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Health Research

ProtecT study

(*Pro*state *te*sting for *c*ancer and *T*reatment)

World's first and largest trial comparing active monitoring, surgery and radiotherapy treatments for localised prostate cancer announces first results

Lack of evidence

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- No evidence that PSA-testing, and treatment of localised prostate cancer improved survival and quality of life
- Increasing burden to health care providers and society
- Uncertainties for patients over best treatment
- Treatment options not compared previously

Lack of evidence

NHS
National Institute for Health Research

Absence of evidence is not evidence of absence…

Parachut
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Gordon C S Sr

Abstract

Objectives To de
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Design Systemat
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Data sources: M
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sites and citation
Study selection:
a parachute duri
Main outcome r
defined as an inj
Results We were
controlled trials
Conclusions As
prevent ill health

HULTON/GETTY

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

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P Pell
sultant

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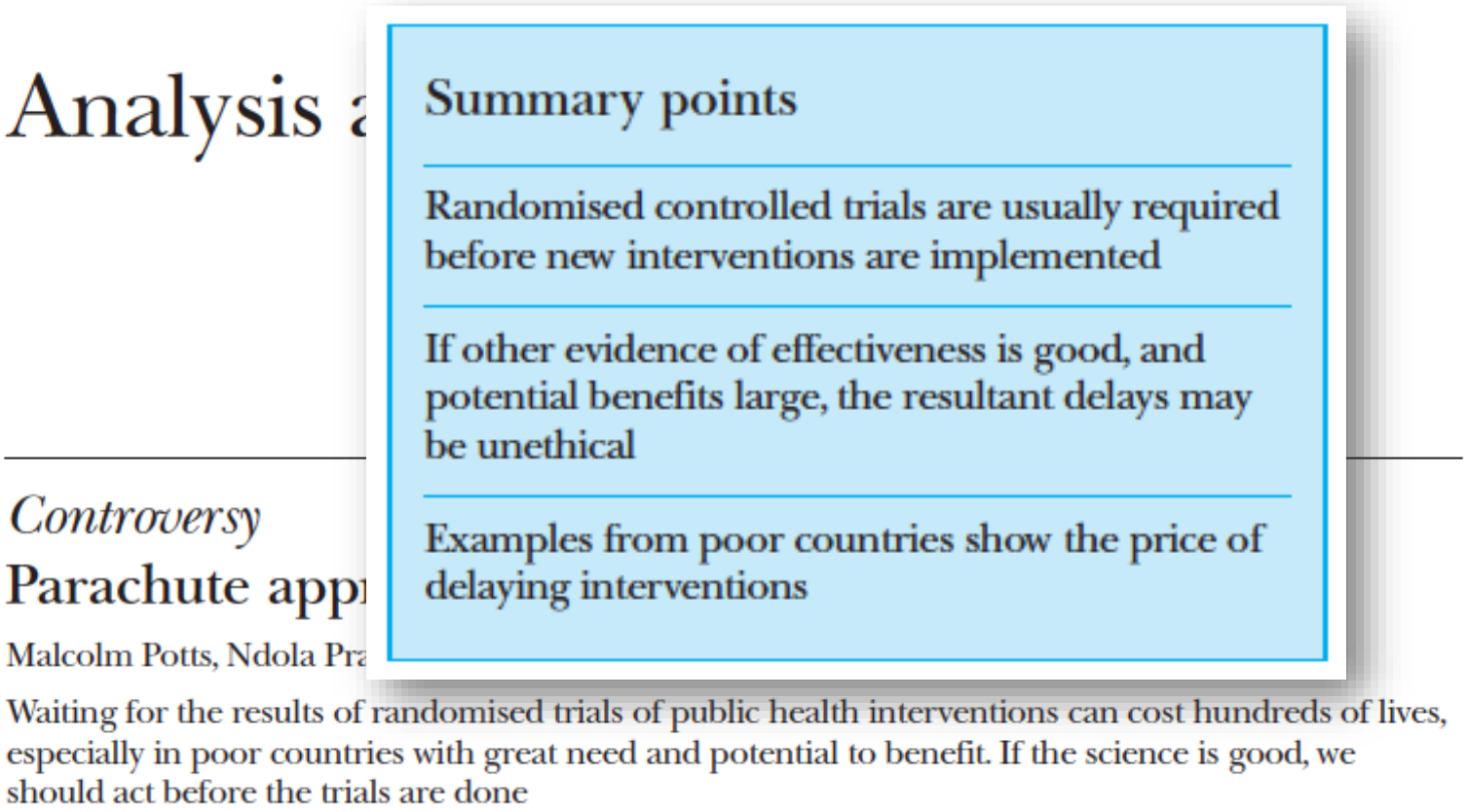
J 2003;327:1459–61

The Parachute

'We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, placebo controlled, crossover trial of the parachute.'

Smith & Pell, BMJ, 2003

The Parachute Story



Analysis a

Summary points

Randomised controlled trials are usually required before new interventions are implemented

If other evidence of effectiveness is good, and potential benefits large, the resultant delays may be unethical

Examples from poor countries show the price of delaying interventions

Controversy

Parachute appr

Malcolm Potts, Ndola Pra

Waiting for the results of randomised trials of public health interventions can cost hundreds of lives, especially in poor countries with great need and potential to benefit. If the science is good, we should act before the trials are done

ProtecT study design

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A major PSA-testing programme and 3-arm randomised trial of treatment effectiveness in prostate cancer:

- Active Monitoring *versus* surgery *versus* radiotherapy
- Primary end-point: prostate cancer-specific survival at 10 years
- All-cause deaths
- Cancer progression
- Patient-reported outcomes

Methods

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- Recruitment from Primary Care Physicians /GP practices
- Fit men, aged 50-69 years
- Prostate Check Clinics by Research Nurses
  - Counseling about prostate cancer
  - Obtaining informed consent
  - Taking blood for PSA-testing
- Invitation to the hospital for prostate biopsies in men with a raised PSA
- Men with prostate cancer were evaluated by clinicians
- Men suitable for the trial (localised disease) offered active-monitoring, surgery or radiotherapy

ProtecT study options

- **Active Monitoring** is a surveillance programme. Men were followed up with PSA-testing and re-evaluation of their disease. They were offered radical treatments if the disease appeared to progress. The purpose was to avoid unnecessary treatment, but to keep them in a 'window-of-curabillity' if treatment became necessary

- **Surgery** was performed as radical prostatectomy with routine follow-up and additional treatments

- **Radiotherapy** with regular follow-up, and additional interventions as necessary

The ProtecT trial: 1999-2008

(*Pro*state *te*sting for *c*ancer and *T*reatment)

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82,429 men tested
2,965 prostate cancers

ProtecT study flow chart

Active monitoring, radical prostatectomy, or radiotherapy for localised prostate cancer: study design and diagnostic and baseline results of the ProtecT randomised phase 3 trial

J Athene Lane*, Jenny L Donovan*, Michael Davis, Eleanor Walsh, Daniel Dedman, Liz Down, Emma L Turner, Malcolm D Mason, Chris Metcalfe, Tim J Peters, David E Neal*, Freddie C Hamdy*, for the ProtecT study group†

Summary

Background Prostate cancer is a major public health problem with considerable uncertainties about the effectiveness of population screening and treatment options. We report the study design, participant sociodemographic and clinical characteristics, and the initial results of the testing and diagnostic phase of the Prostate testing for cancer and Treatment (ProtecT) trial, which aims to investigate the effectiveness of treatments for localised prostate cancer.

Methods In this randomised phase 3 trial, men aged 50–69 years registered at 337 primary care centres in nine UK cities were invited to attend a specialist nurse appointment for a serum prostate-specific antigen (PSA) test. Prostate biopsies were offered to men with a PSA concentration of 3·0 μg/L or higher. Consenting participants with clinically localised prostate cancer were randomly assigned to active monitoring (surveillance strategy), radical prostatectomy, or three-dimensional conformal external-beam radiotherapy by a computer-generated allocation system. Randomisation was stratified by site [illegible] minimised for differences in participant age, PSA [illegible] and clinical stage (T score). The primary endpoint is prostate cancer mortality at a median 10-year follow-up, ascertained by an independent committee, which will be analysed by intention to treat in 2016. This trial is registered with ClinicalTrials.gov, number NCT02044172, and as an International Standard Randomised Controlled Trial, number ISRCTN20141297.

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See Online/Comment
http://dx.doi.org/10.1016/S1470-2045(14)70198-6

*These authors contributed equally
†Members listed in the appendix
University of Bristol, Bristol, UK (J A Lane PhD, Prof J L Donovan PhD, M Davis MSc, E Walsh MSc, D Dedman MSc, L Down BSc,

2,664
Eligible cases

82,429 participants

1,643 (62%)
Randomised

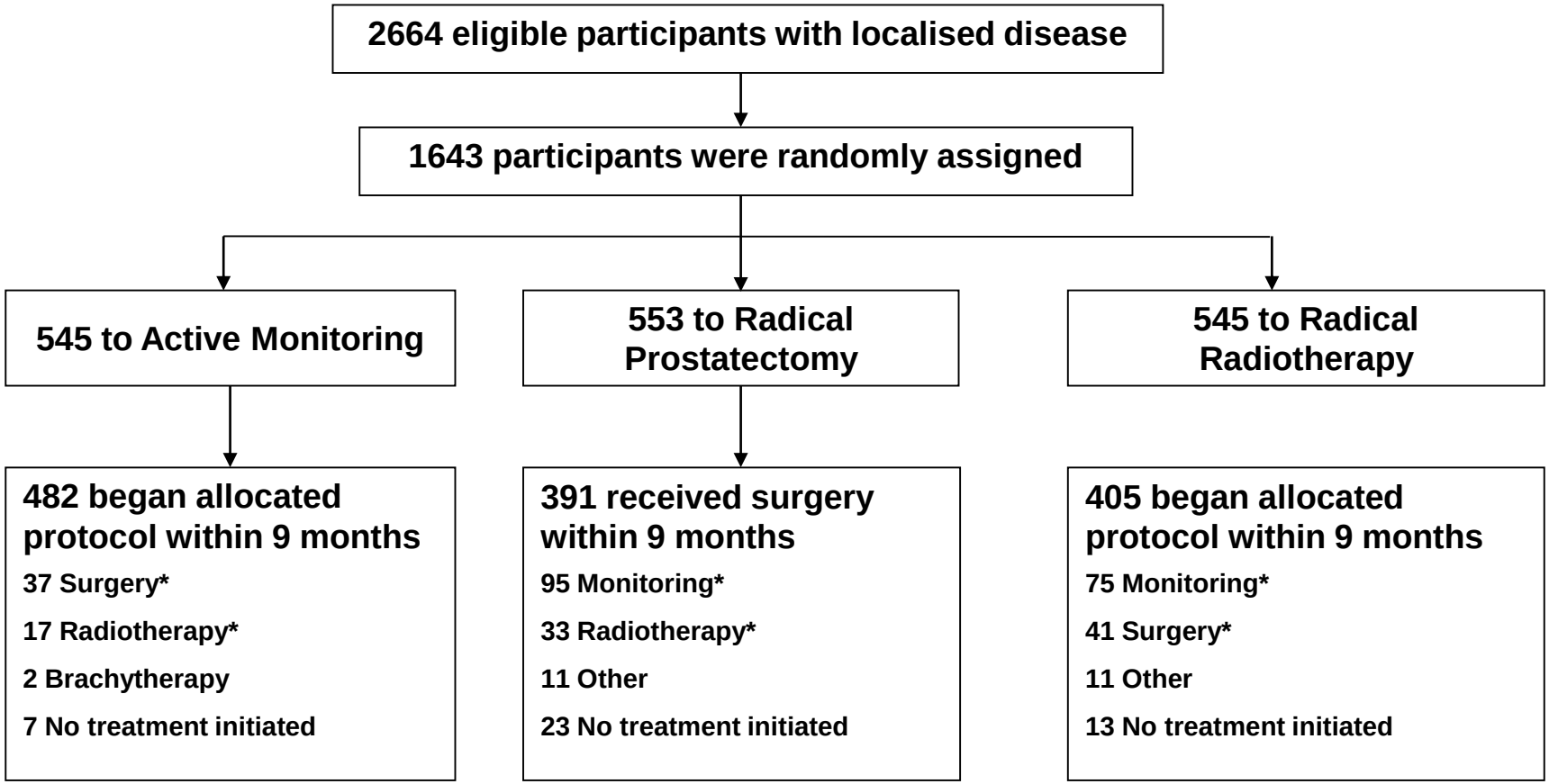
1021 (38%)
Preference

545 Active monitoring	**553** Surgery	**545** Radiotherapy	**521** Active monitoring	**365** Surgery	**135** Radiotherapy

Lane et al, Lancet Oncol 2014

	Active monitoring protocol (n=545)	Surgery (n=553)	Radiotherapy protocol (n=545)
Mean age in years at randomisation (SD[1])	62 (5)	62 (5)	62 (5)
White ethnic origin (%)	535 (99)	542 (99)	529 (98)
African-Caribbean origin (%)	2 (0.4)	3 (0.5)	5 (0.9)
Married or living with partner (%)	457 (84)	458 (84)	460 (85)
Managerial / professional occupation (%)	229 (43)	229 (42)	226 (42)
Known family history prostate cancer (%)	43 (8)	32 (6)	44 (8)
Median PSA[2] in ng/ml (IQR[3])	4.7 (3.7, 6.7)	4.9 (3.7, 6.7)	4.8 (3.7, 6.7)
PSA[2] 10+ ng/ml (%)	57 (10)	57 (10)	58 (11)
Gleason score			
6	421 (77)	422 (76)	423 (78)
7	111 (20)	120 (22)	108 (20)
8-10	13 (2)	10 (2)	14 (3)
Missing	0	1	0
Clinical stage			
T1c	410 (75)	410 (74)	429 (79)
T2	135 (25)	143 (26)	116 (21)

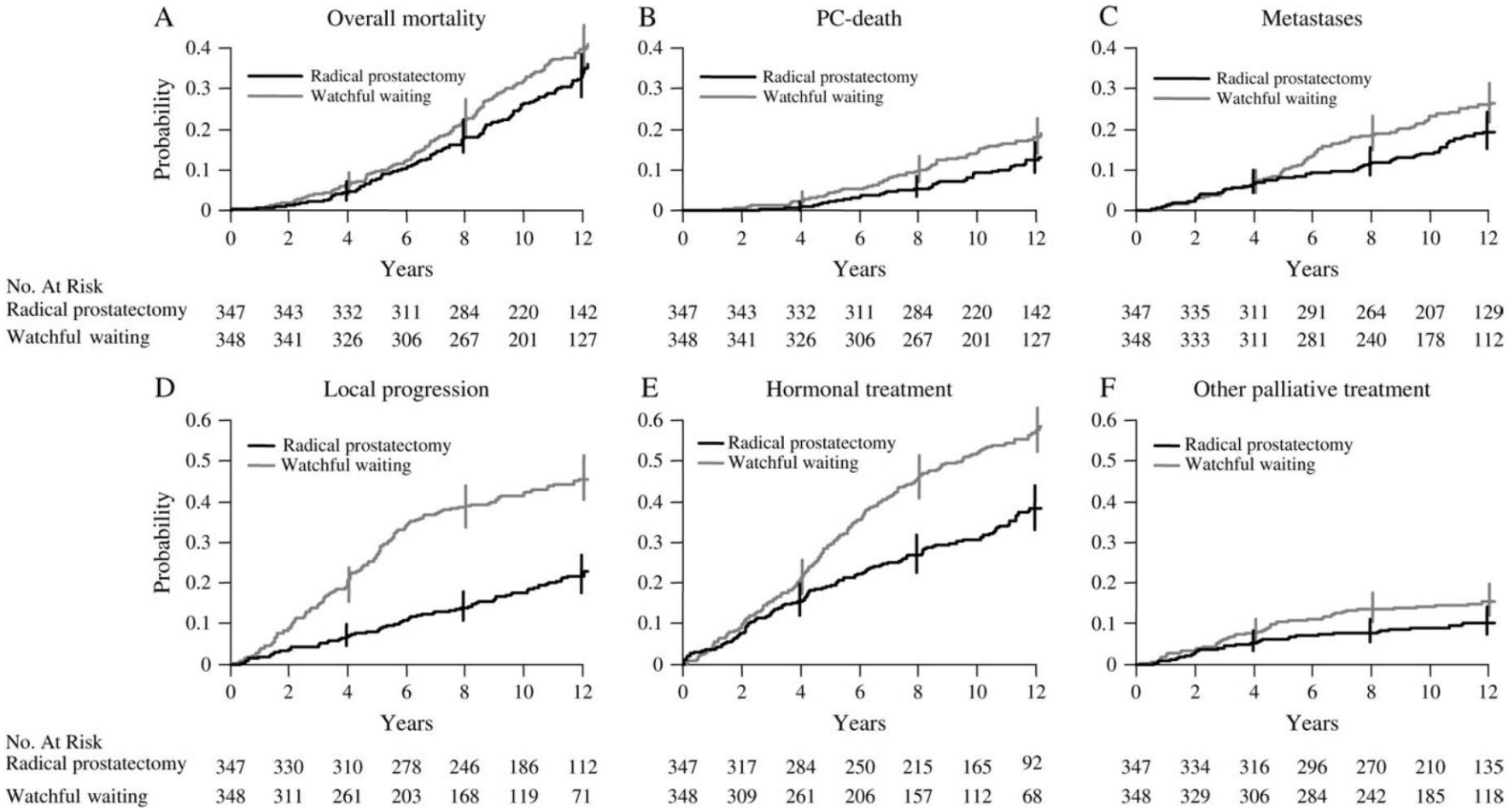
Study accrual (Consort Diagram)



What has been happening in the meantime?

Radical Prostatectomy Versus Watchful Waiting in Localized Prostate Cancer: the Scandinavian Prostate Cancer Group-4 Randomized Trial

Anna Bill-Axelson, Lars Holmberg, Frej Filén, Mirja Ruutu, Hans Garmo, Christer Busch, Stig Nordling, Michael Häggman, Swen-Olof Andersson, Stefan Bratell, Anders Spångberg, Juni Palmgren, Hans-Olov Adami, Jan-Erik Johansson; for the Scandinavian Prostate Cancer Group Study Number 4



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Radical Pro
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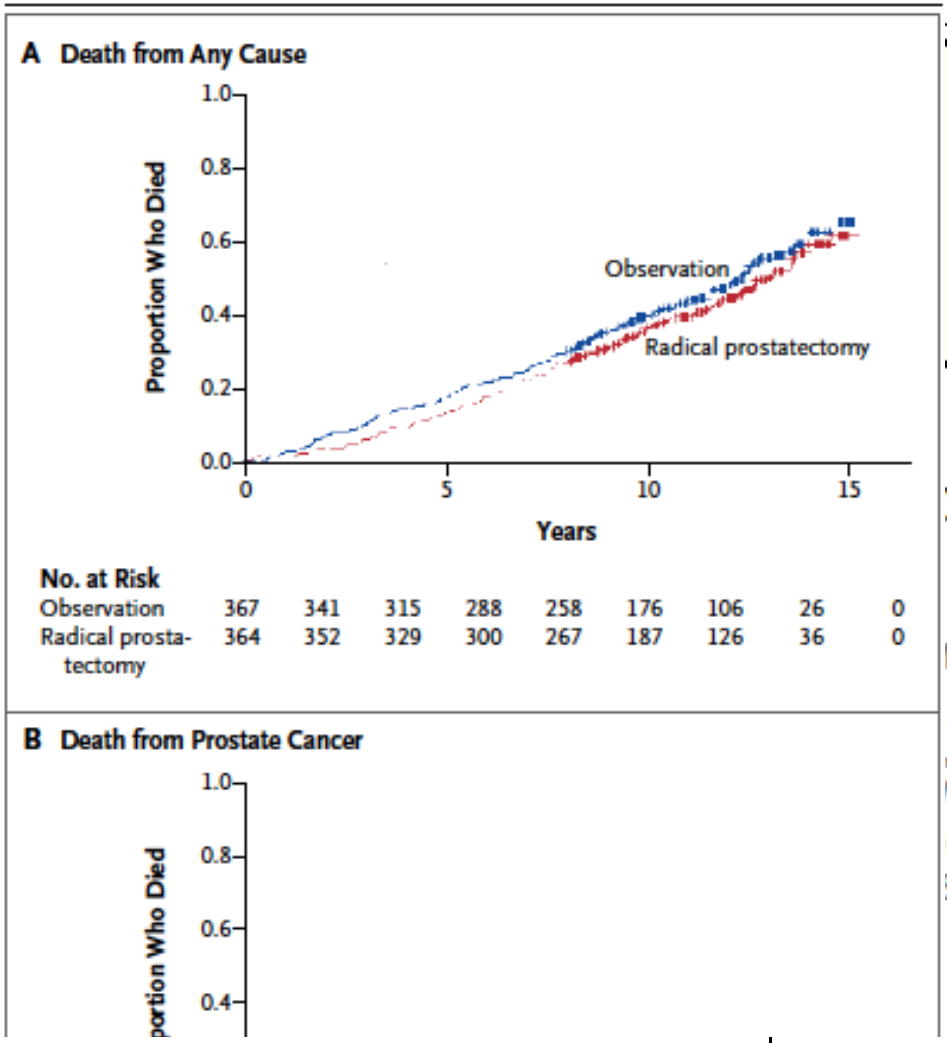
Timothy J. Wilt, M.D
William J. Aronso
Patricia Gilhooly, M.D.,
Glenn Snider, M.D
Parikshit Pandya, M
for the Pros
Michael J. Barry, M.D.,
John T. Wei, M.D.,
, Ruben Cartagena, M.D.,
William Blank, M.D.,
mas Wheeler, M.D.,
Study Group



Risk				0.07
Low	54/148	62/148	1.15 (0.80–1.66)	
Intermediate	70/120	59/129	0.69 (0.49–0.98)	
High	49/80	42/77	0.74 (0.49–1.13)	
Gleason score				0.87
<7	125/261	113/254	0.86 (0.67–1.12)	
≥7	47/86	50/98	0.84 (0.56–1.25)	

Figure 2. Kaplan–Meier Plots of Mortality.

Effect of screening by PSA at 13-y follow-up

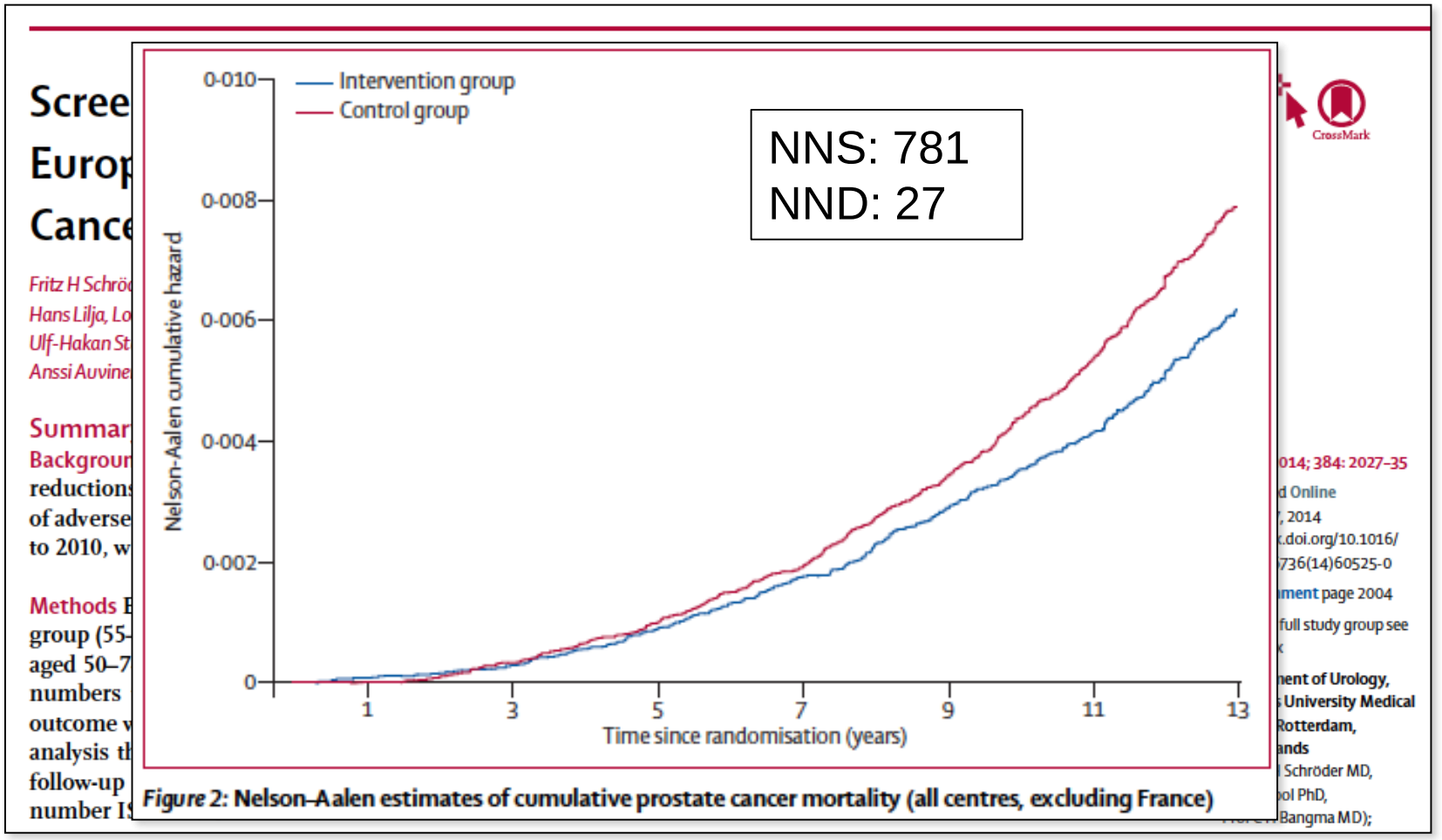


Figure 2: **Nelson–Aalen estimates of cumulative prostate cancer mortality (all centres, excluding France)**

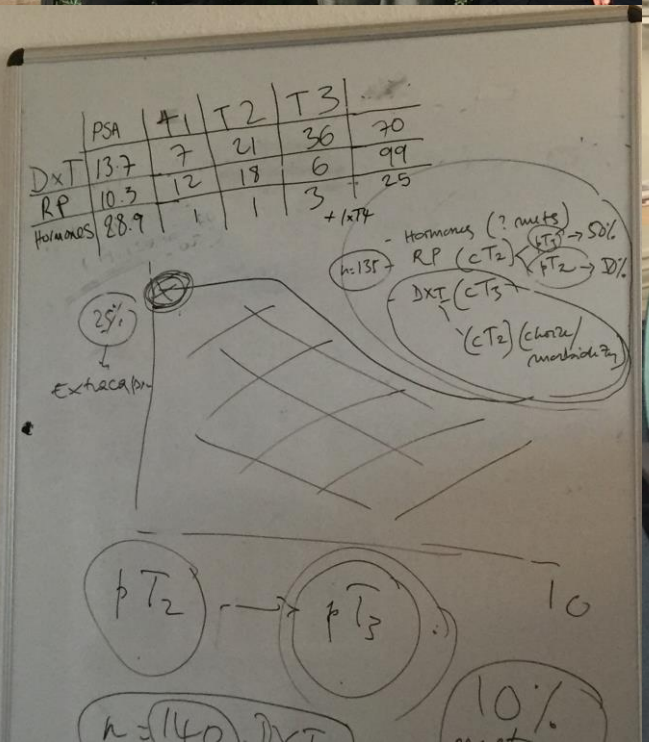
So what went wrong with the evidence?

- Insufficient large-scale randomised controlled trials to compare relative treatment effectiveness (SPCG-4; PIVOT; ProtecT coming of age…)
- Radiotherapy not evaluated against other options
- Screening trials did not evaluate treatment effectiveness
- Genomic diversity and our inability to stratify patients accurately
- ‘Trade-off’ insufficiently considered…

10-year Mortality and Clinical Outcomes


July 2015


23 November 2015


PSA
T1
T2
T3
DxT
13.7
7
21
36
70
RP
10.3
12
18
6
99
Hormones
28.9
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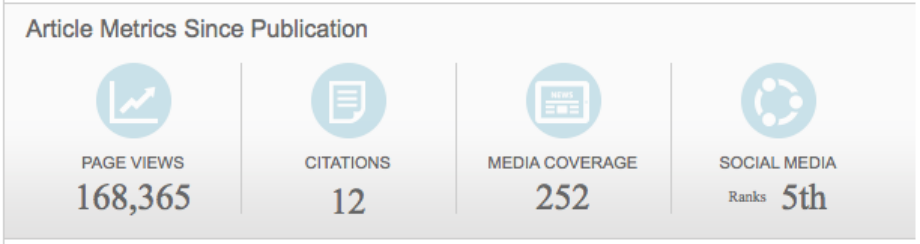
1
3
25
+ IxT4
25%
Extracapsu
pT2
pT3
10


16 December 2015

Metrics:



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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer

F.C. Hamdy, J.L. Donovan, J.A. Lane, M. Mason, C. Metcalfe, P. Holding, M. Davis, T.J. Peters, E.L. Turner, R.M. Martin, J. Oxley, M. Robinson, J. Staffurth, E. Walsh, P. Bollina, J. Catto, A. Doble, A. Doherty, D. Gillatt, R. Kockelbergh, H. Kynaston, A. Paul, P. Powell, S. Prescott, D.J. Rosario, E. Rowe, and D.E. Neal, for the ProtecT Study Group*

ABSTRACT

Prostate cancer-specific deaths

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Variable	Active Monitoring N=545	Surgery N=553	Radiotherapy N=545	P value
PCa mortality	8	5	4	
Pca survival % (95% CI)				
At 5 years	99.4 (98.3-99.8)	100	100	
At 10 years	98.8 (97.4-99.5)	99.0 (97.2-99.6)	99.6 (98.4-99.9)	
Pca deaths per 1000 person-yr (95% CI)	1.5 (0.7-3.0)	0.9 (0.4-2.2)	0.7 (0.3-2.0)	0.48

Prostate cancer-specific deaths

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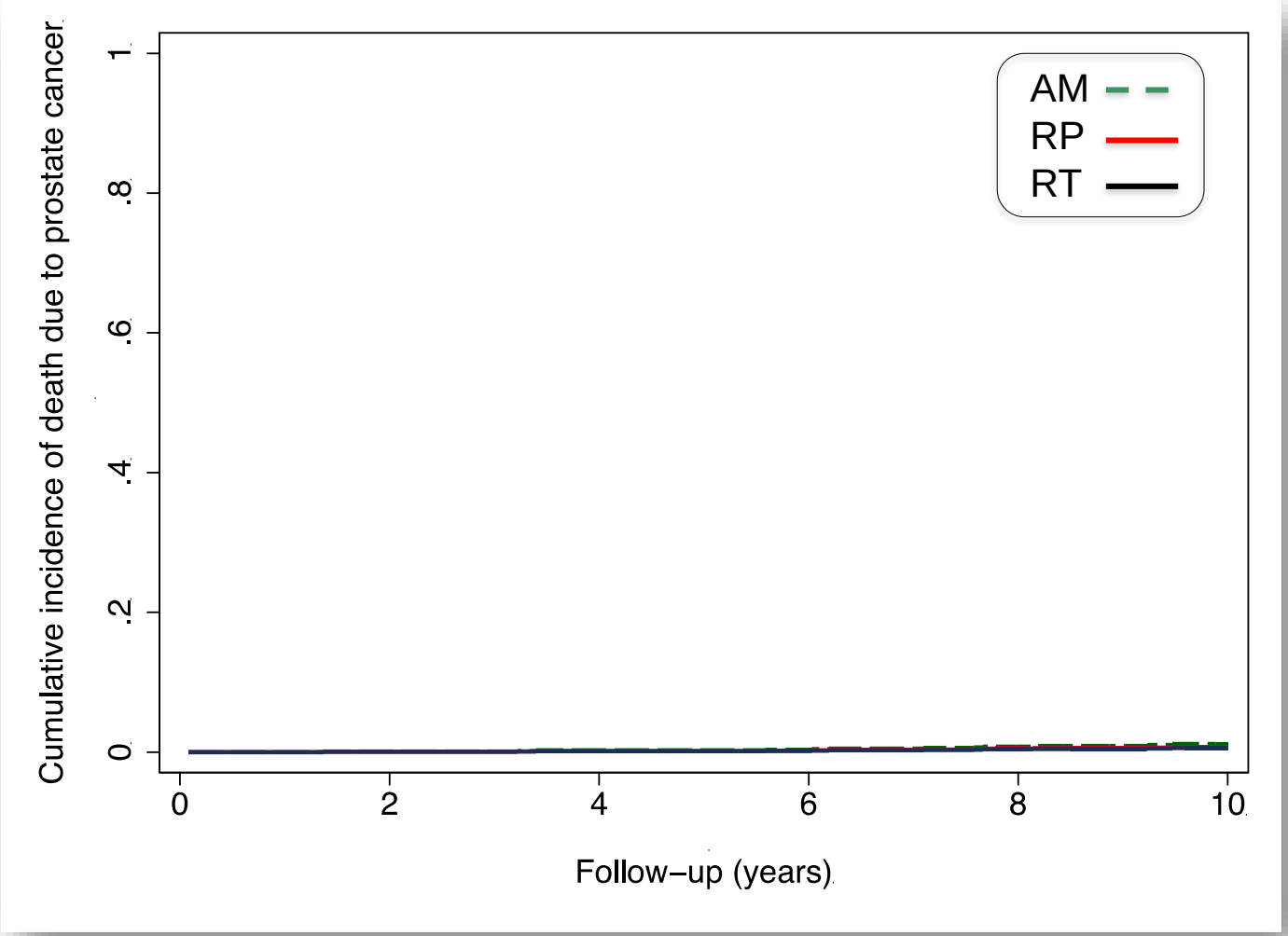
National Institute for Health Research

Hamdy et al, N Eng J Med 2016



1% mortality with no differences between treatment arms

All-cause deaths

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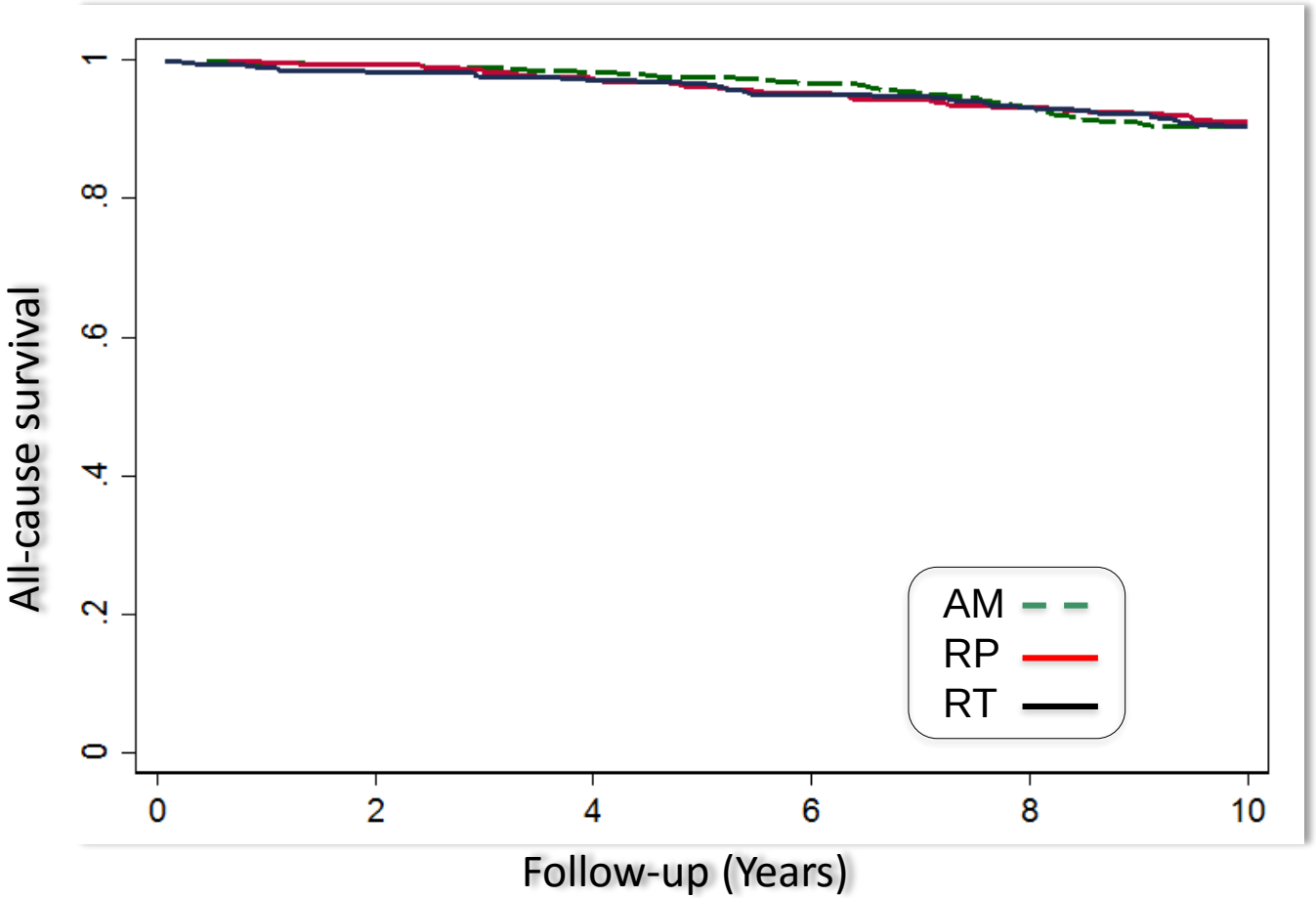
National Institute for Health Research

Variable	Active Monitoring N=545	Surgery N=553	Radiotherapy N=545	P value
Deaths due to any cause	59	55	55	
All-cause per 1000 person-yr (95% CI)	10.9 (8.5-14.1)	10.1 (7.8-13.2)	10.3 (7.9-13.4)	0.87

All-cause deaths

NHS National Institute for Health Research

Hamdy et al, N Eng J Med 2016



10% of men died of all causes with no differences between the arms

Deaths unrelated to prostate cancer

NHS National Institute for Health Research

	AM	RP	RT
Cardiovascular system	16	14	13
Digestive system	2	1	3
Musculoskeletal system	0	0	1
Nervous system	3	2	5
External causes	8	8	6
Neoplasms other than prostate cancer	22	25	23
Total deaths unrelated to prostate cancer	51	50	51

Deaths in three RCTs

	Radical Prostatectomy	Watchful waiting/ observation/ active monitoring	Radical Radiotherapy
SPCG-4[5]			
Prostate cancer	13.5	19.5	
All-cause	39.5	44.8	
PIVOT[6]			
Prostate cancer	5.8	8.4	
All-cause	47.0	49.9	
ProtecT[7]*			
Prostate cancer	c.1.0	c.1.0	c.1.0
All-cause	c.10.0	c.10.0	c.10.0

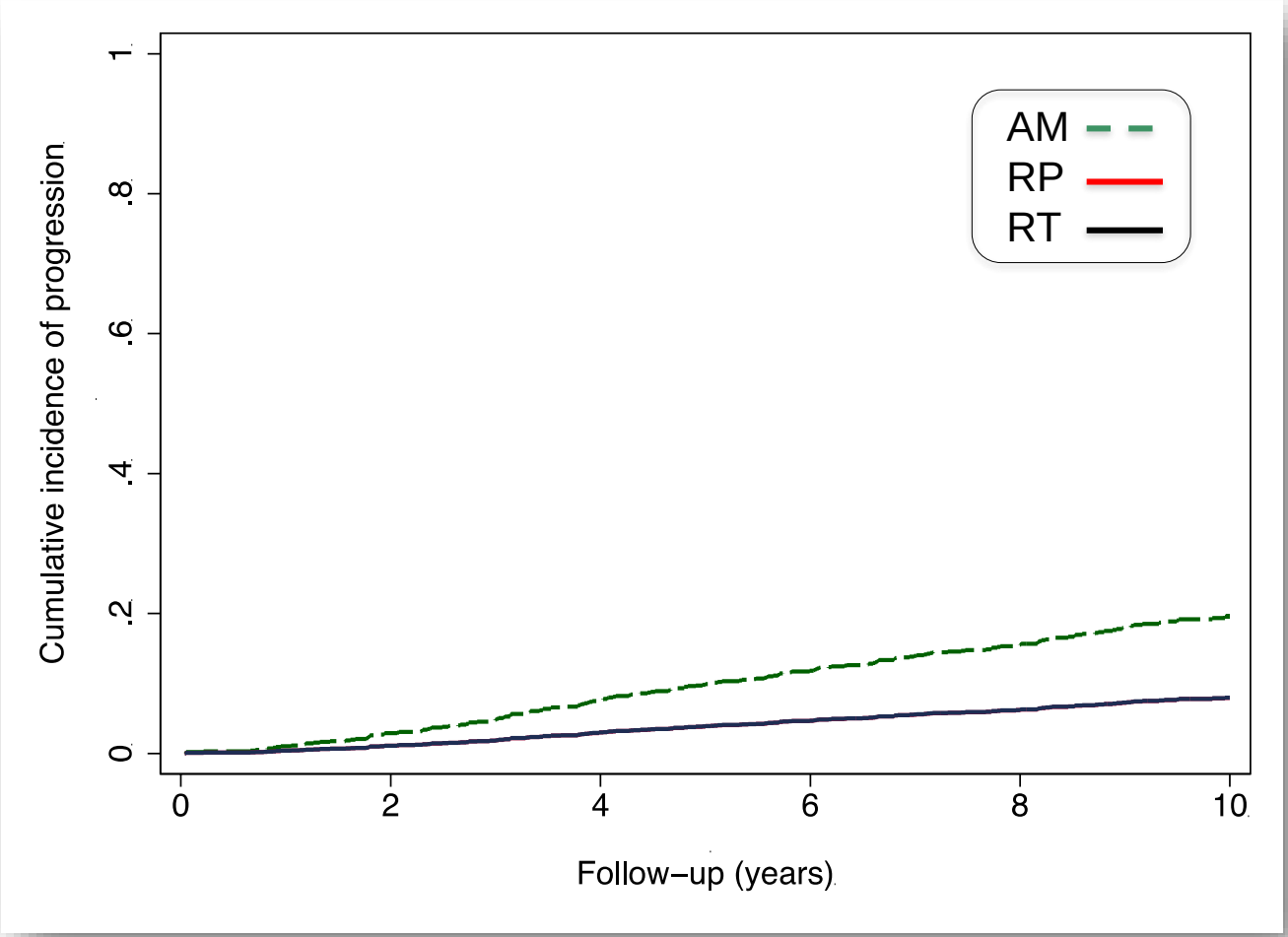
Disease Progression

NHS National Institute for Health Research

Variable	Active Monitoring N=545	Surgery N=553	Radiotherapy N=545	P value
Clinical Progression	112	46	46	
Clinical Progression per 1000 person-yr (95% CI)	22.9 (19.0-27.5)	8.9 (6.7-11.9)	9.0 (6.7-12.0)	<0.001
Metastatic Disease	33	13	16	
Metastatic Disease per 1000 person-yr (95% CI)	6.3 (4.5-8.8)	2.4 (1.4-4.2)	3.0 (1.9-4.9)	
Pca deaths per 1000 person-yr (95% CI)	1.5 (0.7-3.0)	0.9 (0.4-2.2)	0.7 (0.3-2.0)	0.004

Outcomes at 10 years: progression

Hamdy et al, N Eng J Med 2016

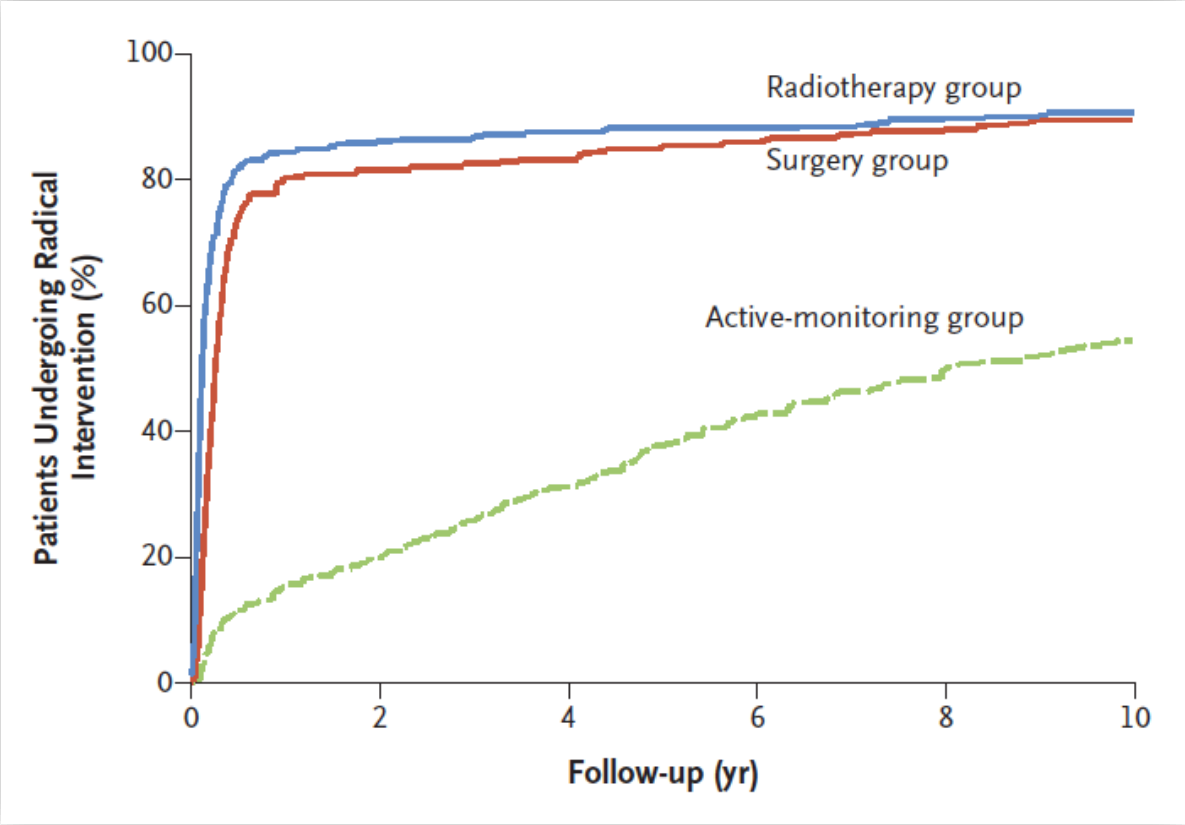


90% of men survived with no differences between the arms

Patients receiving treatments

National Institute for Health Research

Hamdy et al, N Eng J Med 2016



- Approximately 80% of men on active monitoring had no sign of progression
- More than half had received treatment by 10 years
- 44% of men on active monitoring avoided treatment

Numbers needed to treat

- To prevent one man from developing metastases:
  - 27 RPs
  - 33 radiation
- To prevent one man from developing clinical progression
  - 9 RPs or radiation

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

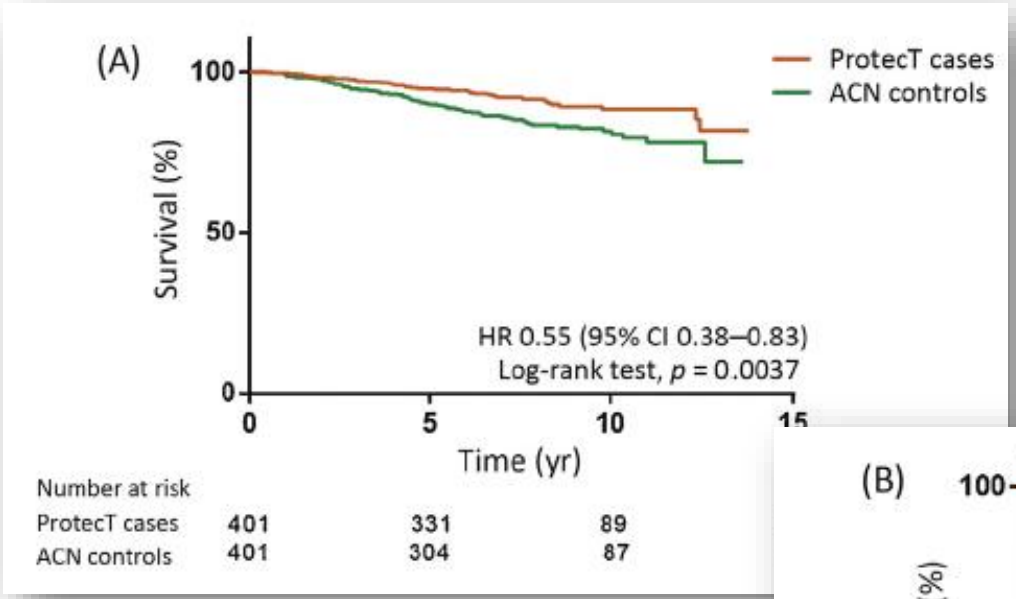
Editorial by XXX on pp. x–y of this issue

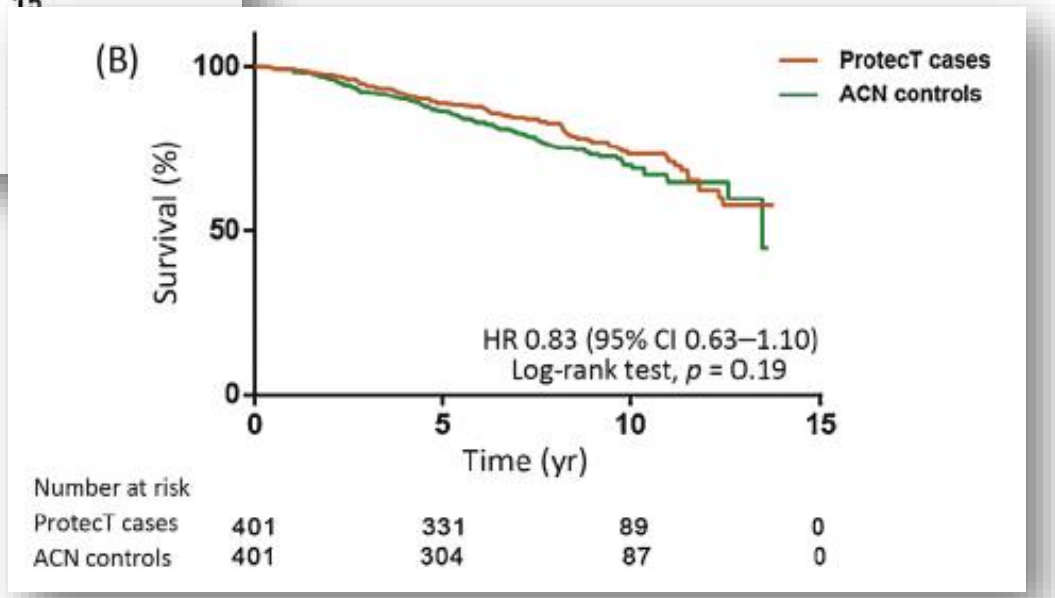
Mortality Among Men with Advanced Prostate Cancer Excluded from the ProtecT Trial

Thomas J. Johnston [a,†,], Greg L. Shaw [a,b], Alastair D. Lamb [a,b,†], Deepak Parashar [c], David Greenberg [d], Tengbin Xiong [a], Alison L. Edwards [a], Vincent Gnanapragasam [a], Peter Holding [e], Phillipa Herbert [a], Michael Davis [f], Elizabeth Mizielinsk [f], J. Athene Lane [f], Jon Oxley [g], Mary Robinson [h], Malcolm Mason [i], John Staffurth [i], Prasad Bollina [j], James Catto [k], Andrew Doble [l], Alan Doherty [m], David Gillatt [n], Roger Kockelbergh [o], Howard Kynaston [p], Steve Prescott [q], Alan Paul [q], Philip Powell [r], Derek Rosario [k], Edward Rowe [n], Jenny L. Donovan [f,†], Freddie C. Hamdy [e,†], David E. Neal [a,e,†,*], for the ProtecT study group [§]*

[a] *Academic Urology Group, University of Cambridge, Cambridge, UK;* [b] *Cancer Research UK Cambridge Institute, Li Ka Shing Centre, Cambridge, UK;* [c] *Statistics and Epidemiology Unit & Cancer Research Centre, University of Warwick, Coventry, UK;* [d] *National Cancer Registration Service – Eastern Office, Public Health England, Cambridge, UK;* [e] *Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK;* [f] *School of Social and Community Medicine, University of Bristol, Bristol, UK;* [g] *Department of Cellular Pathology, North Bristol NHS Trust, Bristol, UK;* [h] *Department of Cellular Pathology, Royal Victoria Infirmary, Newcastle-upon-Tyne, UK;* [i] *Division of Cancer and Genetics, School of Medicine, Cardiff University, Cardiff, UK;* [j] *Department of Urology and Surgery, Western General Hospital, University of Edinburgh, Edinburgh, UK;* [k] *Academic Urology Unit, University of Sheffield, Sheffield, UK;* [l] *Department of Urology, Addenbrooke's Hospital, Cambridge, UK;* [m] *Department of Urology, Queen Elizabeth Hospital, Birmingham, UK;* [n] *Department of Urology, Southmead Hospital and Bristol Urological Institute, Bristol, UK;* [o] *Department of Urology, University Hospitals of Leicester, Leicester, UK;* [p] *Department of Urology, Cardiff and Vale University Health Board, Cardiff, UK;* [q] *Department of Urology, Leeds Teaching Hospitals NHS Trust, Leeds, UK;* [r] *Department of Urology, Freeman Hospital, Newcastle-upon-Tyne, UK*

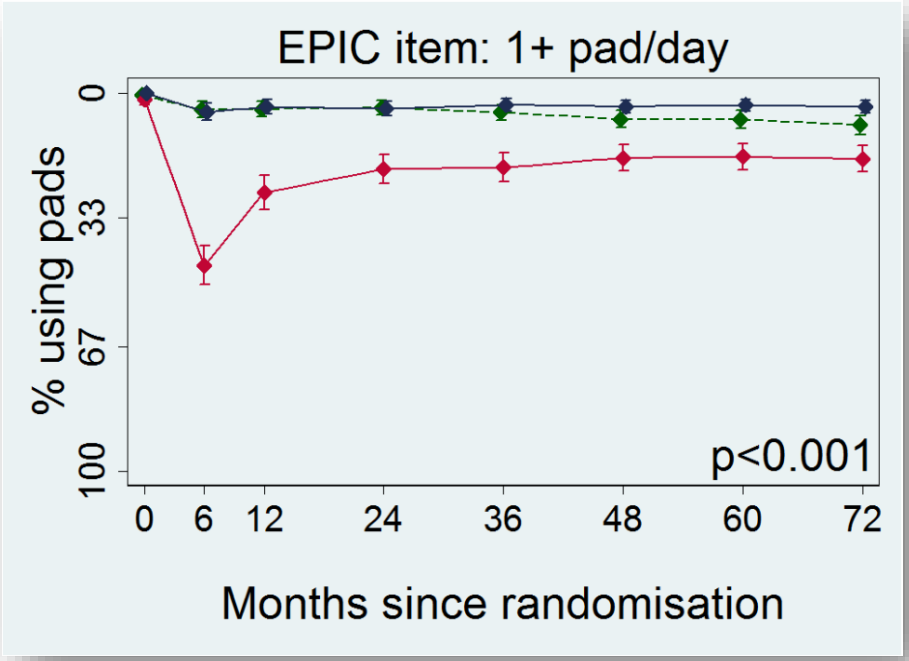
Excluded ProtecT cases

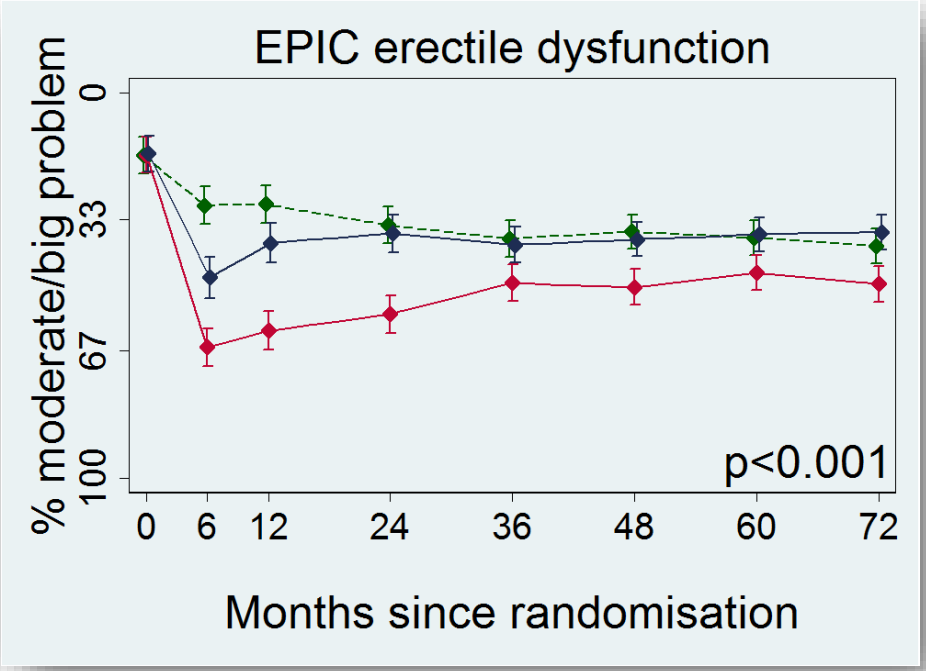




General quality of life

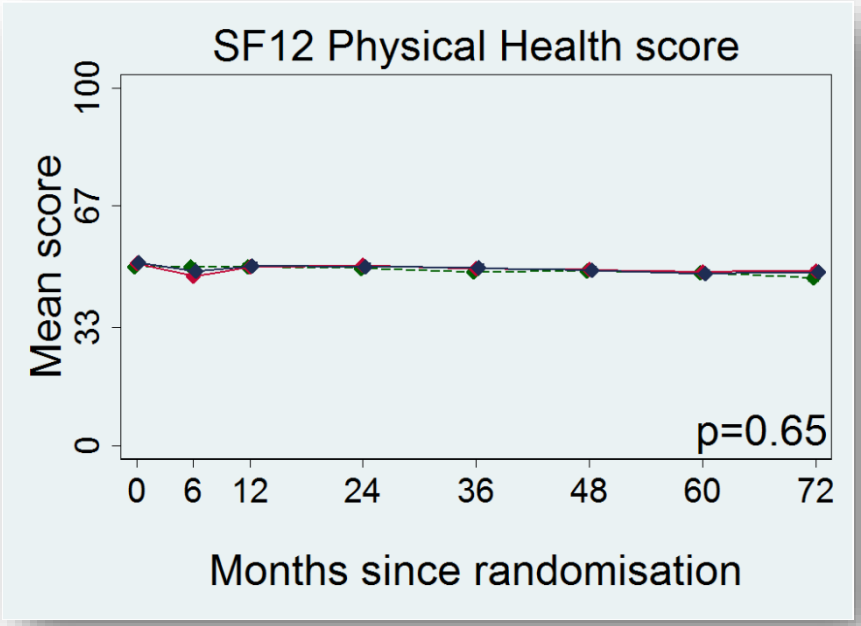
Incontinence and sexual function

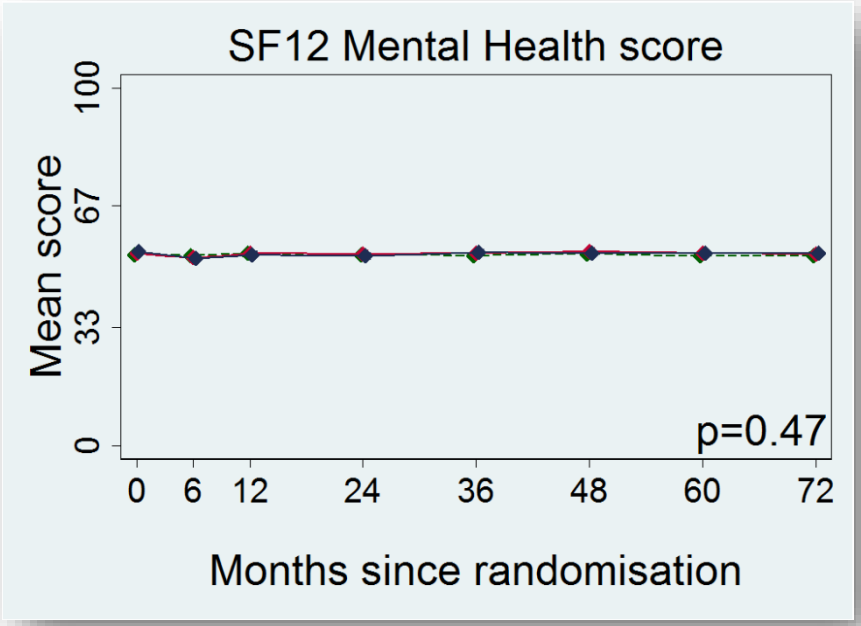




General quality of life

National Institute for Health Research





Better

Worse

Active monitoring

Prostatectomy

Radiotherapy

Anxiety and depression

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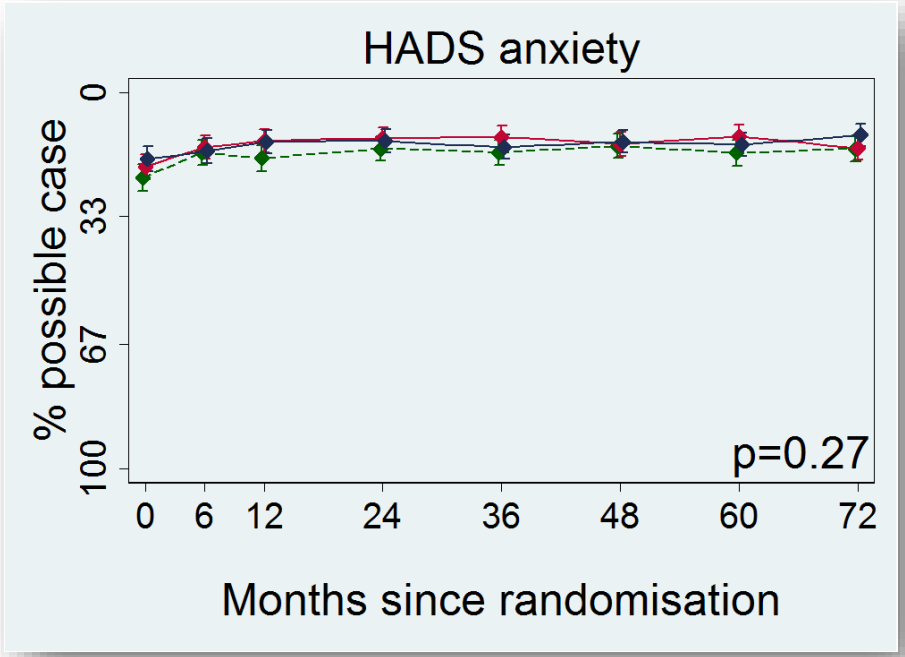
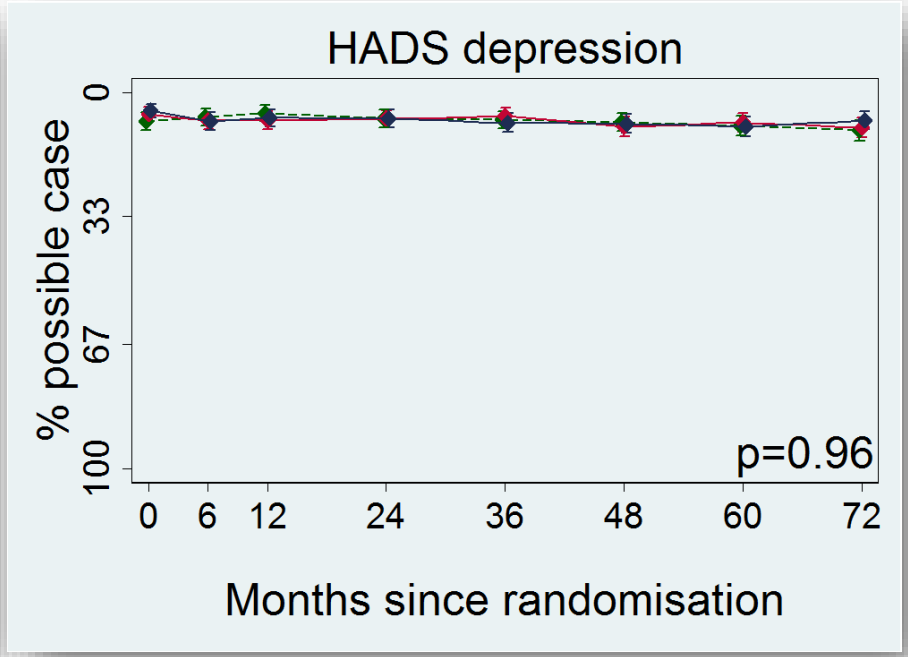




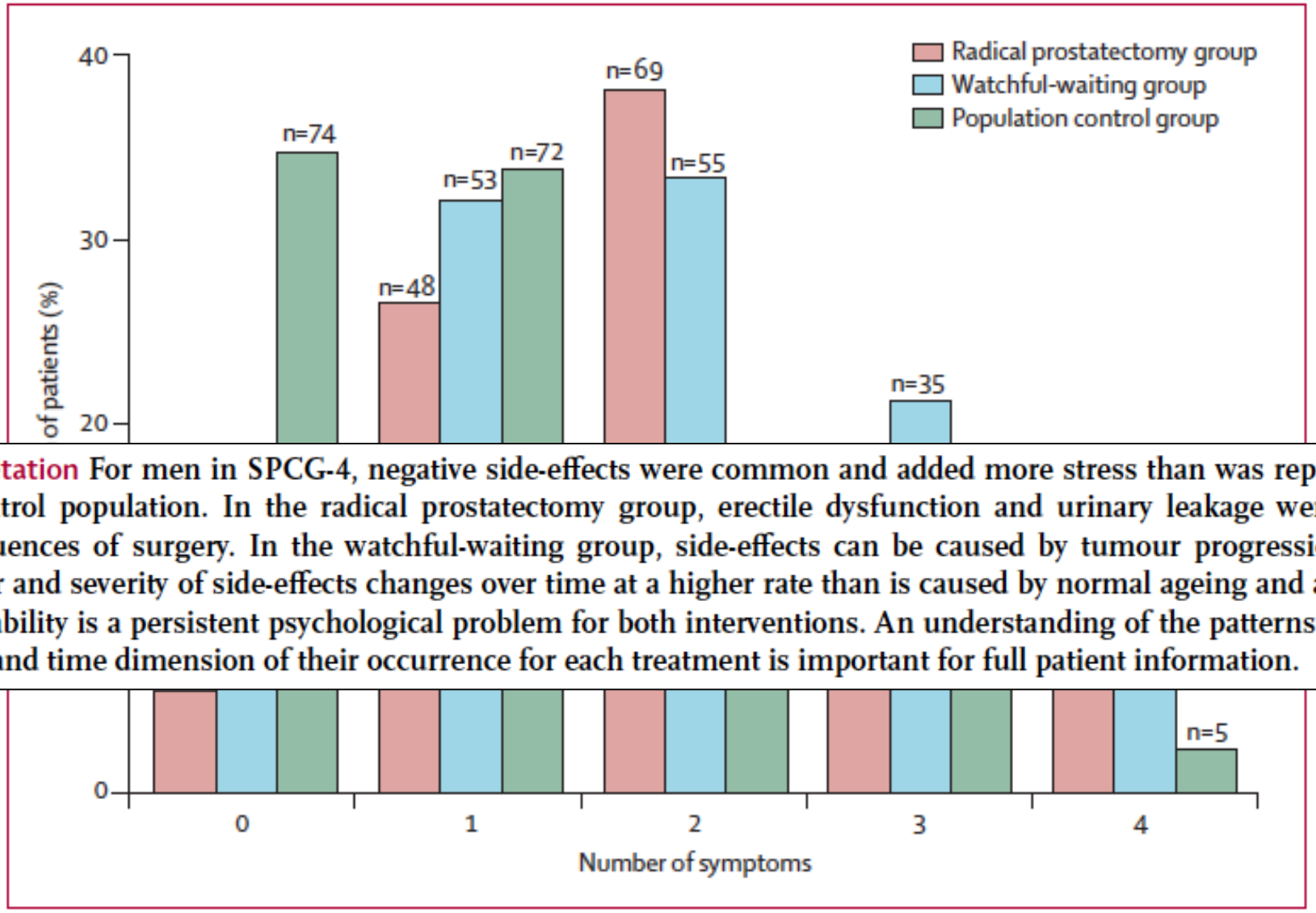
Better

Worse

Active monitoring

Prostatectomy

Radiotherapy



Interpretation For men in SPCG-4, negative side-effects were common and added more stress than was reported in the control population. In the radical prostatectomy group, erectile dysfunction and urinary leakage were often consequences of surgery. In the watchful-waiting group, side-effects can be caused by tumour progression. The number and severity of side-effects changes over time at a higher rate than is caused by normal ageing and a loss of sexual ability is a persistent psychological problem for both interventions. An understanding of the patterns of side-effects and time dimension of their occurrence for each treatment is important for full patient information.

Figure 2: **Distribution of number of physical symptoms (erectile dysfunction, urinary incontinence, weak stream, and nocturia) within the different groups**

Analysis was by intention to treat. Erectile dysfunction defined as an inability to get an erection spontaneously or elicited. Urinary incontinence was defined as leakage once a week or more. Weak stream was defined as a weak stream on more than half of occasions of urination. Nocturia was defined as urination on more than two occasions at night. n=number of patients in group.

Which patients die of prostate cancer?

NHS National Institute for Health Research

Table S4: Individual data for men who died of prostate cancer, ascertained by the Cause-of-Death Committee

Allocation[1]	Age at diagnosis	Gleason score at diagnosis	PSA at diagnosis	Biopsy cores with tumour	Stage at diagnosis	Date of allocation	1st treatment received[1]	Date 1st treatment	2nd treatment received[1]	Date 2nd treatment	Date PSA 10+ng/ml	Date of death
AM	60-64	6	6-9.99	3	T2	Mar 04	AM	Apr 04	RT	Oct 04	Jun 04	Oct 09
AM	65-69	6	<6	1	T1c	Sep 03	AM	Sep 03	ADT	Sep 05	Aug 05	Dec 06
AM	65-69	6	<6	1	T1c	Dec 03	AM	Dec 03	-	-	Nov 09	Aug 14
AM	65-69	7	<6	6	T2	Oct 04	AM	Oct 04	ADT	Jun 07	Mar 07	Dec 12
AM	65-69	7	<6	2	T1c	Mar 04	AM	Mar 04	RT	Feb 07	Mar 05	Dec 14
AM	65-69	7	<6	5	T1c	Jun 05	AM	Jun 05	RT	Nov 10	Apr 10	Feb 13
AM	65-69	7	6-9.99	6	T2	Oct 06	AM	Oct 06	ADT	Apr 09	Mar 09	Mar 10
AM	65-69	7	6-9.99	7	T1c	Jul 08	AM	Jul 08	ADT	May 09	Oct 08	Dec 09
RP	55-59	6	<6	3	T1c	Jan 01	AM	Jan 01	ADT	Mar 08	Jan 08	Jul 10
RP	60-64	6	6-9.99	1	T1c	Aug 00	AM	Aug 00	RT	May 01	Jan 01	Jun 14
RP	60-64	7	<6	3	T2	Aug 03	RP	Oct 03	SRT	Jun 05	Oct 07	Oct 09
RP	65-69	6	6-9.99	1	T1c	Sep 01	AM	Sep 01	-	-	Aug 07	Oct 07
RP	65-69	7	<6	4	T2	Aug 04	RP	Aug 04	SRT	Jan 06	Mar 10	Oct 13
RT	55-59	6	<6	3	T2	Jul 05	RT	Aug 05	ADT	Jul 09	Jan 09	Feb 13
RT	65-69	6	<6	2	T1c	Jun 01	AM	Jun 01	ADT	Aug 05	May 12	Oct 13
RT	65-69	7	<6	2	T1c	Jun 06	AM	Jun 06	RP	Jul 08	Feb 08	Jul 13
RT	65-69	7	<6	2	T1c	Nov 01	RT	Jan 02	ADT	Jan 12	Feb 09	Apr 14

AM = Active Monitoring; RP = Radical Prostatectomy; RT = Radiotherapy; ADT = Androgen Deprivation Therapy; SRT = Salvage Radiotherapy

Hamdy et al, N Eng J Med 2016

Progression

Disease status	Gleason	PSA baseline	D'Amico
Progression (n=204)	3+3=6 (53%) 3+4=7 (28%) 4+3=7 (14%) 8-10 (5%)	6.0 ng/ml	Low (40%) Intermediate (54%) High (5%)
No progression (n=1439)	3+3=6 (81%) 3+4=7 (15%) 4+3=7 (3%) 8-10 (2%)	4.6 ng/ml	Low (72%) Intermediate (27%) High (2%)

In addition: number of cores involved, length and percentage of tumour in individual cores, perineural invasion

P<0.001

RP (n= 391) and Progression

Disease status	Gleason	P stage	Median Tumour volume	Positive margins
Progression (n=19)	3+3=6 (0) 3+4=7 (42%) 4+3=7 (37%) 8-10 (21%)	pT2 (11%) pT3 (89%)	3.6 cc	3 (17%)
No progression (n=372)	3+3=6 (52%) 3+4=7 (15%) 4+3=7 (3%) 8-10 (2%)	pT2 (73%) pT3 (27%)	1.6 cc	26 (7%)

P<0.001

Ongoing analyses

NHS
National Institute for Health Research

- Continue characterisation of men who progressed in the three arms (n=204)
- Analysis of the preference arm (n=>1000)
- Analysis of the combined ITT and preference AM men (n=1167)
- Analysis per treatment received
- Translational research to identify signatures for ‘lethal’ and ‘non-lethal’ disease
- Continue follow-up and calculate ‘trade-off’
- Flag men who declined testing for PCa incidence and death (n=>110,000)
- CAP results - 2017

FULL PAPER

BJC

British Journal of Cancer (2014) 110, 2829–2836 | doi: 10.1038/bjc.2014.242

Keywords: cluster randomised controlled trial; screening; prostate cancer; prostate-specific antigen; prostate cancer mortality; cost-effectiveness

Design and preliminary recruitment results of the Cluster randomised triAl of PSA testing for Prostate cancer (CAP)

E L Turner*[,1], C Metcalfe[1], J L Donovan[1], S Noble[1], J A C Sterne[1], J A Lane[1], K N Avery[1], L Down[1], E Walsh[1], M Davis[1], Y Ben-Shlomo[1], S E Oliver[2], S Evans[3], P Brindle[4], N J Williams[5], L J Hughes[6], E M Hill[1], C Davies[1], S Y Ng[7], D E Neal[6], F C Hamdy[8], R M Martin[1,9] and the CAP trial group

Overall conclusions [1]

NHS
National Institute for Health Research

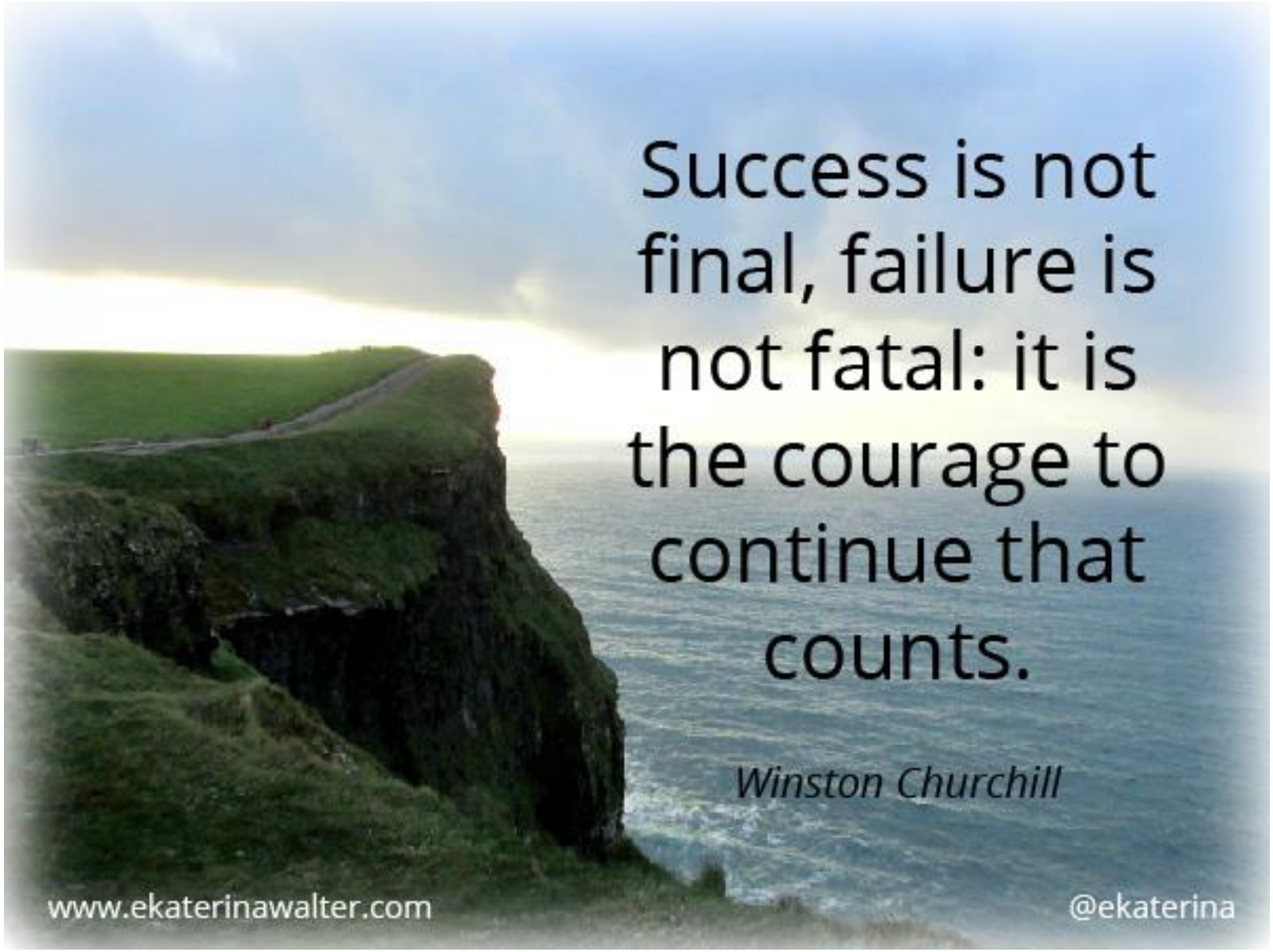
- The risk of death from prostate cancer over an average of 10 years is very low – 1% - most PSA-detected clinically localised prostate cancers grow slowly
- Surgery and radiotherapy reduce the risk of cancer progression and spread, but cause bothersome urinary, sexual and bowel symptoms
- Staying on active monitoring avoids treatment side-effects, but there is an increased risk of cancer progression and spread, and some symptoms increase gradually over time
- Longer follow up (5-10 years) is essential in ProtecT to provide data about the 'trade-off' between the shorter-term effects of radical treatments, the risks of disease progression and if any, the long-term benefits in cancer cure and survival

Overall Conclusions [2]

NHS National Institute for Health Research

- Men who wish to be tested for PSA need to be informed that in most cases, the disease is slow growing, and whilst radical treatments carry side-effects, they can reduce disease progression
- Men can take their time to make a decision about treatment, using ProtecT data about outcomes to balance risks and benefits
- Further research is needed to distinguish 'lethal' from 'non-lethal' prostate cancer, in order to give the right treatment to the right patient at the right time
- Clinicians and Health Care Providers such as the NHS in the UK need to take these results into account when men and their partners are counseled for PSA-testing, and treatment decisions are made if they are found to have clinically localised prostate cancer


111,861 participants
NO
ALL GAMES


Success is not final, failure is not fatal: it is the courage to continue that counts.
Winston Churchill
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