 23

AMED (OVIDSP)

1. exp Prostatic neoplasms/

2. (prostat* adj3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or adeno* or intraepithelial)).tw.

3. exp Prostate/

4. or/1-3

5. prostatectom*.tw.

6. (prostat* adj3 (remov* or resect*)).tw.

7. 5 or 6

8. (watch* adj2 wait*).tw.

9. ((careful* or prostat*) adj2 monitor*).tw.

10. "active surveillance".tw.

11. ((defer* or delay* or expectant*) adj2 (treatment* or management*)).tw.

12. ((observ* or surveillance) adj3 prostat*).tw.

13. or/8-12

14. 4 and 7 and 13

Cochrane Library (Wiley)

#1 MeSH descriptor: [Prostatic Neoplasms] explode all trees

#2 MeSH descriptor: [Prostatic Intraepithelial Neoplasia] explode all trees

#3 (prostat* near/3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or adeno* or intraepithelial)):ti,ab,kw

#4 MeSH descriptor: [Prostate] explode all trees

#5 #1 or #2 or #3 or #4

#6 MeSH descriptor: [Prostatectomy] explode all trees

#7 prostatectom*:ti,ab,kw

#8 (prostat* near/3 (remov* or resect*)):ti,ab,kw

#9 #6 or #7 or #8

#10 MeSH descriptor: [Watchful Waiting] explode all trees

#11 (watch* near/2 wait*):ti,ab,kw

#12 ((careful* or prostat*) near/2 monitor*):ti,ab,kw

#13 (active near surveillance):ti,ab,kw

#14 ((defer* or delay* or expectant*) near/2 (treatment* or management*)):ti,ab,kw

#15 ((observ* or surveillance) near/3 prostat*):ti,ab,kw

#16 #10 or #11 or #12 or #13 or #14 or #15

#17 #5 and #9 and #16

Web of Science Core Collection: Citation Indexes (Thomson Reuters)

Science Citation Index - Expanded (SCI-EXPANDED)

Conference Proceedings Citation Index - Science (CPCI-S)

#26 #25 AND #13

DocType=All document types; Language=All languages;

#25 #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14

DocType=All document types; Language=All languages;

#24 TS=(double blind*)

DocType=All document types; Language=All languages;

#23 TS=(single blind*)

DocType=All document types; Language=All languages;

#22 TS=(placebo*)

DocType=All document types; Language=All languages;

#21 TS=(random*)

DocType=All document types; Language=All languages;

#20 TS=(prospective stud*)

DocType=All document types; Language=All languages;

#19 TS=(follow up stud*)

DocType=All document types; Language=All languages;

#18 TS=(controlled trial*)

DocType=All document types; Language=All languages;

#17 TS=(evaluation stud*)

DocType=All document types; Language=All languages;

#16 TS=(comparative stud*)

DocType=All document types; Language=All languages;

#15 TS=(research design*)

DocType=All document types; Language=All languages;

#14 TS=(clinical trial*)

DocType=All document types; Language=All languages;

#13 #12 AND #6 AND #3

DocType=All document types; Language=All languages;

#12 #11 OR #10 OR #9 OR #8 OR #7

DocType=All document types; Language=All languages;

#11 TS=((observ* or surveillance) NEAR/3 prostat*)

DocType=All document types; Language=All languages;

#10 TS=((defer* or delay* or expectant*) NEAR/2 (treatment* or management*))

DocType=All document types; Language=All languages;

#9 TS=("active surveillance")

DocType=All document types; Language=All languages;

#8 TS=((careful* or prostat*) NEAR/2 monitor*)

DocType=All document types; Language=All languages;

#7 TS=(watch* NEAR/2 wait*)

DocType=All document types; Language=All languages;

#6 #5 OR #4

DocType=All document types; Language=All languages;

#5 TS=(prostat* NEAR/3 (remov* or resect*))

DocType=All document types; Language=All languages;

#4 TS=(prostatectom*)

DocType=All document types; Language=All languages;

#3 #2 OR #1

DocType=All document types; Language=All languages;

#2 TS=(prostat*)

DocType=All document types; Language=All languages;

#1 TS=(prostat* NEAR/3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or adeno* or intraepithelial))

DocType=All document types; Language=All languages;

LILACS (Virtual Health Library)

(((tw:(prostat$)) OR (mh:(prostatic neoplasms))) AND ((tw:(prostatectomy$)) OR (mh:(prostatectomy))) AND ((tw:(watchful$ or wait$)) OR (tw:(active surveillance)) OR (tw:(espera atenta)) OR (tw:(espera vigilante)) OR (tw:(vigilancia active)) OR (tw:(expectant management)) OR (tw:(Gestante expectante)) OR (tw:(Manejo expectante)) OR (tw:(observation)) OR (tw:(observe$)) OR (tw:(observación)) OR (tw:(observação))))

SCOPUS (Elsevier)

(((TITLE-ABS-KEY (prostat* W/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR adeno* OR intraepithelial))) OR (TITLE-ABS-KEY (prostat*))) AND ((TITLE-ABS-KEY (prostatectom*)) OR (TITLE-ABS-KEY (prostat* W/3 (remov* OR resect*))))) AND ((TITLE-ABS-KEY (watch* W/2 wait*)) OR (TITLE-ABS-KEY ((careful* OR prostat*) W/2 monitor*)) OR (TITLE-ABS-KEY ("active surveillance")) OR (TITLE-ABS-KEY ((defer* OR delay* OR expectant*) W/2 (treatment* OR management*))) OR (TITLE-ABS-KEY ((observ* OR surveillance) W/3 prostat*)))) AND ((TITLE-ABS-KEY ("random*")) OR (TITLE-ABS-KEY ("placebo*")) OR (TITLE-ABS-KEY ("single blind*")) OR (TITLE-ABS-KEY ("double blind*")) OR ((TITLE-ABS-KEY ("clinical trial*")) OR (TITLE-ABS-KEY ("research design*")) OR (TITLE-ABS-KEY ("comparative stud*")) OR (TITLE-ABS-KEY ("evaluation stud*")) OR (TITLE-ABS-KEY ("controlled trial*")) OR (TITLE-ABS-KEY ("follow up stud*")) OR (TITLE-ABS-KEY ("prospective stud*"))))

OpenGrey (native interface)

Prostat* and Prostatectom* and active surveillance

Prostat* and Prostatectom* and watch* wait*

WHO International Clinical Trials Registry Search Portal (World Health Organization)

Prostat* and Prostatectom* and active surveillance

Prostat* and Prostatectom* and watchful waiting

ClinicalTrials.gov (US National Institutes of Health)

Prostate and Prostatectomy and watchful waiting

Prostate and Prostatectomy and active surveillance

WHAT'S NEW

Date	Event	Description
4 May 2020	New citation required and conclusions have changed	Previous conclusion (2010 publication): The existing trials provide insufficient evidence to allow confident statements to be made about the relative beneficial and harmful effects of RP and WW for patients with localised prostate cancer. The results of ongoing trials should help to inform treatment decisions for men with screen-detected localised prostate cancer.
4 May 2020	New search has been performed	This review was comprehensively updated to comply with MECIR standards and to incorporate GRADE summary of findings tables

HISTORY

Protocol first published: Issue 3, 2007
Review first published: Issue 11, 2010

CONTRIBUTIONS OF AUTHORS

1. Construction of the search strategy: Anne Cleves
2. Screening of references: Robin Vernooij, Michelle Lancee, and Katja Aben
3. Acquisition of data: Robin Vernooij, Michelle Lancee, and Katja Aben
4. Risk of bias assessments: Robin Vernooij, Michelle Lancee, and Katja Aben

5. SoF and GRADE assessment: Robin Vernooij and Philipp Dahm
6. Statistical analysis: Robin Vernooij
7. Overall interpretation of data: Robin Vernooij, Michelle Lancee, Anne Cleves, Philipp Dahm, Chris Bangma, and Katja Aben
8. Manuscript preparation: Robin Vernooij, Michelle Lancee, Anne Cleves, Philipp Dahm, Chris Bangma, and Katja Aben

DECLARATIONS OF INTEREST

1. Robin Vernooij: none known
2. Michelle Lancee: none known
3. Anne Cleves: none known
4. Philipp Dahm: none known
5. Chris Bangma: none known
6. Katja Aben: none known

SOURCES OF SUPPORT

Internal sources

- Department of Research and Development, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, Netherlands
- Velindre NHS Trust, Cardiff University Library Services, Cardiff, UK
- Urology Section, Minneapolis VA Health Care System, Minneapolis, Minnesota, USA
- Department of Urology, Erasmus University Medical Center, Rotterdam, Netherlands

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The previous version of this review was published in 2010 (Hegarty 2010). Therefore, substantial changes were required to align this update with the current methodological standards of Cochrane Reviews, including more specific definitions of outcomes, a priori subgroup and sensitivity analyses, details of the systematic search, and use of GRADE on a per-outcome basis to assess the certainty of evidence. Specific issues are highlighted below.

1. Title: we have included comparison 2, "Radical prostatectomy versus active monitoring". Therefore, we have adapted the title accordingly and changed "watchful waiting" to "deferred treatment" .
2. Outcome measures: we have focused this Cochrane Review on patient-important outcomes and have excluded information on economic cost outcomes and PSA progression. Additionally, we have renamed the outcomes progression-free survival and metastasis-free survival to, respectively, time to disease progression and time to metastatic disease.
3. Risk of bias: we have described the method used to assess risk of bias in detail. In addition, we have separated risk of performance, detection, and attrition bias for objective and subjective outcomes.
4. GRADE assessment: we have included a GRADE approach on a per-outcome basis to assess the certainty of evidence.
5. Subgroup and sensitivity analyses: we have included subgroup analyses based on patient age, PSA level, Gleason score, and clinical tumour stage.

NOTES

We have based parts of the Methods section of this protocol on a standard template developed by the Cochrane Metabolic and Endocrine Disorders Group, which has been modified and adapted for use by the Cochrane Urology Group.

INDEX TERMS

Medical Subject Headings (MeSH)

Aged; Cause of Death; Disease Progression; Erectile Dysfunction [epidemiology]; Humans; Male; Middle Aged; Palliative Care; Postoperative Complications [epidemiology]; Prostatectomy [adverse effects] [*methods] [mortality]; Prostatic Neoplasms [mortality] [pathology] [surgery] [*therapy]; Quality of Life; Randomized Controlled Trials as Topic; Urinary Incontinence [epidemiology]; *Watchful Waiting