Appendix 1. Full search strategy for Medline made on 12 Sep 2012

1	"watchful wait$".ti,ab	1408
2	(watch$ adj2 wait$).ti,ab	1795
3	"observation".ti,ab	201605
4	"watchful surveillance".ti,ab	3
5	"watchful monitoring".ti,ab	14
6	"active surveillance".ti,ab	2609
7	"active monitoring".ti,ab	177
8	"expectant manag$".ti,ab	1501
9	"expectant monitoring".ti,ab	18
10	"expectant surveillance".ti,ab	3
11	"deferred treatment$".ti,ab	174
12	"deferred therap$".ti,ab	53
13	"delayed treatment$".ti,ab	1752
14	"delayed therap$".ti,ab	264
15	"conservative monitoring".ti,ab	10
16	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15	209461
17	exp PROSTATIC NEOPLASMS/	83203
18	PROSTATIC INTRAEPITHELIAL NEOPLASIA/	1124
19	pin.ti,ab	9241
20	((prostat$ adj3 (cancer$ OR carcinoma$ OR malignan$ OR tumo?r$ OR neoplas$ OR intraepithelial$ OR adeno$))).ti,ab	85456
21	17 OR 18 OR 19 OR 20	109867
22	RANDOMIZED CONTROLLED TRIALS AS TOPIC/	82900
23	RANDOMIZED CONTROLLED TRIAL/	336590
24	RANDOM ALLOCATION/	75700
25	DOUBLE BLIND METHOD/	116906
26	SINGLE BLIND METHOD/	16674
27	CLINICAL TRIAL/	473817
28	"clinical trial, phase i".pt	12527
29	"clinical trial, phase ii".pt	20003
30	"clinical trial, phase iii".pt	7335
31	"clinical trial, phase iv".pt	739
32	"controlled clinical trial".pt	85134
33	"randomized controlled trial".pt	336590
34	"multicenter study".pt	149366
35	"clinical trial".pt	473817
36	exp CLINICAL TRIALS AS TOPIC/	260613
37	22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36	933873
38	(clinical ADJ trial$).ti,ab	185348
39	((singl$ OR doubl$ OR treb$ OR tripl$) AND (blind$3 OR mask$3)).ti,ab	129000
40	PLACEBOS/	31302
41	placebo$.ti,ab	144213
42	"randomly allocated".ti,ab	14778
43	(allocated adj2 random$).ti,ab	17183
44	38 OR 39 OR 40 OR 41 OR 42 OR 43	383691
45	37 OR 44	1064978
46	(case AND report).ti,ab	372325
47	LETTER/	776512

48	HISTORICAL ARTICLE/	286394
49	46 OR 47 OR 48	1422877
50	45 NOT 49	1033939
51	CRYOTHERAPY/	3337
52	CRYOSURGERY/	10459
53	HYPOTHERMIA, INDUCED/	15628
54	cryoablat$.ti,ab	1810
55	(cryo$ ADJ ablat$).ti,ab	351
56	cryotreatment$.ti,ab	65
57	cryotherap$.ti,ab	4776
58	cryotherm$.ti,ab	212
59	(cryo$ ADJ surgery).ti,ab	149
60	51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59	31372
61	((cryo$ OR hypotherm$ OR freez$) adj5 prostat$).ti,ab	709
62	60 AND 21	916
63	61 OR 62	1089
64	PROSTATECTOMY/	19443
65	prostatectom$.ti,ab	18653
66	resection.ti,ab	170070
67	64 OR 65 OR 66	192628
68	(radical OR complete$ OR total OR "en bloc").ti,ab	2057017
69	67 AND 68	69466
70	(LRP OR TLRP OR RALRP OR RAP OR RRP OR RPP OR EERP).ti,ab	7847
71	"heilbronn technique".ti,ab	8
72	70 OR 71	7853
73	69 OR 72	76420
74	exp RADIOTHERAPY/	125988
75	"radiation therap$".ti,ab	46061
76	"radiation treatment$".ti,ab	6068
77	radiotherap$.ti,ab	103759
78	exp RADIOTHERAPY PLANNING/	11242
79	irradiation.ti,ab	133551
80	RADIOTHERAPY, ADJUVANT/	15412
81	74 OR 75 OR 76 OR 77 OR 78 OR 79 OR 80	307483
82	META-ANALYSIS AS TOPIC/	12419
83	"meta analy$".ti,ab	45804
84	metaanaly$.ti,ab	1171
85	META-ANALYSIS/	36142
86	(systematic ADJ review$1).ti,ab	37644
87	(systematic ADJ overview$1).ti,ab	489
88	exp REVIEW LITERATURE AS TOPIC/	6486
89	82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88	93039
90	cochrane.ab	22743
91	embase.ab	20328
92	(psychlit OR psyclit).ab	865
93	(psychinfo OR psycinfo).ab	7698
94	(cinahl OR cinhal).ab	7537
95	"science citation index".ab	1633
96	bids.ab	331
97	cancerlit.ab	560
98	90 OR 91 OR 92 OR 93 OR 94 OR 95 OR 96 OR 97	37065
99	"reference list$".ab	7905

100	bibliograph$.ab	10314
101	hand-search$.ab	3303
102	"relevant journals".ab	586
103	"manual search$".ab	1920
104	99 OR 100 OR 101 OR 102 OR 103	21486
105	"selection criteria".ab	16935
106	"data extraction".ab	8148
107	105 OR 106	23737
108	REVIEW/	1733836
109	107 AND 108	15770
110	COMMENT/	517077
111	LETTER/	776512
112	EDITORIAL/	317040
113	ANIMAL/	5040870
114	HUMAN/	12536636
115	113 NOT (113 AND 114)	3686418
116	110 OR 111 OR 112 OR 115	4846136
117	89 OR 98 OR 104 OR 109	118824
118	117 NOT 116	110572
119	ULTRASOUND, HIGH-INTENSITY FOCUSED, TRANSRECTAL/	306
120	((high intensity adj2 ultraso$)).ti,ab	2103
121	HIFU.ti,ab	1012
122	((high intensity focused ultrasound)).ti,ab	1381
123	"focal therapy".ti,ab	295
124	119 OR 120 OR 121 OR 122 OR 123	2619
125	21 AND 50 AND 124	**99**
126	16 AND 21 AND 50 AND 63 [Limit to: Publication Year 2005-Current]	**10**
127	16 AND 21 AND 50 AND 73 [Limit to: Publication Year 2005-Current]	**94**
128	16 AND 21 AND 50 AND 81 [Limit to: Publication Year 2005-Current]	**82**
129	50 AND 63 AND 81 [Limit to: Publication Year 2005-Current]	**27**
130	50 AND 63 AND 73 [Limit to: Publication Year 2005-Current]	**14**
131	21 AND 50 AND 73 AND 81 [Limit to: Publication Year 2005-Current]	**267**
132	(21 AND 50 AND 81) NOT (128 OR 131) [Limit to: Publication Year 2005-Current]	**947**
133	16 AND 21 AND 63 AND 118 [Limit to: Publication Year 2005-Current]	**5**
134	16 AND 21 AND 73 AND 118 [Limit to: Publication Year 2005-Current]	**25**
135	16 AND 21 AND 81 AND 118 [Limit to: Publication Year 2005-Current]	**27**
136	63 AND 81 AND 118 [Limit to: Publication Year 2005-Current]	**14**
137	63 AND 73 AND 118 [Limit to: Publication Year 2005-Current]	**12**
138	21 AND 73 AND 81 AND 118 [Limit to: Publication Year 2005-Current]	**56**
139	(21 AND 81 AND 118) NOT (135 OR 138) [Limit to: Publication Year 2005-Current]	**61**

Appendix 2. Characteristics of included studies

Comparison	Trial title	Author, year	Country	Population	No.of men	Interventions and Comparisons	Outcomes	Follow up
Observational management v Prostatectomy (3 trials)	Graversen 1990 (1 paper)	Graversen 1990	USA	Dates of enrolment to study: Between May 1967 and March 1975; Setting: Multi-centre (15 participating hospitals); Age: All age; Disease status: stage I or II (T0 – T2).	142	1. Watchful waiting (74 men) 2. Prostatectomy (68 men)	Overall survival.	15 years.
	PIVOT trial (1 paper)	Wilt 2012	USA	Dates of enrolment to study: Nov 1994 to Jan 2002; Setting: multicentre; Mean age: 67yr; Disease status: T1-T2NxM0.	731	1. Observation (367 men) 2. Prostatectomy (364 men)	All cause mortality; Cancer caused mortality; Bone metastases; Urinary incontinence; Bowel dysfunction; Erectile dysfunction.	10 years.
	Scandinavian Prostate Cancer Group Study No 4 (SPCG-4) (6 papers)	Bill-Axelson 2005, 2008, 2011; Johansson 2009, 2011 Steineck 2002;	Sweden, Finland, Iceland	Dates of enrolment to study: Oct 1989 to Feb 1999; Setting: Multi-centre (14 participating hospitals); Age: Mean age 64.7; Disease status: T0d, T1, T2.	695	1. Watchful waiting (348 men) 2. Prostatectomy (347 men)	Death due to prostate cancer; All-caused mortality; Distance metastasis; Local progression; overall distress from all bowel symptoms, overall distress from all urinary symptoms.	8.2 - 12.8 years.
Observational management v Conformal LD radiotherapy (1 trial)	Widmark 2011 (1 paper)	Widmark 2011	Sweden, Denmark and Norway	Dates of enrolment to study: Apr 1986 to Jan 1997; Setting: unknown; Age: up to 75; Disease status: T1b-T2, pN0, G1-G2, M0.	214	1. Watchful waiting (107 men) 2. 3D conformal radiotherapy, either 64 Gy in 32 fractions with 2cm margin, or 64-68 Gy with 1.5cm margin (107 men)	All-cause mortality, Prostate cancer mortality, Distant progression, Recurrence free survival, Clinical progression, Biochemical progression, Local progression.	20 years.

Prostatectomy v Conventional radiotherapy (2 trials)	Akakura 2006(1 paper)	Akakura 2006	Japan	Dates of enrolment to study: 1989 to 1993; Setting: Multi-centre; Age: Mean 68.1, SD 7.0 in surgery group; mean 68.7, SD 6.6 in radiation group; Disease status: T2b-3N0M0, no evidence of lymph node metastasis.	95	1. Prostatectomy (46 men).2. Conventional radiotherapy (49 men): Irradiation by linear accelerator with a 40-50 Gy beam to the whole pelvis followed by a 20 Gy boost to the prostatic area for 6-7 weeks fractionated five times per week. All men received an initial treatment with 8 weeks of neoadjuvant endocrine therapy.	Biochemical progression-free survival at 10 years; Clinical progression-free survival at 10 years; Cause-specific survival at 10 years; Overall survival at 10 years; Adverse effects.	Median follow-up was 102 months.
Cryotherapy v Conventional radiotherapy (2 trials)	Canada trial (3 papers)	Donnelly 2007, 2010; Robinson 2009	Canada	Dates of enrolment to study: Dec 1997 to Feb 2003; Setting: Tom Baker Cancer Center, Calgary, Canada; Age: Median 69.4, range 52.8-81.4 in CT group; median 68.6, range 53.2-78.6 in EBRT group; Disease status: T2 - T3.	244	1. Cryotherapy (122 men). 2. Conventional EBRT (122 men): dose of 68 Gy given in 2 Gy fractions daily, 5 days per week, later increased to 70 Gy and later 73.5 Gy.	Treatment Failure; 5 year overall survival; Biopsy rate at 36 months; Disease-specific survival at 5 years; Genitourinary and gastrointestinal adverse effects; Quality of life.	Median follow-up was 82 months.
	Chin 2008 (1 paper)	Chin 2008	Canada	Setting: London Health Sciences Centre, University of Western Ontario; Age: Median age 70 in each group; Disease status: T2 - T3.	64	1. Cryotherapy (33 men). 2. Conventional EBRT (31 men): 66 Gy in 33 fractions.	Biochemical disease-free survival at 4 years; Overall survival at 4 years; Disease specific survival at 4 years; Positive biopsy rate; Gastrointestinal toxicity; Genitourinary toxicity; Hormonal adverse effects.	Mean follow-up 37 months.

Conventional radiotherapy v Conventional radiotherapy-hypofractionated (2 trials)	Yeoh trial (4 papers)	Yeoh 2003, 2006, 2009, 2011	Australia	Dates of enrolment to study: July 1996 to Aug 2003; Setting: Department of Radiation Oncology and Gastroenterology, Royal Adelaide Hospital; Age: Median age 69 (44 ~ 82 yrs); Disease status: T1, T2, N0 M0.	217	1. Conventional EBRT: 64 Gy in 32 fractions within 6.5 weeks (109 men). 2. Hypofractionated EBRT: 55 Gy in 20 fractions within 4 weeks (108 men).	Gastrointestinal (GI) and genitourinary (GU) toxicity; overall survival rate; biochemical ±clinical relapse; biochemical ±clinical relapse-free survival; cancer-related mortality.	5 years.
	Lukka 2005 (1 paper)	Lukka 2005	Canada	Dates of enrolment to study: March 1995 – December 1998; Setting: 8 Ontario regional cancer centres and 8 additional Canadian centres; Age: Mean 70.3, range 53-84 in group 1; mean 70.0, range 53-84 in group 2; Disease status: T1, T2.	936	1. Conventional EBRT (470 men): 66 Gy in 33 fractions over 45 days. 2. Hypofractionated EBRT (466 men): 52.5 Gy in 20 fractions over 28 days.	Composite of biochemical or clinical failure (BCF); local persistence of tumour on biopsy of the prostate at 2 years; overall survival; acute and late radiation-induced toxicity; prostate cancer-related mortality.	Median follow-up was 5.7 years.
Conventional radiotherapy v Conformal LD radiotherapy (2 trials)	Koper trial (2 papers)	Koper 1999, 2004	Nether-lands	Dates of enrolment to study: June 1994 to March 1996; Setting: Erasmus Medical Center/Daniel den Hoed Cancer Center; Mean age: group1: 70 (6.4); group 2: 69.5 (6.1); Disease status: T1-T4 N0M0.	266	1. Conventional radiotherapy (134 men); 2. Conformal radiotherapy (129 men). All men were treated to a dose of 66 Gy, using the same planning procedure, treatment technique, linear accelerator, and portal imaging procedure.	Gastrointestinal (GI) and genitourinary (GU) toxicity.	2 years.
	Royal Marsden and Institute of Cancer Research study (2 papers)	Dearnaley 1999; Tait 1997	UK	Dates of enrolment to study: 1988 to 1995; Setting: Tertiary care, single centre; Median age (range): 69 (51-80) in group 1, 68 (50-83) in group 2; Disease status: T1-T4 N0M0.	225	1. Conventional radiotherapy (111 men): 60 to 64 Gy in 2 Gy fractions. 2. Conformal radiotherapy (114 men): 60 to 64 Gy in 2 Gy fractions.	Overall survival; Biochemical progression free survival; Late GI toxicity; Late GU toxicity.	2 - 5 years.

Conformal LD radiotherapy v Conformal HD radiotherapy (5 trials)	Dutch trial (7 papers)	Al-Mamgani 2008, 2011; Heemsbergen 2007; Peeters 2005, 2006a,b; van der Wielen 2008	Nether-lands	Dates of enrolment to study: between June 1997 and February 2003; Setting: multi-center; Age: mean 68.6 and 68.8, range 50.3-82.9 and 48.7-83.6; Disease status: T1-T4.	669	1. 3D conformal radiotherapy 68 Gy (331 men). 2. 3D conformal radiotherapy 78 Gy (333 men).	freedom from failure; biochemical progression free survival; clinical progression free survival; overall survival; late GI toxicity; late GU toxicity; prostete cancer related deaths.	2 - 7 years.
	MRC RT01 pilot trial (1 paper)	Dearnaley 2005	UK	Dates of enrolment to study: between Jul 1995 and Dec 1997; Setting: Royal Marsden NHS Trust and Institute of Cancer Research; Age: median 66 and 69; Disease status: T1b-T3b N0 M0.	127	1. Conformal radiotherapy, standard dose (64 men): 64 Gy in 2 Gy fractions. 2. Conformal radiotherapy, high dose (63 men): 74 Gy in 2 Gy fractions.	Biochemical (PSA) failure; Local or metastatic failure; Hormone therapy restarted; acute GU toxicity; acute GI toxicity; late GU toxicity; late GI toxicity; prostate cancer caused deaths.	5 years.
	MRC RT01 (3 papers)	Dearnaley 2007a,b; Syndikus 2010.	UK	Dates of enrolment to study: Jan 1998 to Dec 2002; Setting: multi-centre; Age: median 67 (IQR 63-71); Disease status: T1b-T3a N0 M0.	843	1. Conformal radiotherapy, standard dose (421 men): 64 Gy in 2 Gy fractions. 2. Conformal radiotherapy, high dose (422 men): 74 Gy in 2 Gy fractions.	Biochemical-progression-free survival; 5-year overall survival; Progression-free survival; Freedom from local progression; Freedom from salvage androgen suppression; Metastases-free survival; Bowel dysfunction; Urinary or bladder dysfunction; Sexual dysfunction; prostate cancer mortality.	5 years.
	GETUG 06 Tial (2 papers)	Beckendorf 2004, 2011	France	Dates of enrolment to study: Sep 1999 to Feb 2002; Setting: Multicentre; Age: mean 67; Disease status: T1b-T3a, N0M0.	306	1. Conformal radiotherapy, standard dose (153 men): 70 Gy in 2 Gy fractions. 2. Conformal radiotherapy, high dose (153 men): 80 Gy in 2 Gy fractions.	Biochemical relapse alone; PSA and clinical relapse; Free from relapse; All cause death; Cancer cause death; RTOG rectal and urinary toxicity grade 2 and worse.	61 months.
	Zietman trial (2 papers)	Zietman AL, 2005, 2010	USA	Dates of enrolment to study: between Jan 1996 and Dec 1999; Setting: 2 US academic institutions; Age: 67 (45~91) in 70.2 Gy arm, 66 (47~78) in 79.2 Gy arm; Disease status: T1-T2, N0, Nx.	393	1. External beam radiation 70.2 Gy (197 men); 2. External beam radiation 79.2 Gy (195 men).	Freedom from biochemical failure 5 yrs after treatment (measured by PSA level); Acute and late GU and GI morbidity, overall survival, prostate cancer-related mortality.	5.5 - 8.9 years.

Conformal HD radiotherapy v Conformal LD radiotherapy-hypofractionated (4 trials)	Arcangeli 2010 (2 papers)	Arcangeli 2010, 2011	Italy	Dates of enrolment to study: Jan 2003 to Dec 2007; Setting: single centre; Mean age: 75 years; Disease status: no evidence of distant metastases.	168	1. hypofractionated (62 Gy/20 fractions/5 weeks, 4 fractions per week): 83 men. 2. conventional fractionation radiotherapy (80 Gy/40 fractions/8 weeks): 85 men.	Acute and late GU and GI toxicity; biochemical failure; freedom from biochemical failure; distant metastasis rates; all cause mortality; cancer related mortality.	4 years.
	Marzi 2009 (1 paper)	Marzi 2009	Italy	Dates of enrolment to study: March 2003 to June 2008; Setting: single centre; Age: all; Disease status: T1-T4.	162	1. Conformal radiotherapy hypofractionated: 62 Gy in 20 fractions over 5 weeks (57 men); 2. Conformal radiotherapy: 80 Gy in 40 fractions over 8 weeks (57 men).	Late rectal toxicity.	Median followup was 30 months.
	Norkus 2009 (2 papers)	Norkus 2009 a,b	Lithuania	Dates of enrolment to study: 2004; Setting: single centre; Age: median 63 (range 53-75) in group 1, median 65 (range 50-78) in group 2; Disease status: T1-T3.	91	1. Hypofractionated external beam radiotherapy: 57 Gy given as 13 fractions of 3 Gy plus 4 fractions of 4.5 Gy (47 men). 2. Conventionally fractionated external beam radiotherapy: 74 Gy given in 37 fractions of 2 Gy (44 men).	Biochemical (PSA) response; acute gastrointestinal (GI) and genitourinary (GU) toxicity; overall survival; prostate cancer-related mortality.	3 - 12 months.
	CHHiP trial (1 paper)	Dearnaley 2012	UK	Dates of enrolment to study: Oct 2002 to Aug 2006; Setting: multicentre; Age: median 67 - 68 (range 44-82); Disease status: T1b – T3a N0M0.	457	1. Conventional fractionation: 74 Gy in 37 fractions at 2 Gy per fraction (153 men). 2. Hypofractionation: 60 Gy in 20 fractions at 3 Gy per fraction (153 men). 3. Hypofractionation: 57 Gy in 19 fractions at 3 Gy per fraction (151 men).	Acute bowel toxicity; Acute bladder toxicity; Late bowel toxicity; Late bladder toxicity; Sexual dysfunction.	50.5 months.
Conventional radiotherapy v Conformal HD radiotherapy (1 trial)	M. D. Anderson randomized dose-escalation trial (4 papers)	Kuban 2008, 2011; Pollack 2002; Storey 2000.	USA	Dates of enrolment to study: 1993 to 1998; Setting: M. D. Anderson Cancer Center, University of Texas; Median age 69 for each arm; Disease status: T1-T3 N0M0.	305	1. Conventional radiotherapy (150 men): 70 Gy, given in daily 2 Gy fractions. 2. 3D conformal radiotherapy (151 men): 78 Gy, given in daily 2 Gy fractions.	freedom from biochemical or clinical failure; freedom from distant metastasis; overall survival; disease-specific survival; late GI toxicity; late GU toxicity; prostate cancer-related mortality.	Median follow-up of 5 - 8 years.

LD: low dose; HD: high dose.

Appendix 3. Assessment of risk of bias for included randomized trials (please refer to www.cochrane-handbook.org for instructions on how to complete the tables).

Outcomes measured:
a - all cause mortality.
b - cancer related mortality.
c - gastrointestinal and genitourinary toxicity.

Study ID: CHHiP trial

Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Computer-generated random permuted blocks were used
Allocation concealment	Low risk	Independent randomisation was via telephone to the ICR-CTSU.
Blinding of participants and personnel	High risk	Treatment allocation was not masked and, because of the trial's size, assessors could not be blinded to toxicity or clinical assessments.
Blinding of outcome assessment	High risk	Treatment allocation was not masked and, because of the trial's size, assessors could not be blinded to toxicity or clinical assessments.
Incomplete outcome data	Low risk	Losses to follow-up are disclosed
Selective reporting	Low risk	Pre-planned analyses.
Other bias	Low risk	No other sources of bias identified.

Study ID: PIVOT trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Randomization was stratified according to site and implemented by means of a central interactive telephone system
Allocation concealment	Low risk	Protocol
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect mortality or biochemical/clinical relapse.
Blinding of outcome	Low risk	After randomization, a central pathologist reviewed the biopsy and radical-prostatectomy specimens, and a

assessment		central laboratory measured PSA.
Incomplete outcome data	Low risk	Losses to follow-up described and were low
Selective reporting	Low risk	Protocol
Other bias	Low risk	Not identified
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Randomization was stratified according to site and implemented by means of a central interactive telephone system
Allocation concealment	Low risk	Protocol
Blinding of participants and personnel	HIGH risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Blinding of outcome assessment	High risk	Toxicity outcomes are patient-reported and therefore at high risk of bias.
Incomplete outcome data	High risk	Moderate losses to follow-up, 23% in each group.
Selective reporting	Low risk	Protocol
Other bias	Low risk	Not identified

Study ID: GETUG 06 Tial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	Not stated
Allocation concealment	Unclear risk	Not stated
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect mortality or biochemical/clinical relapse.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect mortality or biochemical/clinical relapse.
Incomplete outcome data	Low risk	Lost to follow-up described
Selective reporting	Unclear risk	No protocol available
Other bias	Low risk	Not identified

Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	Not stated
Allocation concealment	Unclear risk	Not stated
Blinding of participants and personnel	HIGH risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Blinding of outcome assessment	HIGH risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Incomplete outcome data	Low risk	Lost to follow-up described
Selective reporting	Unclear risk	No protocol available
Other bias	Low risk	Not identified

Study ID: Widmark 2011

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear	No details available.
Allocation concealment	Unclear	No details available.
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect mortality or biochemical/clinical relapse.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect mortality or biochemical/clinical relapse.
Incomplete outcome data	Unclear	No details available.
Selective reporting	Unclear	No details available.
Other bias	Unclear	No details available.

Study ID: Yeoh trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**

Random sequence generation	Low risk	Blocked computer-generated random numbers (Yeoh EE 2003)
Allocation concealment	Unclear risk	Not clear
Blinding of participants and personnel	Low risk	Unlikely to pose any conceptual risks to the ascertainment of mortality
Blinding of outcome assessment	Low risk	Unlikely to pose any conceptual risks to the ascertainment of mortality
Incomplete outcome data	Low risk	Report Kaplan Meier estimates, log-rank test results.
Selective reporting	Low risk	Pre-specified
Other bias	Low risk	Not identified

Study ID: Royal Marsden trial

Risk of bias table for outcome a		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	"Randomised permuted blocks design from an independent randomisation service offered by the Clinical trials and Statistics Unit, institute of Cancer Research".
Allocation concealment	Low risk	Allocation carried out by independent randomisation service.
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality.
Incomplete outcome data	Low risk	Losses of follow-up disclosed, losses were low and balanced between intervention groups.
Selective reporting	Unclear risk	Not clear which outcomes were pre-specified.
Other bias	Low risk	No other sources of bias identified.
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	"Randomised permuted blocks design from an independent randomisation service offered by the Clinical trials and Statistics Unit, institute of Cancer Research".

Allocation concealment	Low risk	Allocation carried out by independent randomisation service.
Blinding of participants and personnel	High risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Blinding of outcome assessment	High risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Incomplete outcome data	Low risk	Losses of follow-up disclosed, losses were low and balanced between intervention groups.
Selective reporting	High risk	Some cut-off values reporting.
Other bias	Low risk	No other sources of bias identified.

Study ID: Zietman trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Central randomization
Allocation concealment	Low risk	Randomized by external body: randomized centrally by the American College of Radiology statistical office on protocol 95-09 of the Proton Radiation Oncology Group between January 1996 and December1999.
Blinding of participants and personnel	Low risk	Unlikely to pose any conceptual risks to the ascertainment of mortality and biochemical outcomes
Blinding of outcome assessment	Low risk	Unlikely to pose any conceptual risks to the ascertainment of mortality and biochemical outcomes
Incomplete outcome data	Low risk	Follow-up data completed
Selective reporting	unclear	No clear
Other bias	Low	Not identified
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Central randomization
Allocation concealment	Low risk	Randomized by external body: randomized centrally by the American College of Radiology statistical office on protocol 95-09 of the Proton Radiation Oncology Group between January 1996 and December1999.
Blinding of participants and	High risk	Lack of blinding is likely to poses conceptual risks to

personnel		toxicity assessment
Blinding of outcome assessment	High risk	Lack of blinding is likely to poses conceptual risks to toxicity assessment
Incomplete outcome data	Low risk	Follow-up data completed
Selective reporting	Unclear	No clear
Other bias	Low	Not identified

Study ID: SPCG-4

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low	Stratification according to tumor grade and randomization center. The randomization list was computer generated, and the block size was unknown to the investigators
Allocation concealment	Unclear	Not stated
Blinding of participants and personnel	Low	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality.
Blinding of outcome assessment	Low	"Blinding to analyst". The pathologists were blinded to patient outcome and assignment. Only the results from the central review are used. Members of the endpoint committee were blinded to patients' group assignment and treatment received." Or, "Blinded evaluation (2005)".
Incomplete outcome data	Low	Losses of follow-up disclose
Selective reporting	Low	Outcomes pre-specified
Other bias	Low	Not other sources of bias identified.
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	The randomization list was computer generated (Bill-Axelson,2002)
Allocation concealment	Unclear risk	Not stated
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk	Outcome assessment was obtained by asking patients to return questionnaire after intervention, from which the blinding of assessor is impossible.

Incomplete outcome data	Low risk	88% and 87% of participants return questionnaires from prostatectomy and watchful waiting, respectively.
Selective reporting	Unclear risk	Study report doesn't make clear if this outcom were pre-specified.
Other bias	Low risk	No other sources of bias identified.

Study ID: Graversen1990

Risk of bias table for outcome a		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	More elderly patients in placebo group
Allocation concealment	Unclear risk	Not stated
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality.
Incomplete outcome data	High risk	Outcome data incomplete.
Selective reporting	Unclear risk	Not stated
Other bias	High risk	31 stage I and 20 stage II patients were assigned to placebo; 31 stage I and 30 stage II patients were assigned to prostatectomy.

Study ID: Canada trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information given
Allocation concealment	Unclear risk	No information given
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect treatment failure, overall survival, biopsy rate, disease-specific survival.
Blinding of outcome assessment	Low risk	No blinding mentioned, but we judge that lack of blinding is unlikely to affect treatment failure, overall survival,

		biopsy rate, disease-specific survival.
Incomplete outcome data	Low risk	Losses to follow-up are fairly low
Selective reporting	Unclear risk	No information given
Other bias	Low risk	No other sources of bias identified
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information given
Allocation concealment	Unclear risk	No information given
Blinding of participants and personnel	High risk (need further discussion)	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk (need further discussion)	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of adverse effects
Incomplete outcome data	Low risk	Losses to follow-up are fairly low
Selective reporting	Unclear risk	No information given
Other bias	Low risk	No other sources of bias identified

Study ID: MRC RT01

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Computer-based minimisation algorithm
Allocation concealmentLow	Low risk	Central allocation
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect overall survival
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect overall survival
Incomplete outcome data	Unclear risk	Losses to follow-up are disclosed and appear balanced across groups for other outcomes reported, but we can't adjust for losses to follow-up for overall survival since this outcome isn't formally reported.
Selective reporting	Low risk	Outcomes pre-specified in trial protocol

Other bias	Low risk	No other sources of bias identified.
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Computer-based minimisation algorithm
Allocation concealmentLow	Low risk	Central allocation
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of adverse effects
Incomplete outcome data	Low risk	Adjustment made for losses to follow-up in calculation of the hazard ratios and cumulative proportions reported.
Selective reporting	Low risk	Outcomes pre-specified in trial protocol
Other bias	Low risk	No other sources of bias identified.

Study ID: Chin 2008

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information given
Allocation concealment	Unclear risk	No information given
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect biochemical disease-free survival, disease specific survival, overall survival and positive biopsy
Blinding of outcome assessment	Low risk	No blinding mentioned, but we judge that lack of blinding is unlikely to affect biochemical disease-free survival, disease specific survival, overall survival and positive biopsy
Incomplete outcome data	Unclear risk	No information given
Selective reporting	Unclear risk	No information given
Other bias	Low risk	No other sources of bias identified.
Risk of bias table for outcome c		

	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information given
Allocation concealment	Unclear risk	No information given
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of adverse effects
Incomplete outcome data	Unclear risk	No information given
Selective reporting	Unclear risk	No information given
Other bias	Low risk	No other sources of bias identified.

Study ID: MRC RT01 pilot trial

Risk of bias table for outcome b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low	Randomised permuted block design
Allocation concealment	Low	Independent randomisation was undertaken by ICR Clinical Trials and Statistics Unit.
Blinding of participants and personnel	Low	unlikely to pose any conceptual risks to the ascertainment of biochemical failure or local/metastatic failure
Blinding of outcome assessment	Low	unlikely to pose any conceptual risks to the ascertainment of biochemical failure or local/metastatic failure
Incomplete outcome data	Low	Losses of follow-up disclosed
Selective reporting	Unclear	Unclear whether outcomes reported were pre-specified in the protocol.
Other bias	Low	Not identified
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low	Randomised permuted block design

Allocation concealment	Low	Independent randomisation was undertaken by ICR Clinical Trials and Statistics Unit.
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of adverse effects
Incomplete outcome data	Low	Losses of follow-up disclosed
Selective reporting	Unclear	Unclear whether outcomes reported were pre-specified in the protocol.
Other bias	Low	Not identified

Study ID: Akakura 2006

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No details given, but may be reported in the earlier design paper
Allocation concealment	Unclear risk	No details given, but may be reported in the earlier design paper
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect biochemical progression-free survival, clinical progression-free survival, cause-specific survival and overall survival
Blinding of outcome assessment	Low risk	No blinding mentioned, but we judge that lack of blinding is unlikely to affect biochemical progression-free survival, clinical progression-free survival, cause-specific survival and overall survival
Incomplete outcome data	Unclear risk	No information given
Selective reporting	Unclear risk	No information given
Other bias	Low risk	No other sources of bias identified

Study ID: Arcangeli 2010

Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information

Allocation concealment	Unclear risk	No information
Blinding of participants and personnel	High risk	Lack of blinding is likely to poses conceptual risks to toxicity assessment
Blinding of outcome assessment	High risk	Lack of blinding is likely to pose conceptual risk to the toxicity assessment.
Incomplete outcome data	Low risk	No lost to follow-up
Selective reporting	Unclear risk	No protocol information
Other bias	Low risk	Not identified
Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information
Allocation concealment	Unclear risk	No information
Blinding of participants and personnel	Low risk	We judge that blinding is less likely to poses high risk on survival and biochemical/clinical outcomes
Blinding of outcome assessment	Low risk	We judge that blinding is less likely to poses high risk on survival and biochemical/clinical outcomes
Incomplete outcome data	Low risk	No lost to follow-up
Selective reporting	Unclear risk	No protocol information
Other bias	Low risk	Not identified

Study ID: Kopper trial

Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Blinding of outcome assessment	High	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Incomplete outcome data	Low	Follow-up completed in (Kopper 2004)

Selective reporting	Unclear	Not clear which outcomes were pre-specified.
Other bias	Low	No other sources of bias identified

Study ID: Lukka 2005

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	"Patients were assigned…according to a central computer-generated randomization schedule…"
Allocation concealment	Low risk	Central allocation
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect overall survival.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect measurement of overall survival.
Incomplete outcome data	Low risk	Losses to follow-up are balanced across groups, and taken into account in analysis.
Selective reporting	Low risk	Methods section implies that all outcomes reported were pre-specified and approved by the study Steering Committee. The primary outcome was altered to an outcome of increasing importance in emerging literature, before the data were unblinded.
Other bias	Low risk	No other sources of bias identified.
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	"Patients were assigned…according to a central computer-generated randomization schedule…"
Allocation concealment	Low risk	Central allocation
Blinding of participants and personnel	High risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Blinding of outcome assessment	High risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Incomplete outcome data	Low risk	Losses to follow-up are balanced across groups, and taken into account in analysis.
Selective reporting	Low risk	Methods section implies that all outcomes reported were pre-specified and approved by the study Steering Committee. The primary outcome was altered to an outcome of increasing importance in emerging literature, before the data were unblinded.

Other bias	Low risk	No other sources of bias identified.

Study ID: Marzi 2009

Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information.
Allocation concealment	Unclear risk	No information.
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of adverse effects
Incomplete outcome data	High risk	Losses to follow-up are fairly high and no information is given about the patients lost to follow-up.
Selective reporting	Unclear risk	Not clear which outcomes were pre-specified.
Other bias	Low risk	No other sources of bias identified.

Study ID: Norkus 2009

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear	Methods not stated
Allocation concealment	Unclear	Methods not stated
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality and disease control.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality and disease control.
Incomplete outcome data	Low risk	Low losses to follow-up
Selective reporting	Low risk	The two 2009 papers list the planned endpoints and report the early 12-month findings. It's unlikely that other pre-specified outcomes would be omitted at this stage of the trial.
Other bias	Low risk	No other bias identified

Study ID: Dutch trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Random assignment was performed with a minimization technique with stratification for treatment group
Allocation concealment	Low risk	Random assignment was performed with a minimization technique with stratification for treatment group
Blinding of participants and personnel	Low risk	Not clear but low risk for mortality
Blinding of outcome assessment	Low risk	Not clear but low risk for mortality
Incomplete outcome data	Low risk	Losses to follow-up disclosed.
Selective reporting	Unclear risk	Not clear which outcomes were pre-specified.
Other bias	Low risk	No other sources of bias identified.
Risk of bias table for the rest outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Random assignment was performed with a minimization technique with stratification for treatment group
Allocation concealment	Low risk	Random assignment was performed with a minimization technique with stratification for treatment group
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of toxicity
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of toxicity
Incomplete outcome data	Low risk	Losses to follow-up disclosed.
Selective reporting	Unclear risk	Not clear which outcomes were pre-specified.
Other bias	Low risk	No other sources of bias identified.

Study ID: M. D. Anderson trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**

Random sequence generation	Unclear risk	No information.
Allocation concealment	Unclear risk	No information.
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality and disease progression outcomes.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality and disease progression outcomes.
Incomplete outcome data	Unclear risk	No data on losses to follow-up
Selective reporting	Unclear risk	Not clear which outcomes were pre-specified.
Other bias	Low risk	No other sources of bias identified.
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information.
Allocation concealment	Unclear risk	No information.
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of toxicity
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of toxicity
Incomplete outcome data	Unclear risk	No data on losses to follow-up
Selective reporting	Unclear risk	Cut-points may have been chosen based on significance.
Other bias	Low risk	No other sources of bias identified.