

Supplementary Appendix

Supplement to: Hamdy FC, Donovan JL, Lane JA , et al. Fifteen-year outcomes after monitoring, surgery, or radiotherapy for prostate cancer. N Engl J Med. DOI: 10.1056/NEJMoa2214122

This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix

(Hamdy FC et al. 15-year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer)

Table of Contents

ProtecT Study Group Investigator list	2
Supplementary Figures	4
Figure S1. Time since randomisation at which prostate cancer deaths occurred amongst those allocated to active monitoring, radical prostatectomy, and radiotherapy	4
Figure S2 All-cause mortality	5
Figure S3 Long-term androgen-deprivation	6
Figure S4 Clinical Progression	7
Figure S5 Forest plot of sub-group analysis of age	8
Figure S6 Prostate cancer-specific and other-cause mortality in 2020 among men alive with metastatic disease in 2015	9
Supplementary Tables	10
Table S1 ProtecT participant prostate cancer risk-stratification according to major systems at baseline and by random allocation	10
Table S2 Number up-staged from cT1/T2 at baseline biopsy to pT3/T4 according to prostatectomy specimen among those receiving prostatectomy within 12 months of diagnosis	12
Table S3 Number up-graded from baseline biopsy to prostatectomy specimen among those receiving prostatectomy within 12 months of randomization (irrespective of allocation)	13
Table S4: Characteristics of patients who received radical prostatectomy and died of prostate cancer	14
Table S5: Baseline characteristics of patients who developed metastases	15
Table S6. Analysis exploring definite, probable, and possible prostate cancer death	16
Table S7: Hazard ratio estimates from the model that accommodate the changing relative treatment effect on prostate cancer mortality for the comparison between radiotherapy and active monitoring	17
Table S8 Underlying causes of death overall and by random allocation.....	18
Table S9 Breakdown of evidence of clinical progression and metastases by randomized group	19
Table S10 Baseline measures of all 545 participants randomized to active monitoring and 133 who had started AM and had not undergone radical treatment, were alive, and not on androgen-deprivation therapy	20
Table S11: Key factors compared between younger (age 50-64) and older (65-69) men at baseline	21

PROTECT STUDY GROUP INVESTIGATOR LIST

Principal Investigators:

Freddie C. Hamdy (Chief Investigator), Jenny L. Donovan, David E. Neal.

Trial Co-ordinator:

J. Athene Lane.

Trial Statisticians:

Chris Metcalfe, Grace J Young, Tim J. Peters.

Clinical Centre leads:

Bristol (David Gillatt, Edward Rowe), Edinburgh (Prasad Bollina), Newcastle (Phillip Powell, Edgar Paez), Sheffield (Freddie Hamdy, Derek Rosario), Cardiff (Howard Kynaston, Owen Hughes), Leicester (Roger Kockelbergh), Cambridge (David Neal, Andrew Doble, Vincent Gnanapragasam), Leeds (Stephen Prescott, Alan Paul), Birmingham (Alan Doherty)

Urologists:

John B. Anderson*, Jonathan Aning, Richard J Bryant, James Catto, Garrett Durkan, Anthony Kouparis, Hing Leung, Param Mariappan, Alan McNeill, Raj Persad, Hartwig Schwaibold, David Tulloch, Michael Wallace.

Nurses:

Lead: Peter Holding. *Site leads:* Susan Bonnington*, Lynne Bradshaw, Deborah Cooper, Emma Elliott, Phillipa Herbert, Joanne Howson, Amanda Jones, Teresa Lennon, Norma Lyons, Hilary Moody, Claire Plumb, Tricia O'Sullivan, Elizabeth Salter, Pauline Thompson, Sarah Tidball, Jan Blaikie, Catherine Gray. Tonia Adam, Sarah Askew, Sharon Atkinson, Tim Baynes, Carole Brain, Viv Breen, Sarah Brunt, Sean Bryne, Jo Bythem, Jenny Clarke, Jenny Cloete, Susan Dark, Gill Davis, Rachael De La Rue, Jane Denizot, Elspeth Dewhurst, Anna Dimes, Nicola Dixon, Penny Ebbs, Ingrid Emmerson, Jill Ferguson, Ali Gadd, Lisa Geoghegan, Alison Grant, Collette Grant, Rosemary Godfrey, Louise Goodwin, Susie Hall, Liz Hart, Andrew Harvey, Chloe Hault, Sarah Hawkins, Sharon Holling, Alastair Innes, Sue Kilner, Fiona Marshall, Louise Mellen, Andrea Moore, Sally Napier, Julie Needham, Kevin Pearse, Anna Pisa, Mark Rees, Elliw Richards, Lindsay Robson, Janet Roxburgh, Nikki Samuel, Irene Sharkey, Michael Slater, Donna Smith, Pippa Taggart, Helen Taylor, Vicky Taylor, Ayesha Thomas, Briony Tomkies, Nicola Trewick, Claire Ward, Christy Walker, Ayesha Williams, Colin Woodhouse, Elizabeth Wyber.

Oncologists:

Leads: Malcolm Mason, John Staffurth

Amit Bahl, Richard Benson, Mark Beresford, Catherine Ferguson, John Graham, Chris Herbert, Grahame Howard, Nick James, Peter Kirkbride, Alastair Law, Carmel Loughrey, Duncan McClaren, Helen Patterson*, Ian Pedley, Trevor Roberts*, Angus Robinson, Simon Russell, Paul Symonds, Narottam Thanvi, Subramaniam Vasanthan, Paula Wilson.

Histopathologists:

Leads: Jon Oxley, Mary Robinson

Selina Bhattarai, Neeta Deshmukh, John Dormer, Malee Fernando, John Goepel, David Griffiths, Ken Grigor, Patricia Harnden, Nick Mayer, Murali Varma, Anne Warren.

Radiologists and medical physicists:

Helen Appleby, Dominic Ash, Dean Aston, Steven Bolton, Graham Chalmers, John Conway, Nick Early, Tony Geater, Lynda Goddall, Claire Heymann, Deborah Hicks, Liza Jones, Susan Lamb, Geoff Lambert,

Gill Lawrence, Geraint Lewis, John Lilley, Aileen MacLeod, Pauline Massey, Alison McQueen, Rollo Moore, Lynda Penketh, Janet Potterton, Neil Roberts, Helen Showler, Pam Shuttleworth, Stephen Slade, Alasdair Steele, James Swinscoe, Marie Tiffany, John Townley, Jo Treeby, Michael Weston, Joyce Wilkinson, Lorraine Williams, Lucy Wills, Owain Woodley, Sue Yarrow.

Researchers and data managers:

Lucy Brindle, Linda Davies, Michael Davis, Dan Dedman, Elizabeth Down, Kirsty Garfield, Hanan Khazragui, Richard M. Martin, Nicola Mills, Sian Noble, Hilary Taylor, Marta Tazewell, Emma L. Turner, Julia Wade, Eleanor Walsh.

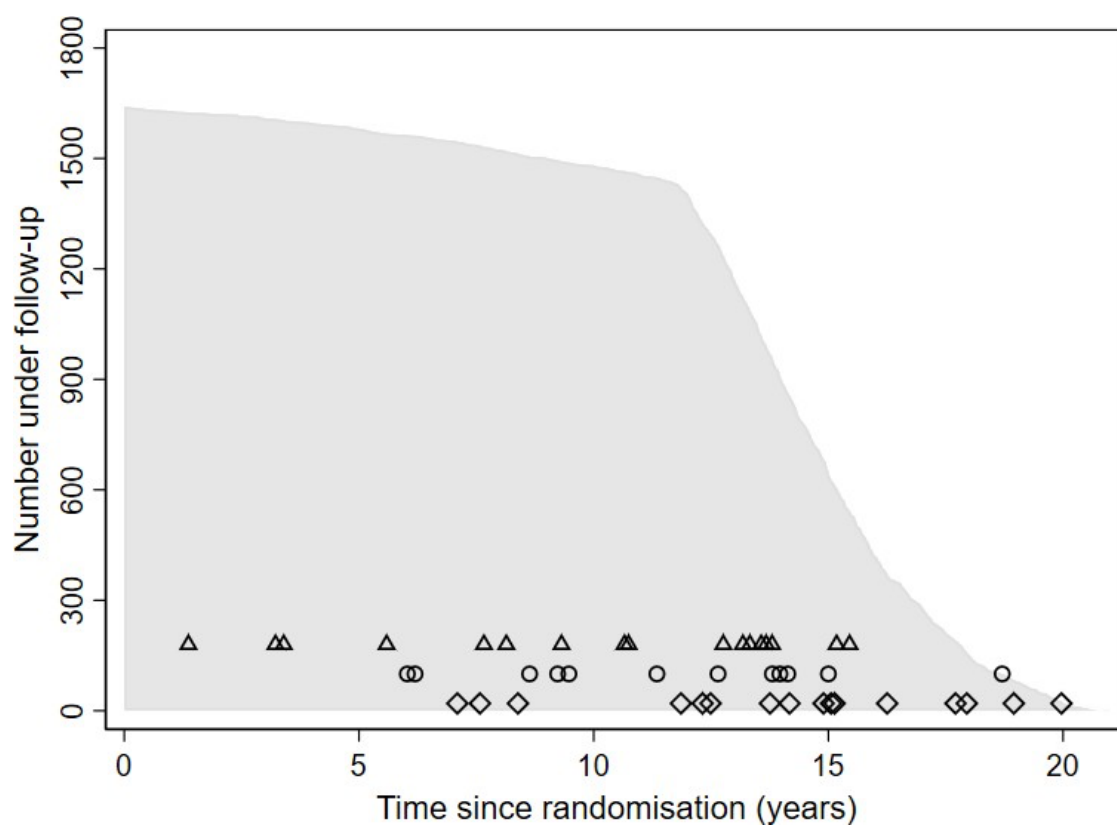
Administrative support:

Susan Baker, Elizabeth Bellis-Sheldon, Chantal Bougard, Joanne Bowtell, Catherine Brewer, Chris Burton, Jennie Charlton, Nicholas Christoforou, Rebecca Clark, Susan Coull, Christine Croker, Rosemary Currer, Claire Daisey, Gill Delaney, Rose Donohue, Jane Drew, Rebecca Farmer, Susan Fry, Jean Haddow, Alex Hale, Susan Halpin, Belle Harris, Barbara Hattrick, Sharon Holmes, Helen Hunt, Vicky Jackson, Donna Johnson, Mandy Le Butt, Jo Leworthy, Tanya Liddiatt, Alex Martin, Jainee Mauree, Susan Moore, Gill Moulam, Jackie Mutch, Kathleen Parker, Christopher Pawsey, Michelle Purdie, Teresa Robson, Lynne Smith, Carole Stenton, Tom Steuart-Feilding, Beth Stott, Chris Sully, Caroline Sutton, Carol Torrington, Zoe Wilkins, Sharon Williams, Andrea Wilson, Ashleigh Weaver.

*Deceased

Supplementary Figures

Figure S1. Time since randomisation at which prostate cancer deaths occurred amongst those allocated to Active Monitoring (triangles, n=17), Prostatectomy (circles, n=12) and Radiotherapy (diamonds, n=16). The height of the shaded area indicates the number of men under follow-up for all three groups combined. (See also related **Table S6**)



Prostate cancer deaths by quinquennium of the follow-up period in the three allocated groups

	0 to 5 years	>5 to 10 years	>10 to 15 years	>15 to 20 years	Total
Active Monitoring	3	4	8	2	17
Prostatectomy	0	5	6	1	12
Radiotherapy	0	3	6	7	16
Total	3	12	20	10	45

NB Please also see related **Table S7** Hazard ratio estimates from the model that accommodate the changing relative treatment effect on prostate cancer mortality for the comparison between radiotherapy and active monitoring.

Figure S2 All-cause mortality (active monitoring: green dash; prostatectomy: red; radiotherapy: blue)

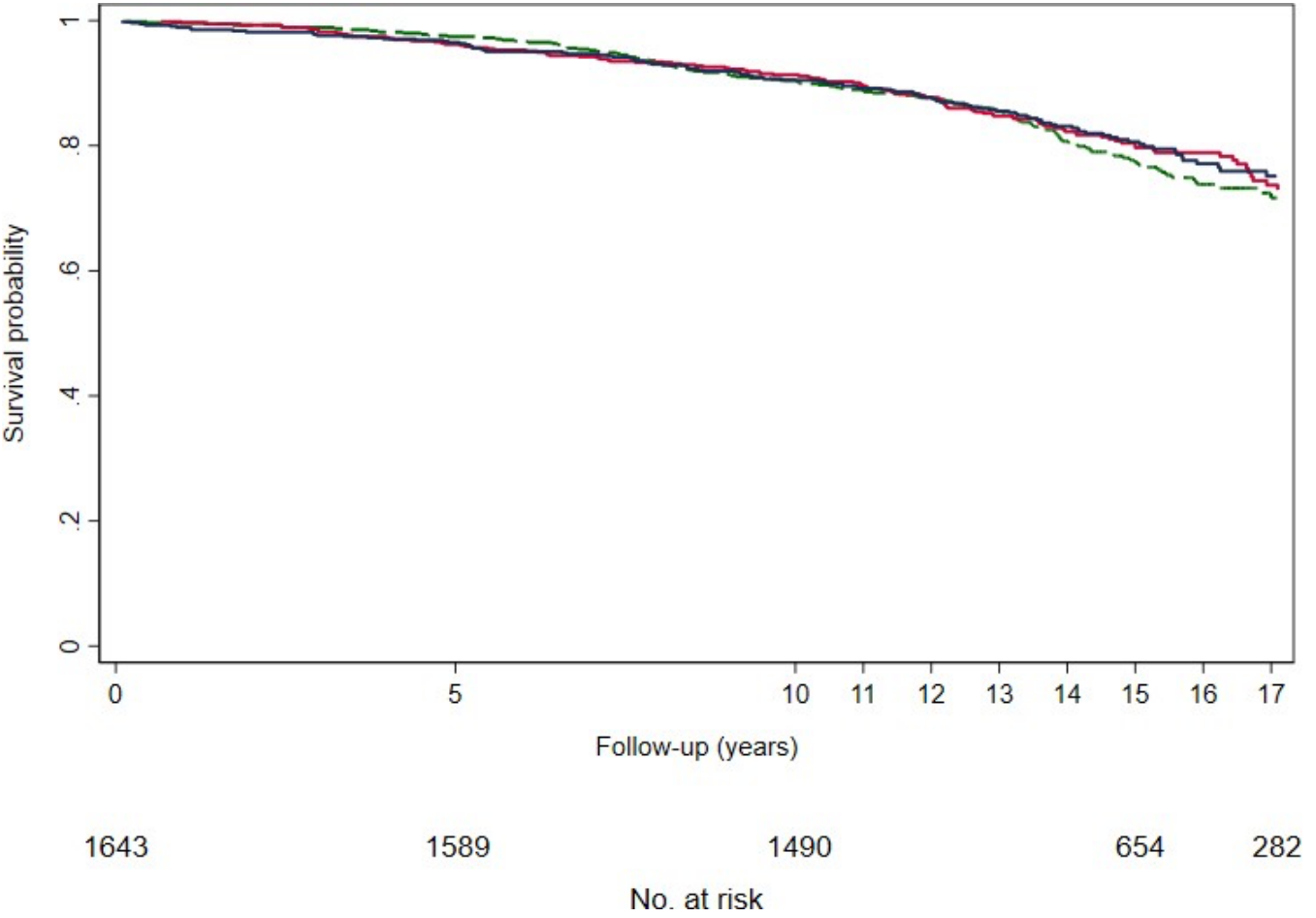
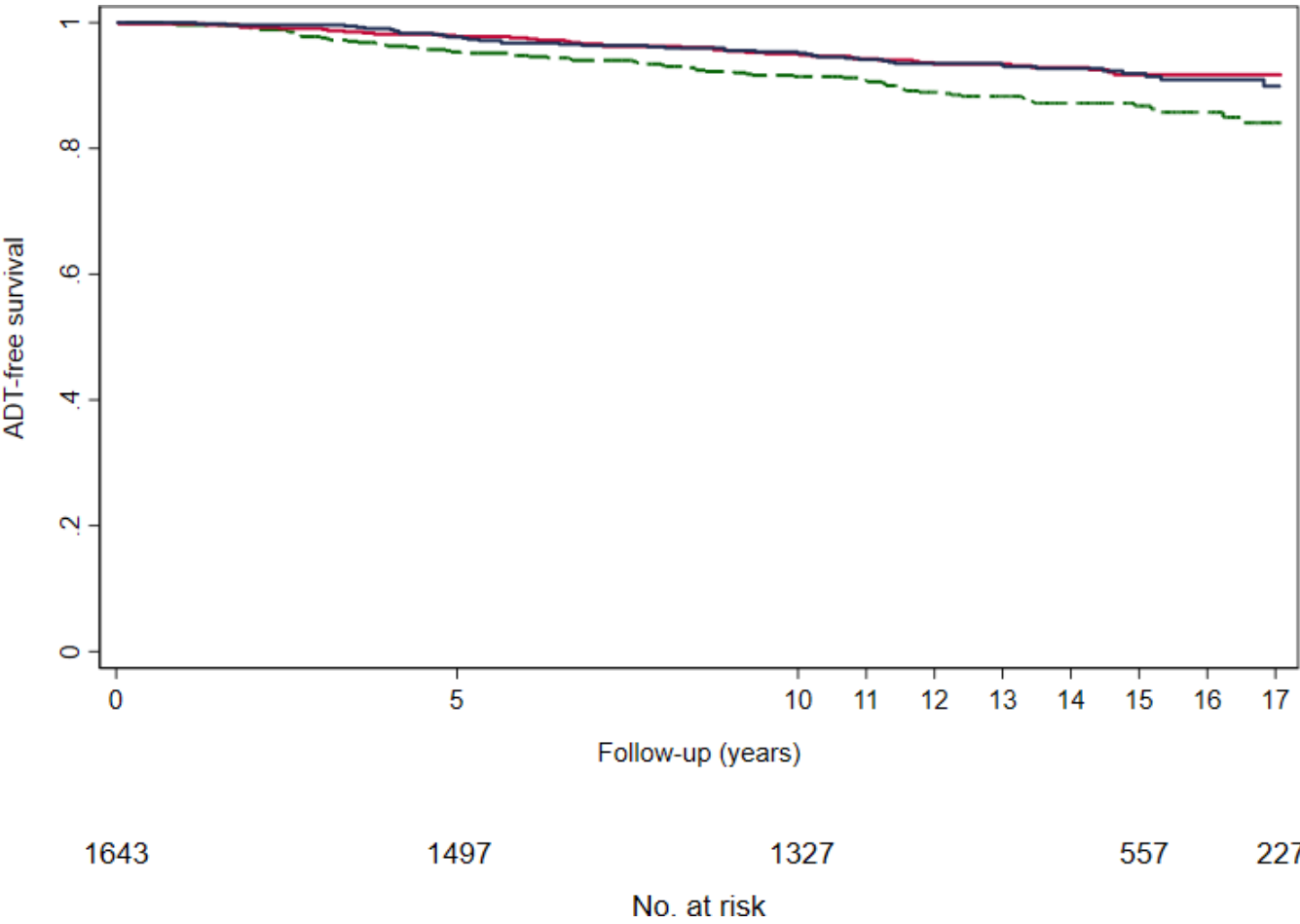


Figure S3. Onset of androgen deprivation therapy (Active Monitoring: green dash; Prostatectomy: red; Radiotherapy: blue)



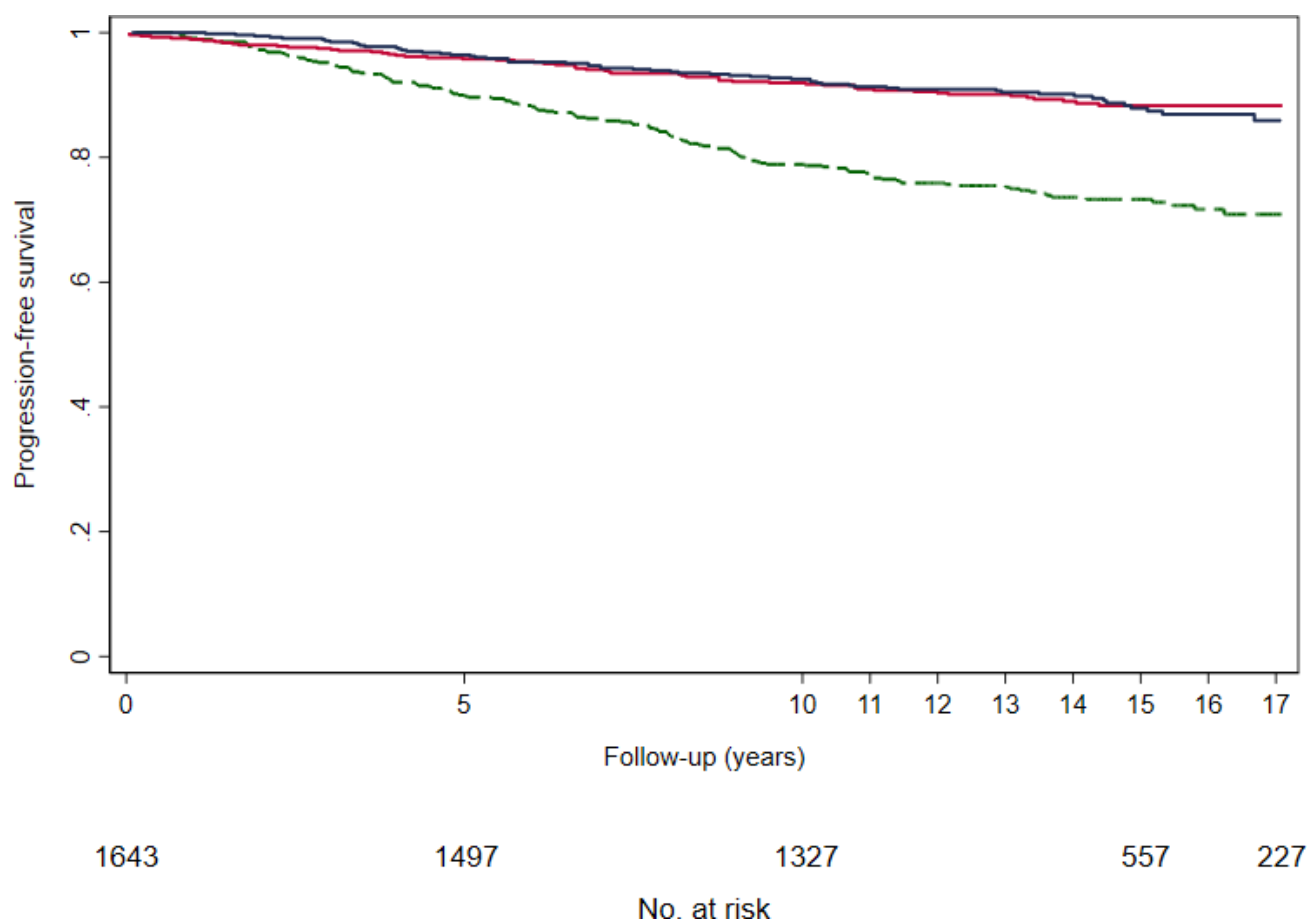


Figure S4. Clinical Progression (Active Monitoring: green dash; Prostatectomy: red; Radiotherapy: blue)

Figure S5 Forest plot of sub-group analysis of age

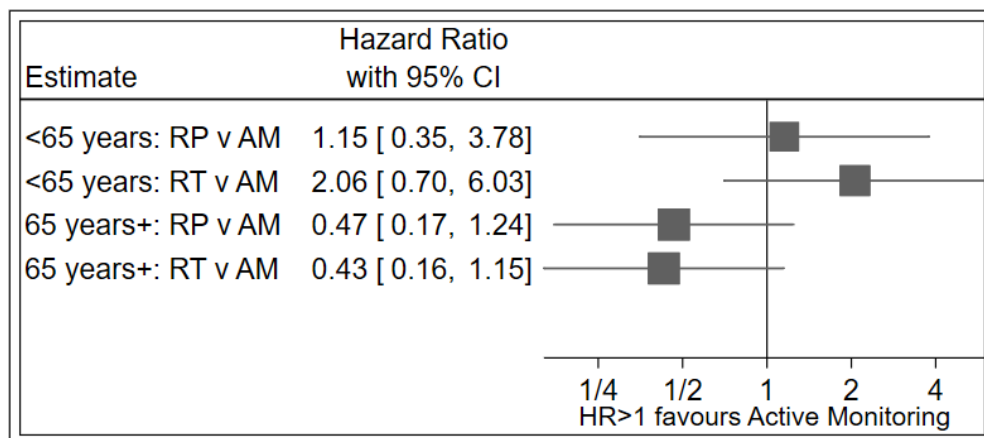
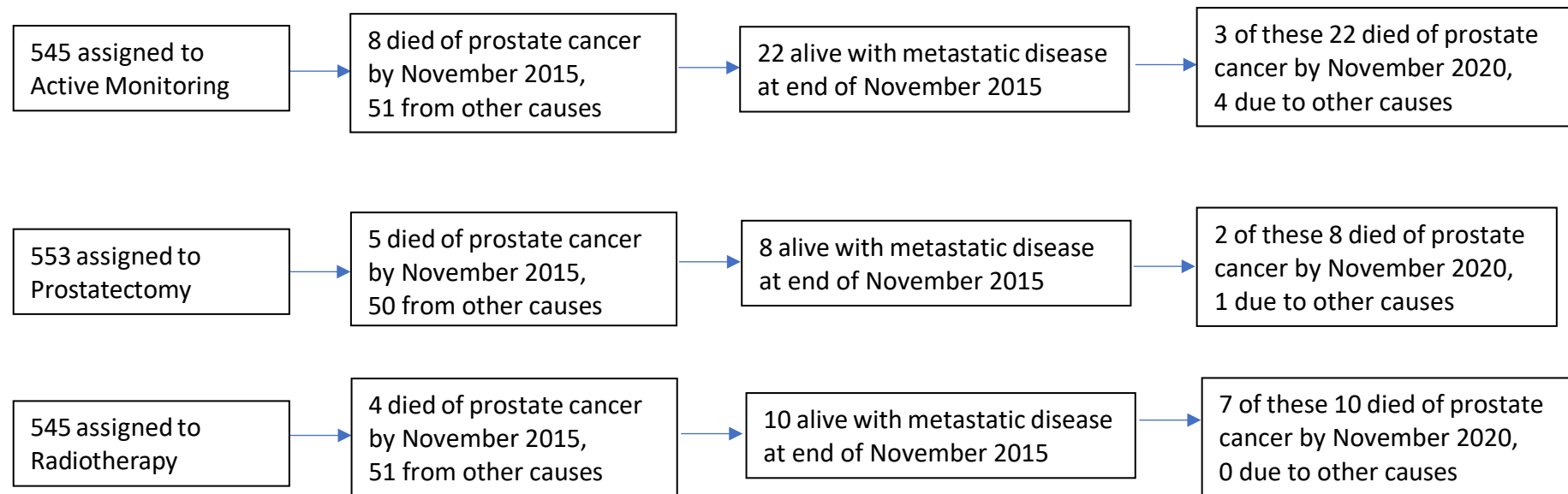


Figure S6. Prostate cancer-specific and other-cause mortality in 2020 among men alive with metastatic disease in 2015



Supplementary Tables

Table S1. ProtecT participant prostate cancer risk-stratification at baseline and by random allocation according to major stratification systems.

	CAPRA ¹ system scores (n=1619)			D'Amico risk stratification ² (n=1530 ³)			Cambridge Prognostic groups ⁴ (n=1642)		
	Score 0-2	Score 3-5	Score 6-10	Low	Intermediate	High	Group 1	Group 2	Groups 3-5
Active Monitoring	381	143	13	328	129	49	382	116	47
Prostatectomy	382	150	8	343	118	54	395	112	45
Radiotherapy	388	135	19	343	122	44	384	109	52
Overall	1151 (71%)	428 (26%)	40 (2%)	1014 (66%)	369 (24%)	147 (10%)	1161 (71%)	337 (21%)	144 (9%)

¹**CAPRA:** (Cancer of the Prostate Risk Assessment score). The score is calculated using points assigned to: age at diagnosis, PSA at diagnosis, Gleason score of the biopsy, clinical stage and percent of biopsy cores involved with cancer. These variables are outlined below. A CAPRA score of 0-2 indicates **low-risk**; CAPRA score of 3-5 indicates **intermediate-risk**, and CAPRA score of 6-10 indicates **high-risk**.

Variable	Specific Patient's level	Points to be assigned
Age at diagnosis	Under 50 years	0
	50 years or older	1
PSA at diagnosis	Less than or equal to 6 ng/ml	0
	Between 6.1 and 10 ng/ml	1
	Between 10.1 and 20 ng/ml	2
	Between 20.1 and 30 ng/ml	3
	More than 30 ng/ml	4
Gleason score of the biopsy (primary/secondary)	No pattern 4 or 5	0
	Secondary pattern 4 or 5	1
	Primary pattern 4 or 5	3
Clinical stage (T stage)	T1 or T2	0
	T3a	1
Percent of biopsy cores involved with cancer	34 percent or more	1

Footnotes ^{2, 3, 4} – see overleaf

² D'Amico's risk classification. PSA less than or equal to 10 ng/ml, Gleason 6 (3+3), clinical stage T1-T2a indicates **low-risk**; PSA between 10-20 ng/ml, Gleason score of 7 (3+4 or 4+3), clinical stage T2b indicates **intermediate risk**; PSA more than 20 ng/ml, Gleason score equal or higher than 8, clinical stage T2c-T3a indicates **high-risk**.

³ 108 T2s excluded as could not be recoded as a/b/c

⁴ Cambridge Prognostic Groups.

Group 1: low risk. Grade group 1 (Gleason score 3+3=6), PSA less than 10 ng/ml, clinical stage T1-T2;

Group 2: favorable intermediate risk. Grade group 2 (Gleason score 3+4=7) OR PSA 10-20 ng/ml and clinical stage T1-T2;

Group 3: intermediate risk. Grade group 2 (Gleason score 3+4=7), PSA 10 to 20 ng/ml, clinical stage T1-T2; OR: Grade group 3 (Gleason score 4+3=7) and clinical stage T1-T2;

Group 4: high risk. One of the following: Grade group 4 (Gleason score 8) or PSA >20 ng/ml OR clinical stage T3;

Group 5: high risk: Two criteria as in Group 4 OR Grade group 5 (Gleason score 9-10) OR clinical stage T4.

Low risk prostate cancer is similar to CPG 1.

Medium or intermediate risk prostate cancer is similar to CPG 2 and CPG 3.

High risk prostate cancer is similar to CPG 4 and CPG 5

Table S2. Number up-staged from cT1/T2 at baseline biopsy to pT3/T4 according to prostatectomy specimen among those receiving prostatectomy within 12 months of randomization (irrespective of allocation). Key percentages below table.

Pathological (pT) stage from prostatectomy	Clinical (cT) stage at diagnosis		Total
	T1	T2	
pT2a	60	13	73
pT2b	26	12	38
pT2c	196	39	235
pT3a	68	56	124
pT3b	5	6	11
pT4	3	0	3
Missing	3	1	4
Total	361	127	488

Key percentages:

138/484 (29%) cT1/T2 at baseline (biopsy) were upstaged to pT3 or pT4

76/358 (21%) cT1 at baseline (biopsy) were upstaged to pT3 or pT4

62/126 (49%) cT2 at baseline (biopsy) were upstaged to pT3 or pT4

Table S3. Number up-graded from baseline biopsy to prostatectomy specimen among those receiving prostatectomy within 12 months of randomization (irrespective of allocation). Key percentages below table.

	Grade Group from biopsy					
Grade Group from prostatectomy	1	2	3	4	5	Total
1	230	8	1	1	0	240
2	121	67	6	2	0	196
3	9	17	8	2	1	37
4	1	2	1	3	1	8
5	2	1	1	0	0	4
Missing	0	3	0	0	0	3
Total	366	95	17	8	2	488

Key percentages:

Upgraded from biopsy to prostatectomy 155 / 483 (32%)

Upgraded from Grade Group 1 (3+3=6) at biopsy to Grade Group 2 or higher at prostatectomy 133 / 363 (37%)

Found with Grade Group 2 or higher at prostatectomy 245 / 485 (51%)

Table S4: Characteristics of patients who received radical prostatectomy and died of prostate cancer.

Age	Year randomised	Baseline PSA	Baseline Gleason /stage	RP year	RT salvage year	Death	Path grading	Path staging	CAPRA score
68	RT 2000	5.9	GGG1; 3+3=6; T2a	2002	2002	2020	GGG2; 3+4=7	pT3bN0M0*#	1
66	RP 2001	8.05	GGG4; 4+4=8; T1c	2002	X	2020	GGG2; 3+4=7	pT2bN0M0	5
64	RT 2001	7.37	GGG1; 3+3=6; T1c	2002	2008	2020	GGG3; 4+3=7	pT2cN0M0*	2
60	RP 2003	4.45	GGG3; 4+3=7; T2b	2003	2005	2009	GGG5; 4+5=9	pT3aN0M0*	4
67	RP 2004	3.95	GGG2; 3+4=7; T2b	2004	2006	2013	GGG2; 3+4=7	pT3aN0M0	2
56	AM 2005	4.3	GGG1; 3+3=6; T1c	2006	2014	2018	GGG2; 3+4=7	pT3aN0M0	1
66	RP 2005	3.15	GGG2; 3+4=7; T2b	2005	2009	2020	GGG2; 3+4=7	pT3bN0M0*#	3
65	RT 2006	4.8	GGG2; 3+4=7; T1c	2008	2009	2013	GGG5; 5+4=9	pT3aN1M0*	2
63	RT 2006	7.6	GGG3; 4+3=7; T1c	2008	2009	2018	GGG5; 4+5=9	pT3aN0M0	5
54	RP 2008	4.35	GGG1; 3+3=6; T2b	2008	2014	2020	GGG2; 3+4=7	pT3aN0M0	X
66	RP 2008	4.2	GGG2; 3+4=7; T2a	2009	2014	2020	GGG4; 4+4=8	pT3aN0M0*	2
58	AM 2006	4.95	GGG1; 3+3=6; T2a	2010	2011	2020	GGG3; 4+3=7	pT3bN0M0#	1
57	RP 2006	9.05	GGG1; 3+3=6; T1c	2010	X	2020	GGG4; 4+4=8	pT4N1M0*#	3

RT: Radical Radiotherapy; RP: Radical prostatectomy; AM: Active Monitoring; GGG: Gleason Grade Group.

*Positive surgical margin; # seminal vesicle involvement

Upgraded at radical prostatectomy: 10/13 (77%); Low-risk GGG1 disease at baseline: 6/13 (46%); CAPRA score 0-2 7/13 (77%); Upstaged at radical prostatectomy: 13/13 (100%); Received salvage radiotherapy: 11/13 (84%); Received radical prostatectomy within 2 years of diagnosis: 10/13 (77%); Lymph node involvement (N1): 2/13 (15%).

Table S5. Baseline characteristics of patients who developed metastases.

	Metastatic disease (n=104)	Whole cohort (n=1643)
Grade group 1 (%)	53 (51%)	1268 (77%)
Grade group 2 (%)	32 (31%)	275 (17%)
Grade groups 3-5 (%)	19 (18%)	99 (6%)
cT1	56 (54%)	1249 (76%)
cT2	48 (46%)	394 (24%)
CAPRA Score 0-2 (%)	49 (48%)	1151 (71%)
CAPRA Score 3-5 (%)	45 (44%)	428 (26%)
CAPRA Score 6-10 (%)	9 (9%)	40 (2%)
D'Amico low risk (%)	35 (41%)	1014 (66%)
D'Amico intermediate risk (%)	34 (40%)	369 (24%)
D'Amico high risk (%)	17 (20%)	147 (10%)
Cambridge Prognostic Group 1 (%)	45 (43%)	1161 (71%)
Cambridge Prognostic Group 2 (%)	34 (33%)	337 (21%)
Cambridge Prognostic Group 3+ (%)	25 (24%)	144 (9%)
Mean age (standard deviation)	63 (5)	62 (5)
Mean PSA (standard deviation)	6.8 (3.8)	5.8 (3.0)

Table S6: Analysis exploring definite, probable, and possible prostate cancer death

Allocation	Definite/probable prostate cancer death	Definite/probable and possible prostate cancer death	Randomized
Active monitoring	17 (3.2%)	20 (3.7%)	545
Prostatectomy	12 (2.2%)	12 (2.2%)	553
Radiotherapy	16 (2.9%)	16 (2.9%)	545
	45 (2.7%)	48 (2.9%)	1,643

No evidence against the null hypothesis of no difference in the rate of prostate cancer-specific death across the three groups (p=0.27)

Table S7. Hazard ratio estimates from the model that accommodate the changing relative treatment effect on prostate cancer mortality for the comparison between radiotherapy and active monitoring. The likelihood ratio test of the null hypothesis of no difference in prostate cancer mortality over median 15-year follow-up between the three allocated groups gives $p=0.51$

Comparison	Prostate cancer deaths / person years		Hazard ratio (95% CI)
	Radical treatment	Active Monitoring	
Prostatectomy versus Active Monitoring	12 / 7766	17 / 7633	0.66 (0.32, 1.39)
Radiotherapy versus Active Monitoring			
Up to 12.76 years	6/6498	9/6534	0.62 (0.23, 1.66)
After 12.76 years	10/1130	8/1100	1.18 (0.49, 2.88)

NB Please also see related **Figure S1**. Time since randomisation at which prostate cancer deaths occurred amongst those allocated to Active Monitoring, Prostatectomy, and Radiotherapy – above.

Table S8. Underlying causes of death overall and by random allocation

Causes of death	Active monitoring	Prostatectomy	Radiotherapy	Total
Prostate cancer	17	12	16	45
Other cancers	58	52	54	164
Cardiovascular (circulatory, respiratory)	34	37	30	101
Other	22	13	19	54
Total with codes	113	102	103	318
Unavailable (deaths in Scotland not available)	11	15	12	38

Table S9. Breakdown of evidence of clinical progression and metastases by randomized group.

	Active monitoring (n=545)	Prostatectomy (n=553)	Radiotherapy (n=545)
Evidence of clinical progression			
None	404 (74%)	495 (90%)	485 (89%)
Clinical restaging (DRE and CT/other scans)	69 (13%)	15 (3%)	17 (3%)
Long-term androgen-deprivation	21 (4%)	17 (3%)	16 (3%)
Evidence of metastases			
Metastases assumed from PSA>100	1 (<1%)	0	0
Regional node metastases	15 (3%)	4 (<1%)	4 (<1%)
Visceral / distant node metastases	2 (<1%)	1 (<1%)	3 (<1%)
Bony metastases	16 (3%)	9 (2%)	4 (<1%)
Prostate cancer specific death	17 (3%)	12 (2%)	16 (3%)

NB. A hierarchical approach was taken – any evidence of prostate cancer death, IF NOT bony metastases IF NOT any visceral / distant node metastases IF NOT regional node metastases IF NOT any evidence of long-term androgen-deprivation IF NOT evidence of clinical progression from digital rectal examination (DRE), CT or other scans restaging. No men fell solely into the other categories of progression (ureteric obstruction, rectal fistula, or the need for a permanent catheter).

Table S10. Baseline measures of all 545 participants randomized to active monitoring and 133 who had started AM and had not undergone radical treatment and were alive and not on androgen-deprivation therapy (ADT).

	Allocated to AM	
Baseline measures	No radical treatment subsequent to AM, no ADT & alive in Nov 2020 (n=133)	Whole group (n=545)
Mean age in years (SD)	63 (5)	62 (5)
Mean PSA ng/ml (SD)	4.6 (2.3)	5.7 (3.0)
Grade group 1 (%)	119 (89)	419 (77)
Grade group 2 (%)	12 (9)	93 (17)
Grade group 3-5 (%)	2 (2)	33 (6)
T1 (%)	119 (89)	410 (75)
T2 (%)	14 (11)	135 (25)
D'Amico Low Risk	113 (87)	328 (65)
D'Amico Intermediate Risk	12 (9)	129 (25)
D'Amico High Risk	5 (4)	49 (10)
CAPRA Score 0-2	115 (91)	382 (70)
CAPRA Score 3-5	12 (9)	116 (21)
CAPRA Score 6-10	0	47 (9)
Cambridge Prognostic Group 1	119 (89)	381 (71)
Cambridge Prognostic Group 2	10 (8)	143 (27)
Cambridge Prognostic Group 3-5	4 (3)	13 (2)

Table S11. Key factors compared between younger (age 50-64) and older (65-69) aged men at baseline.

	Age <65 years (n=1034)	Age 65 years+ (n=609)
Grade group 1 (%)	832 (81)	436 (72)
Grade group 2 (%)	153 (15)	122 (20)
Grade group 3-5 (%)	48 (5)	51 (8)
T1 (%)	787 (76)	462 (76)
T2 (%)	247 (24)	147 (24)
Received prostatectomy/radiotherapy / allocated to active monitoring, (%)	58/340 (17)	20/205 (10)
Received prostatectomy/radiotherapy / allocated to prostatectomy, (%)	282/353 (80)	158/200 (79)
Received prostatectomy/radiotherapy / allocated to radiotherapy, (%)	297/341 (87)	164/204 (80)
Prostate cancer deaths (%)	21 (2)	24 (4)
All cause deaths (%)	168 (16)	188 (31)