PACE trial update

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Hamburg: 23 November 2018

The ROYAL MARSDEN
NHS Foundation Trust

Where are we today with hypofractionation?

NHS

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4 Large RCT's of "moderate hypofractionation"

NHS

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CHHIP (UK)

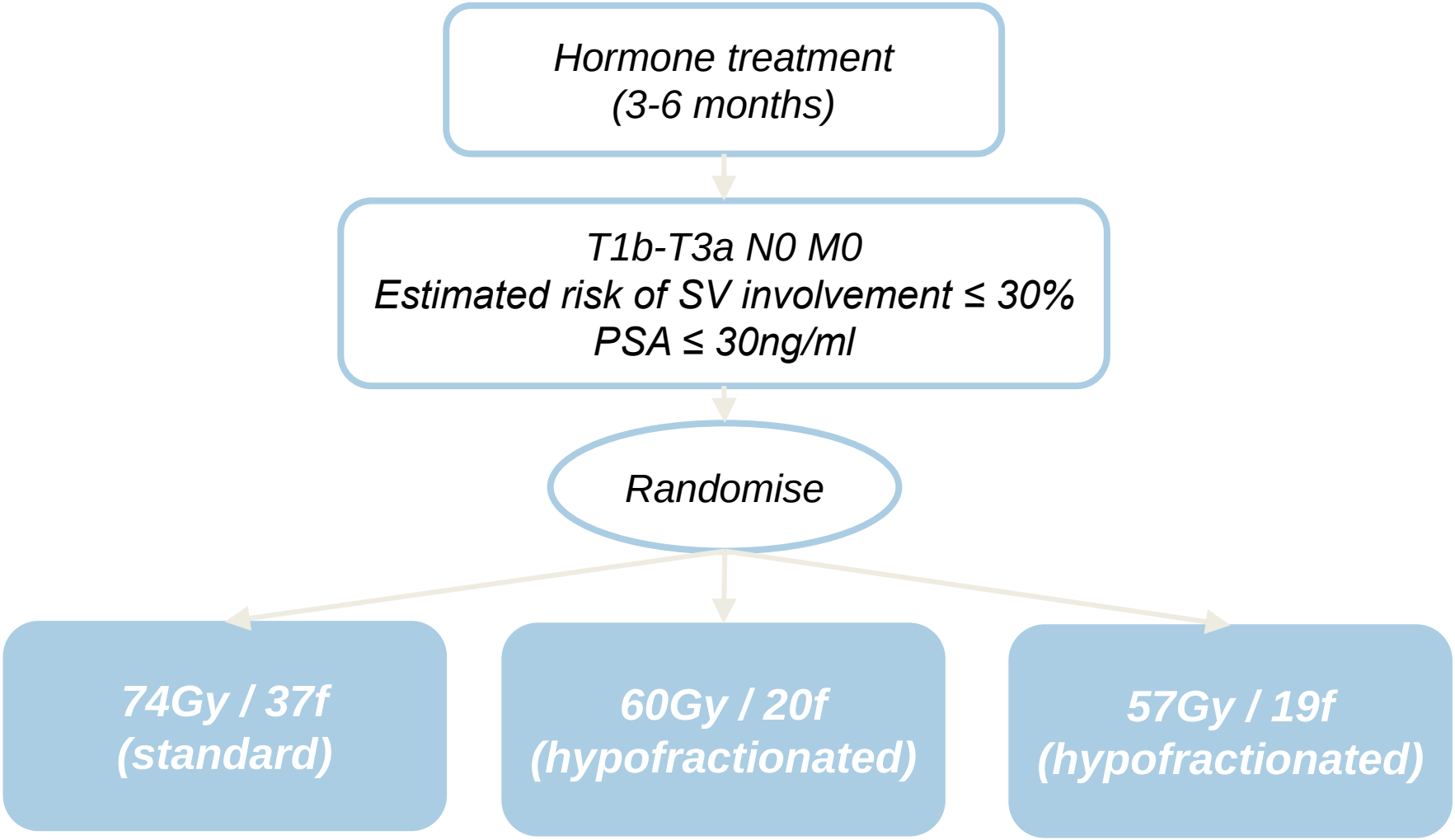
PROFIT (Canada)

RTOG 0415 (USA)

HYPRO (Dutch)

NHS

Trial schema

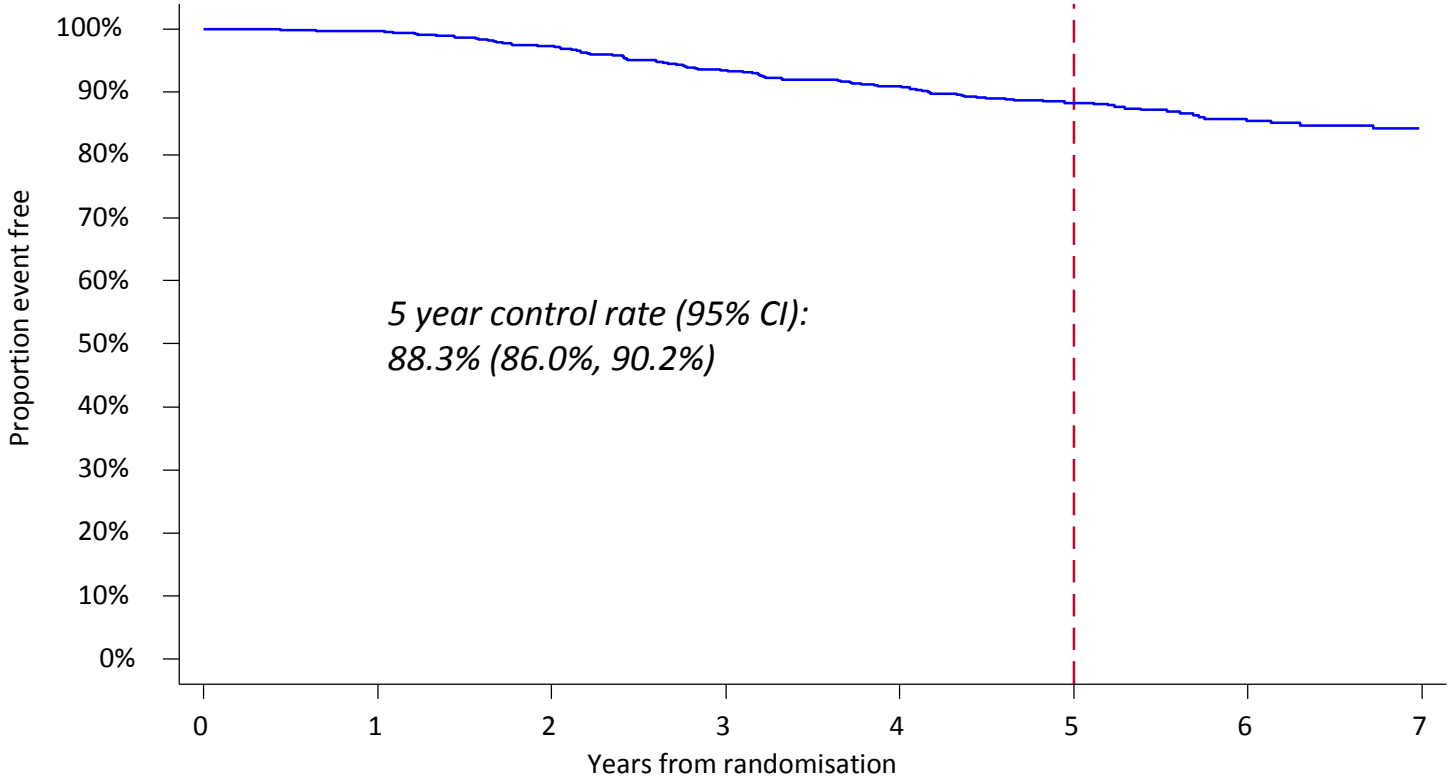


Lancet Oncol. 2016 Aug;17(8):1047-60.

Baseline characteristics

	(N=3216)
	%
Age (Median)	***69***
Risk group	
High Risk	***12***
Intermediate Risk	***73***
Low Risk	***15***
Pre-hormone PSA (ng/ml)	***10***

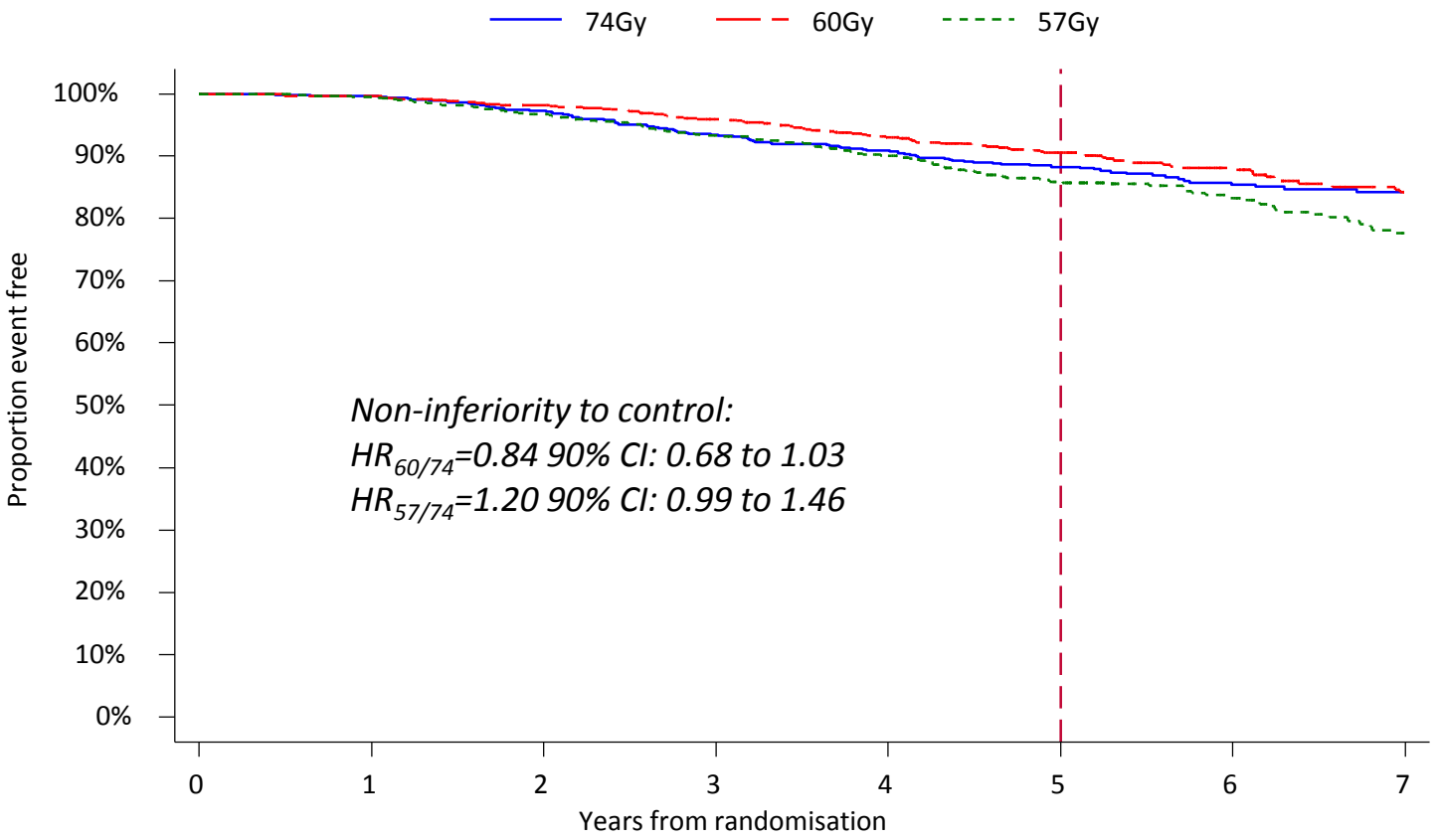
Time to biochemical failure/prostate cancer recurrence – control arm



Number at risk (events)

74Gy	1065	(4)	1037	(24)	991	(39)	926	(24)	795	(20)	495	(11)	284	(3)	167

Time to biochemical failure/prostate cancer recurrence – primary analysis

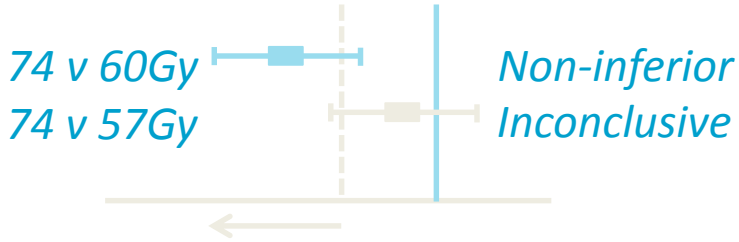


Number at risk (events)

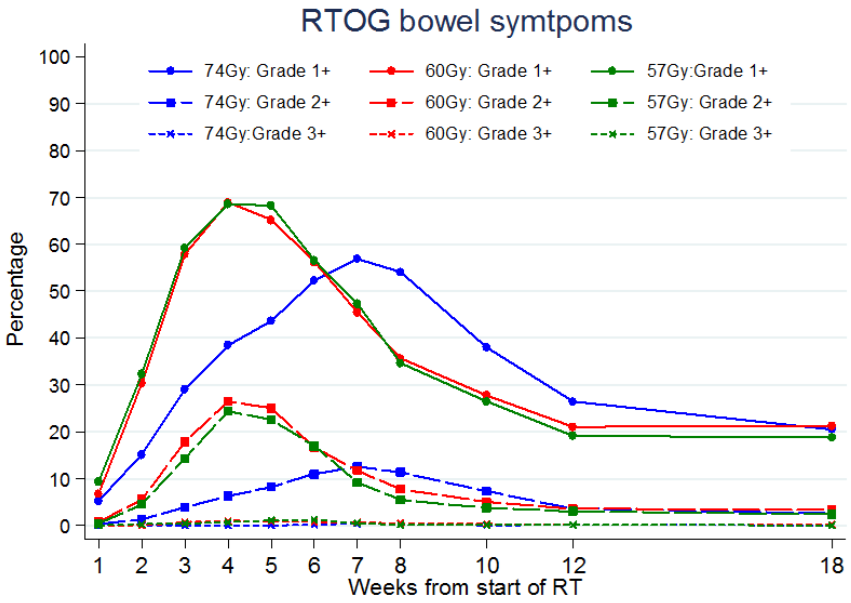
74Gy	1065	(4)	1037	(24)	991	(39)	926	(24)	795	(20)	495	(11)	284	(3)	167
60Gy	1074	(4)	1042	(15)	1011	(23)	965	(28)	816	(18)	533	(10)	280	(10)	176
57Gy	1077	(5)	1044	(30)	1004	(35)	944	(31)	798	(31)	492	(9)	262	(13)	151

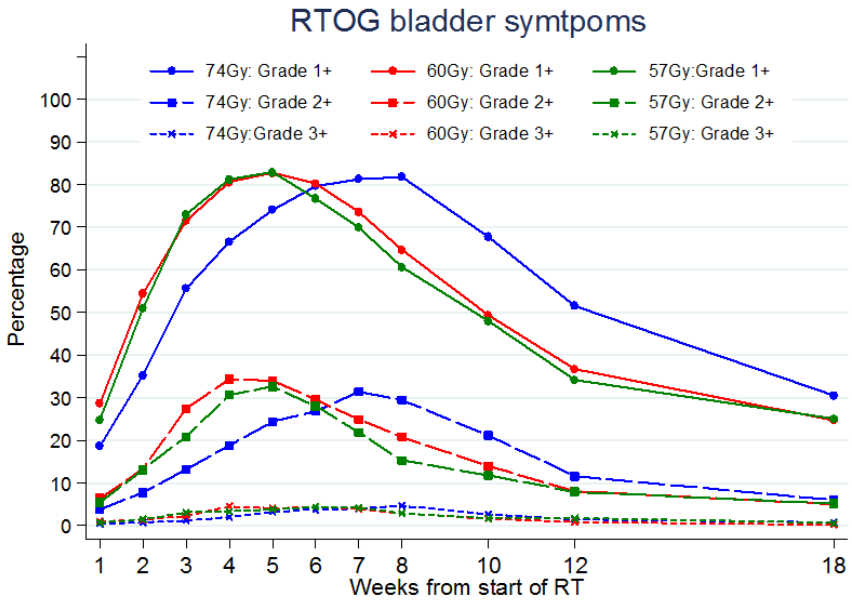
Non-inferiority analysis (ITT)

Biochemical failure or prostate cancer recurrence	74Gy/37f (n=1065)	60Gy/20f (n=1074)	57Gy/19f (n=1077)
Number of events	138	119	164
KM 5 year proportion event-free estimate (95% CI)	88.3 (86.0, 90.2)	90.5 (88.4, 92.2)	85.8 (83.3, 87.9)
Hazard ratio (90% CI)		**0.83 (0.68, 1.02)**	**1.19 (0.99, 1.44)**
Pr(HR<1.208)		**p=0.003**	**p=0.91**
Log rank p-value		p=0.14	p=0.13
		p=0.003	
Absolute difference at 5 years (90% CI)		**1.86 (-0.26, 3.62)**	**-2.10 (-4.74, 0.16)**
Absolute difference at 5 years (90% CI)		-3.84 (-6.52, -1.58)	

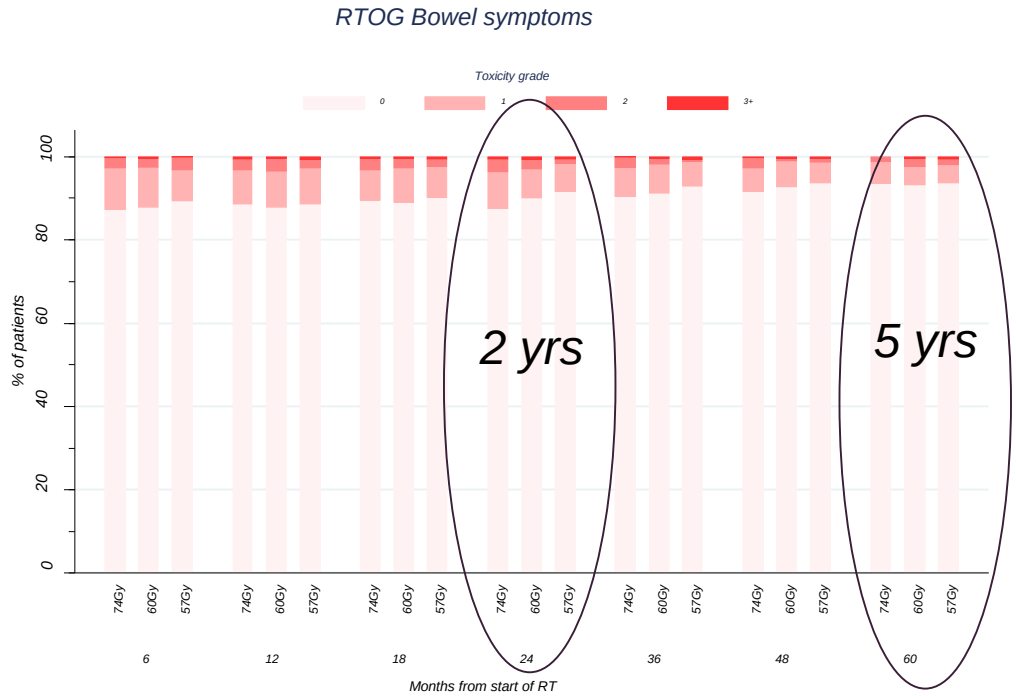


Short-term side-effects – bowel and bladder





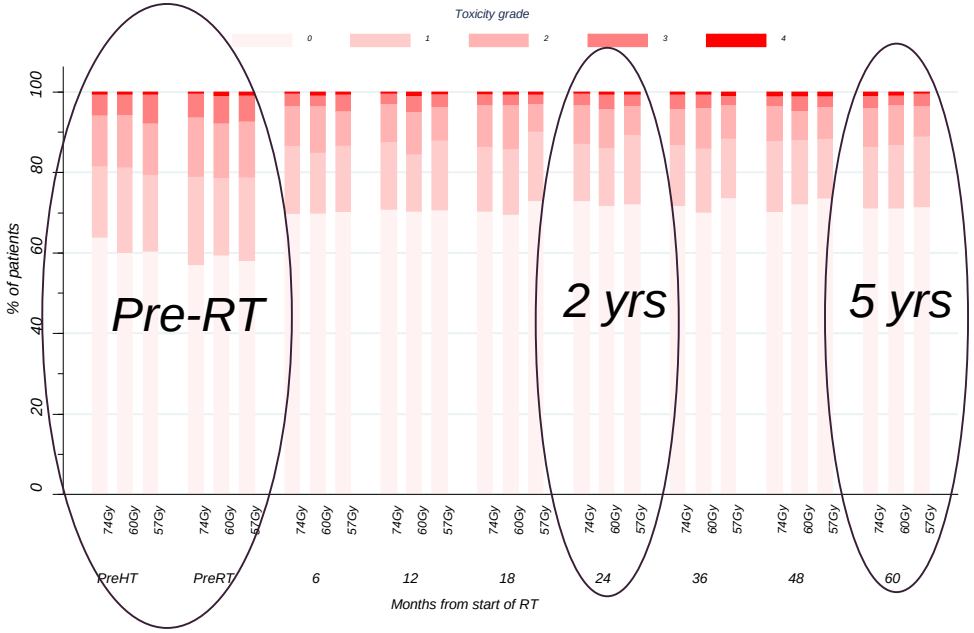
Late side-effects – RTOG bowel



G2+: 2 year incidence

74Gy	60Gy	57Gy
3.8%	2.9%	1.8%
	p=0.31	p=0.007

Late side-effects – LENT-SOM bladder



Comment: bladder symptoms less common at 2 and 5 years than pre-treatment

G2+: 5 year incidence

74Gy	60Gy	57Gy
13.5%	13.2% p=0.93	11.2% p=0.30

What about “profound” hypofractionation?

Can we go above 3 Gy/fraction?

Biologically effective dose of 36.25 Gy in 5 fractions

	BED if α/β ratio = 5	BED if α/β ratio = 4	BED if α/β ratio = 3	BED if α/β ratio = 2.7	BED if α/β ratio = 1.5
78 Gy in 39 fractions	109 Gy	117 Gy	130 Gy	135 Gy	182 Gy
36.25 Gy in 5 fractions	88 Gy	101 Gy	123Gy	134 Gy	211 Gy
40 Gy in 5 fractions	104 Gy	120 Gy	147 Gy	158 Gy	253 Gy

Until 2013, state of the evidence base…

	Fractionation	Stage	PSA	Gleason	Low risk	Int risk	High risk	5 yr bRFS: low risk	5 yr bRFS High risk
Freeman 2011 (38) 41 patients	35-36.35 Gy in 5 #	Low risk	<10	3+4			None	93%	
Madsen et al 2007 (39) 40 pts	33.5 Gy in 5 #	T1c or T2a	10 or less	Gl 6 or less	100%			48 month bRFS 90%	
King 2011 (40) 67 men	36.25 Gy in 5 #	T1c or T2a/b	<10	3+4 or less			None	4-year bRFS 94%	
Katz 2010 (41) 304 patients	35 Gy-36.25 Gy in 5 #	92% T1c	Median 5.8	73% Gl6 23 % Gl 7	70%		4%	1.3 % failed so far (17-30 month FU)	
Jabbari et al 2011 (42) 20 pt cohort	38 Gy in 4 fraction	T1c-T3a	Median 7.5	Any				Median follow up 18.3 months 100% bRFS	
Kang et al 2011 (43) 44 patients	32-36 Gy in 4 #	T1c-T3	Median 15.8	4-9	5%		29%	100%	90.9%
Boike et al 2011 (44) 45 patients	45-50 Gy in 5 # (dose escalation cohorts)	T1c-T2b	Median 5.6	6-7 (36% Gleason 3+4)	40%		0%	Median follow up 12-30 months 100% bRFS	
McBride 2012 (45) 45 patients	36.25-37.5 in 5 #				100%		0%	3 yr bRFS 97.7%	
Tang et al 2008 (46) 30 pts	35 Gy in 5 weekly #	T1-T2b	All <10 Median 6	All Gleason 6	100%		0%	Median PSA at 6 months 1.8	
Lee et al 2012 (47) 29 pts	36 Gy in 5 #	79% T2	Median 7.96	Median Gleason 6	14 %		21%	41 month bRFS 86%	

Contents lists available at ScienceDirect

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journal homepage: www.thegreenjournal.com

Original article

Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials ☆

Christopher R. King [a,*], Debra Freeman [b], Irving Kaplan [c], Donald Fuller [d], Giampaolo Bolzicco [e], Sean Collins [f], Robert Meier [g], Jason Wang [a], Patrick Kupelian [a], Michael Steinberg [a], Alan Katz [h]

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Clinical Investigation

Health-Related Quality of Life After Stereotactic Body Radiation Therapy for Localized Prostate Cancer: Results From a Multi-institutional Consortium of Prospective Trials

Christopher R. King, PhD, MD,* Sean Collins, MD,† Donald Fuller, MD,‡ Pin-Chieh Wang, PhD,* Patrick Kupelian, MD,* Michael Steinberg, MD,* and Alan Katz, MD, JD§

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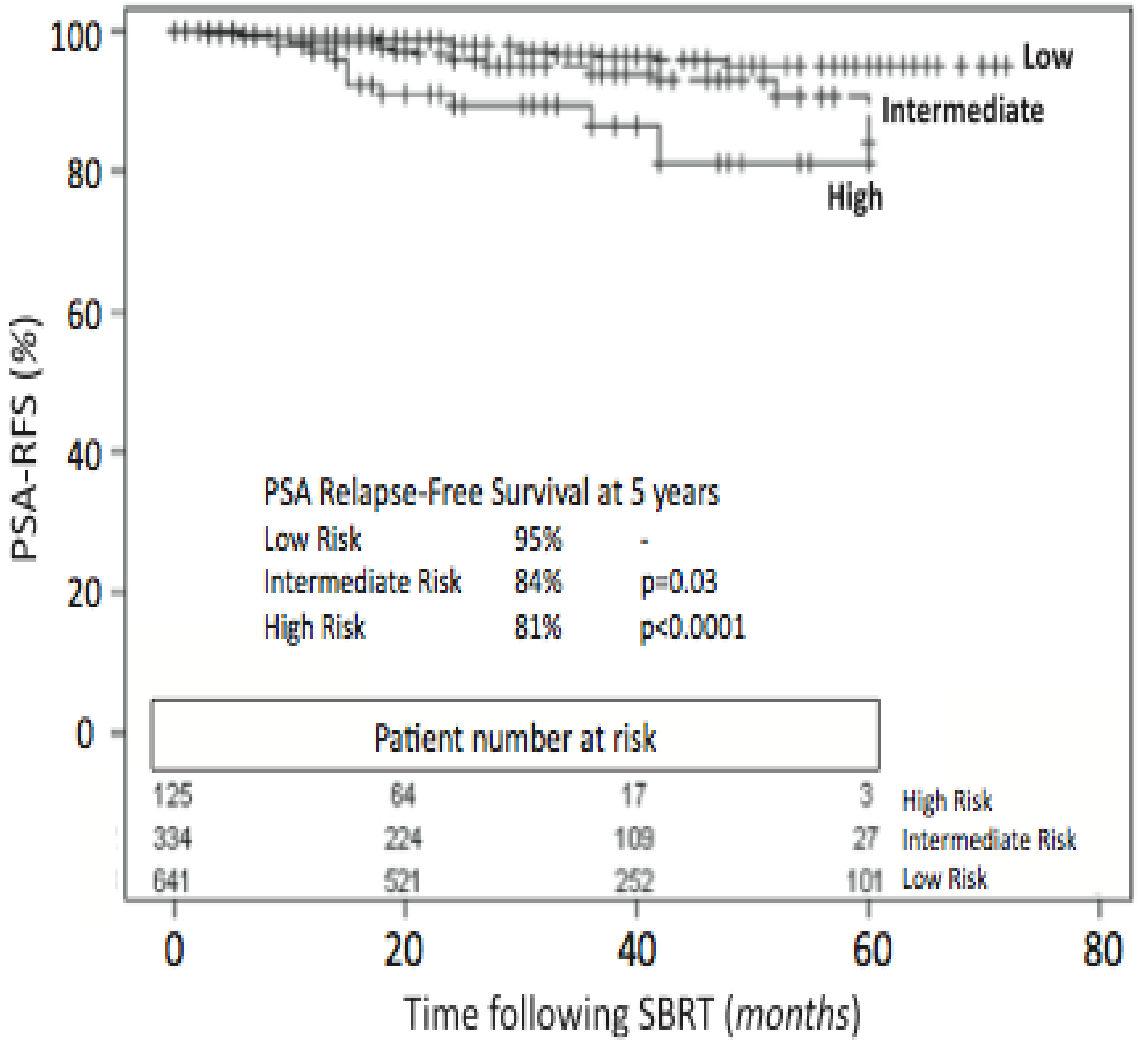
Results


100
80
60
40
20
0
PSA-RFS (%)
Low
Intermediate
High
PSA Relapse-Free Survival at 5 years
Low Risk 95% -
Intermediate Risk 84% p=0.03
High Risk 81% p<0.0001
Patient number at risk
125 64 17 3 High Risk
334 224 109 27 Intermediate Risk
641 521 252 101 Low Risk
0 20 40 60 80
Time following SBRT (months)

"It is ASTRO's opinion that data supporting the use of SBRT for prostate cancer have matured to a point where **SBRT could be considered an appropriate alternative** for select patients with low to intermediate risk disease."

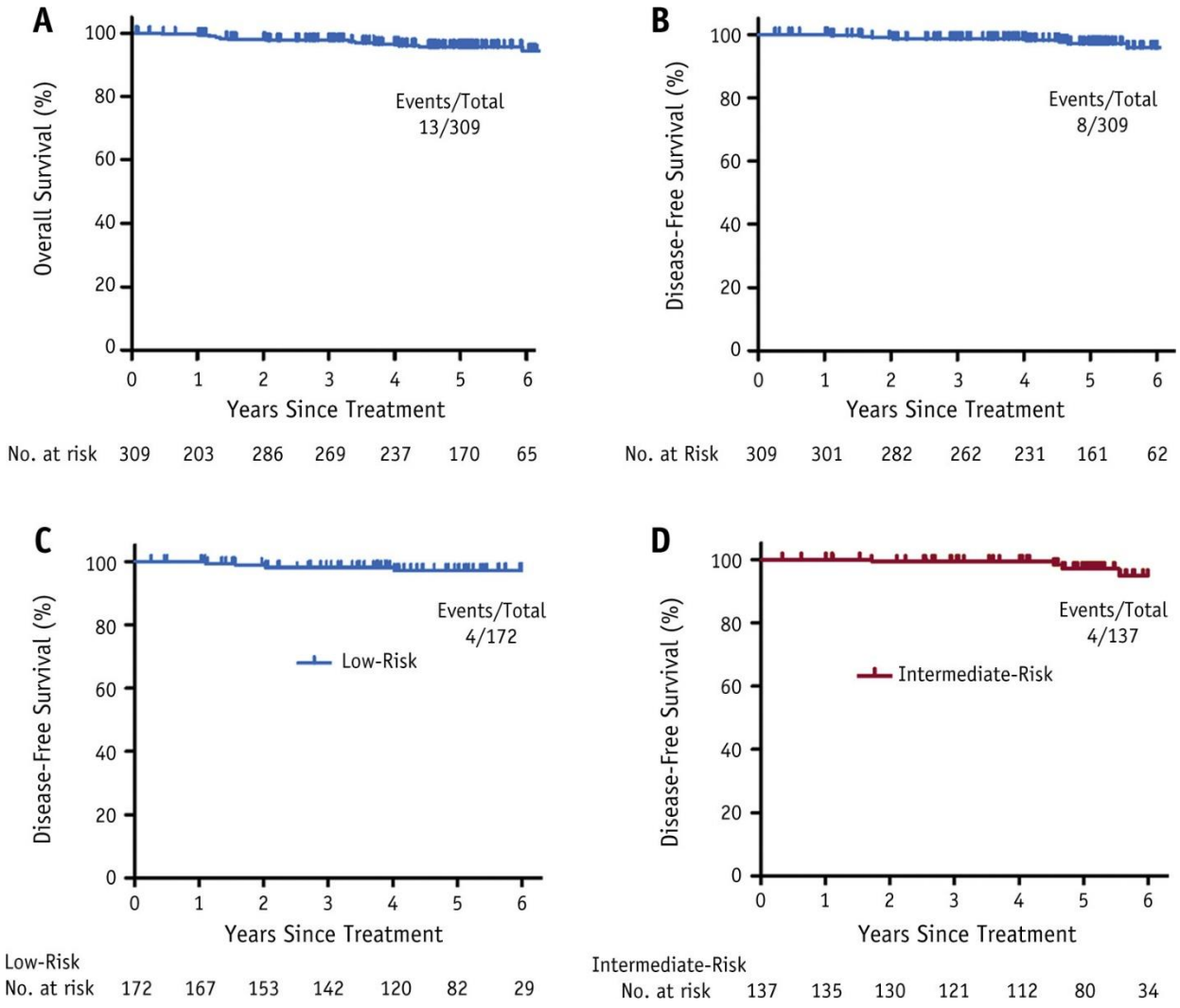
Multicenter Trial of Stereotactic Body Radiation Therapy for Low- and Intermediate-Risk Prostate Cancer: Survival and Toxicity Endpoints

309 patients, prospective, multicentre Phase II
40 Gy in 5 to CTV, 36.25 Gy in 5 to PTV
5 year PFS 97.1%

Abstract 74; Table 1

	GU Toxicity				GI Toxicity		
	Gr1	Gr2	Gr3	Gr4+	Gr1	Gr2	Gr3+
Any time	165 (53%)	108 (35%)	5 (2%)	0	183 (59%)	31 (10%)	0
< 3 mos	182 (59%)	79 (26%)	0	0	169 (55%)	25 (8%)	0
> 3 mos	87 (28%)	38 (12%)	5 (2%)	0	38 (12%)	6 (2%)	0

Int J Radiat Oncol Biol Phys. 2018 Oct 1;102(2


A
Overall Survival (%)
100
80
60
40
20
0
Events/Total
13/309
0 1 2 3 4 5 6
Years Since Treatment
No. at risk 309 203 286 269 237 170 65
B
Disease-Free Survival (%)
Events/Total
8/309
Years Since Treatment
No. at Risk 309 301 282 262 231 161 62
C
Disease-Free Survival (%)
Events/Total
4/172
Low-Risk
Years Since Treatment
Low-Risk
No. at risk 172 167 153 142 120 82 29
D
Disease-Free Survival (%)
Events/Total
4/137
Intermediate-Risk
Years Since Treatment
Intermediate-Risk
No. at risk 137 135 130 121 112 80 34

Hypo Trial

Ultrahypofractionation for prostate cancer: Outcome from the Scandinavian phase 3 HYPO-RT-PC trial Widmark et al

42.7Gy 7F (6.1Gy) 2.5 weeks

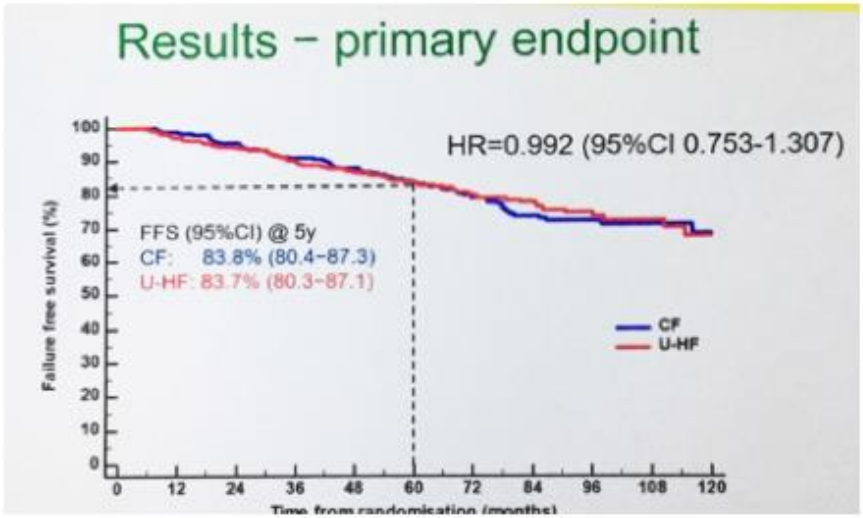
- Open, randomised, phase III trial
  - Intermediate/high-risk prostate cancer*
  - 1200 patients accrued
    - July 2005-Nov 2015
  - No androgen deprivation therapy

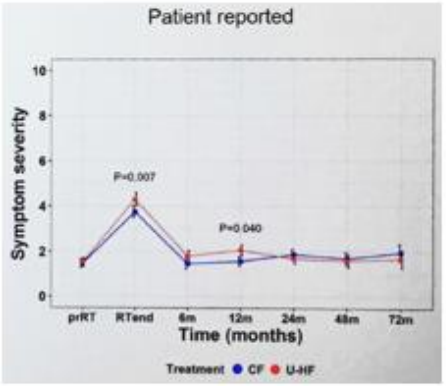
RANDOMISE

Conventional fractionation (CF): 39*2.00 Gy = 78.0 Gy over 8 weeks

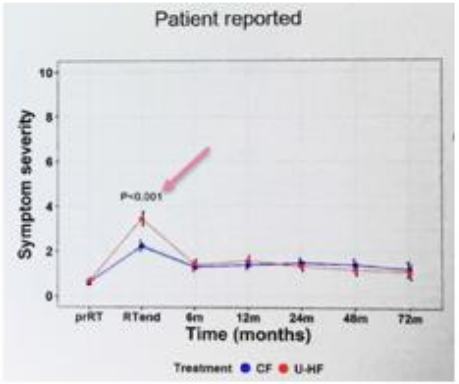
Ultrahypofractionation (U-HF): 7*6.10 Gy = 42.7 Gy over 2.5 weeks

Equieffective for late normal tissue complication probability (α/β=3 Gy)





Bladder



Bowel

PACE (Prostate Advances in Comparative Evidence)

Study Summary

Title The PACE trial: International Randomised Study of Prostatectomy vs Stereotactic Body Radiotherapy (SBRT) and Conventional Radiotherapy vs SBRT for Early Stage Organ-Confined Prostate Cancer.

Aim In the primary management of early stage organ-confined prostate cancer, to assess whether hypofractionated stereotactic body radiotherapy (SBRT) offers benefit over prostatectomy or conventional radiotherapy.

CyberKnife
MultiPlan
Fuse
Contour
Align
Plan
Visualize
Setup
Isocentric
Conformal
Sequential
Evaluate
Dose Calculation
Algorithm
Ray-Tracing
Resolution
High
Uncertainty %
0
Calculate
Prescription
Prescription
Reference Point
Use max dose point
Dose (cGy)
4769.74
Point
Go to >>
7.50,19.00,366.75
Set to Cross-hair Point
Save Plan
Save Plan
Standard
Display
ACCURAY
A
L
R
P
143

PACE

Design

Multicentre, international phase 3 randomised controlled study comprising two parallel randomisations with a common experimental arm.

Objectives

In PACE-A:

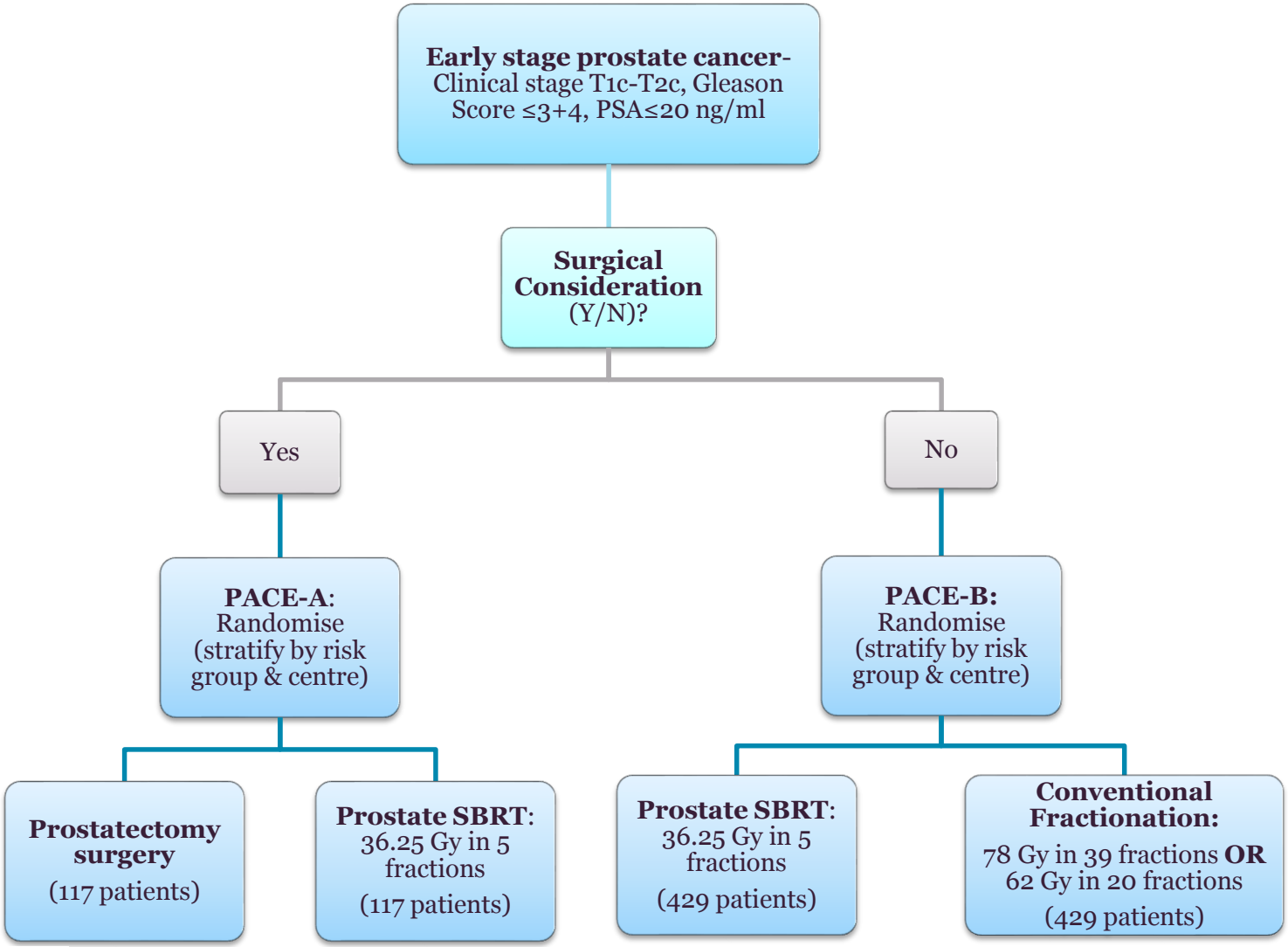
Primary: To determine whether there is improved quality of life following prostate SBRT compared with prostatectomy two years from completion of trial treatment.

In PACE-B:

Primary: To determine whether prostate SBRT is non inferior to conventional radiotherapy for freedom from biochemical/clinical failure in low/ intermediate risk prostate cancer.

PACE (Prostate Advances in Comparative Evidence)

Study Schema



PACE (Prostate Advances in Comparative Evidence)

Study Summary

Primary end-points

In PACE-A:

Co-primary patient reported outcomes:

(1) Urinary incontinence (number of absorbent pads required per day to control leakage) measured by The Expanded Prostate Cancer Index (EPIC) questionnaire.

(2) Bowel bother summary score from the EPIC questionnaire.

The main time point of interest is 2 years post treatment.

In PACE-B:

Freedom from biochemical (Phoenix definition for conventional radiotherapy and SBRT arms, >0.2 ng/ml for surgical arm) or clinical (commencement of androgen deprivation therapy) failure. The main time point of interest is 5 years from randomisation.

PACE

In PACE-A and PACE-B, common secondary objectives:

local failure
distant failure
disease-free survival
disease-specific survival
overall survival
toxicity
quality of life in generic and organ specific domains

PACE

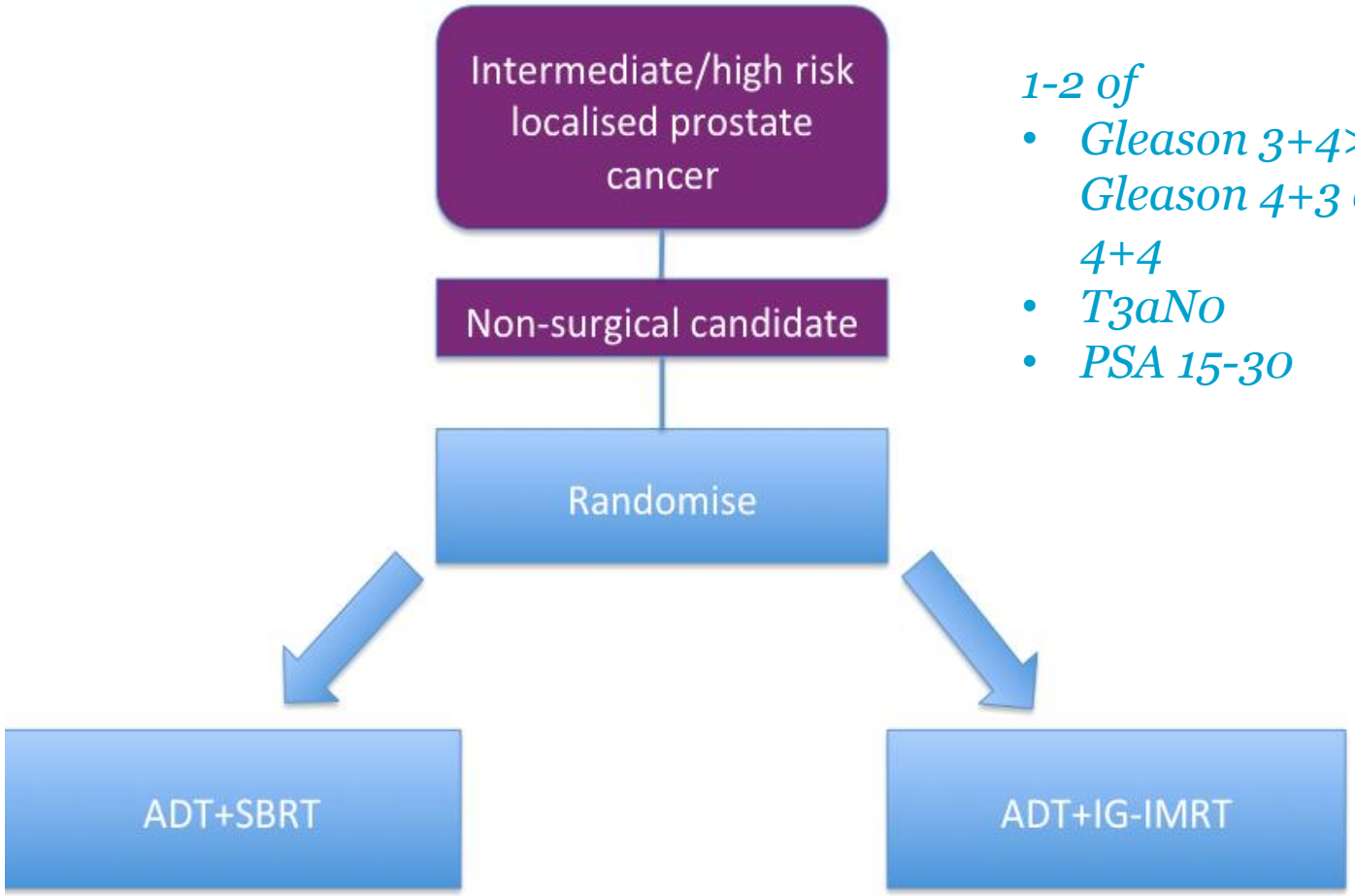
Inclusion Criteria

- Histological confirmation of prostate adenocarcinoma with a minimum of 10 biopsy cores taken within the last 18 months (unless on active surveillance and not clinically indicated – see section 9, Patient selection).
- Gleason score ≤ 3+4
- Men aged ≥18 years at randomisation
- Clinical and/or MRI stage T1c –T2c, N0-X, M0-X
- PSA ≤ 20 ng/ml
- Pre-enrolment PSA must be completed within 60 days of randomisation
- Patients belonging in one of the following risk groups according to the National Comprehensive Cancer Network (www.nccn.org):

  Low risk:
  Clinical stage T1-T2a and Gleason ≤ 6 and PSA < 10 ng/ml, or

  Intermediate risk (includes any one of the following):
  Clinical stage T2b orT2c or PSA 10-20 ng/ml, or Gleason 7 (3+4 for PACE)
- WHO performance status 0 – 2
- Ability of the research subject to understand and the willingness to sign a written informed consent document

Proposed PACE C trial



1-2 of

- *Gleason 3+4>50% cores, Gleason 4+3 or Gleason 4+4*
- *T3aN0*
- *PSA 15-30*

Current Status Summary

PACE (Prostate Advances in Comparative Evidence)

Current Status

PACE-A

- Open to Recruitment
- 9 centres open
- 93 patients recruited (target 234)

PACE-B

- Closed to Recruitment (05 Jan 2018)
- Recruited 874 patients (Target 858)
- Recruited to target 6 months ahead of target
- Patients have all received treatment and are in follow-up
- Up to 12 week Acute toxicity analysis planned

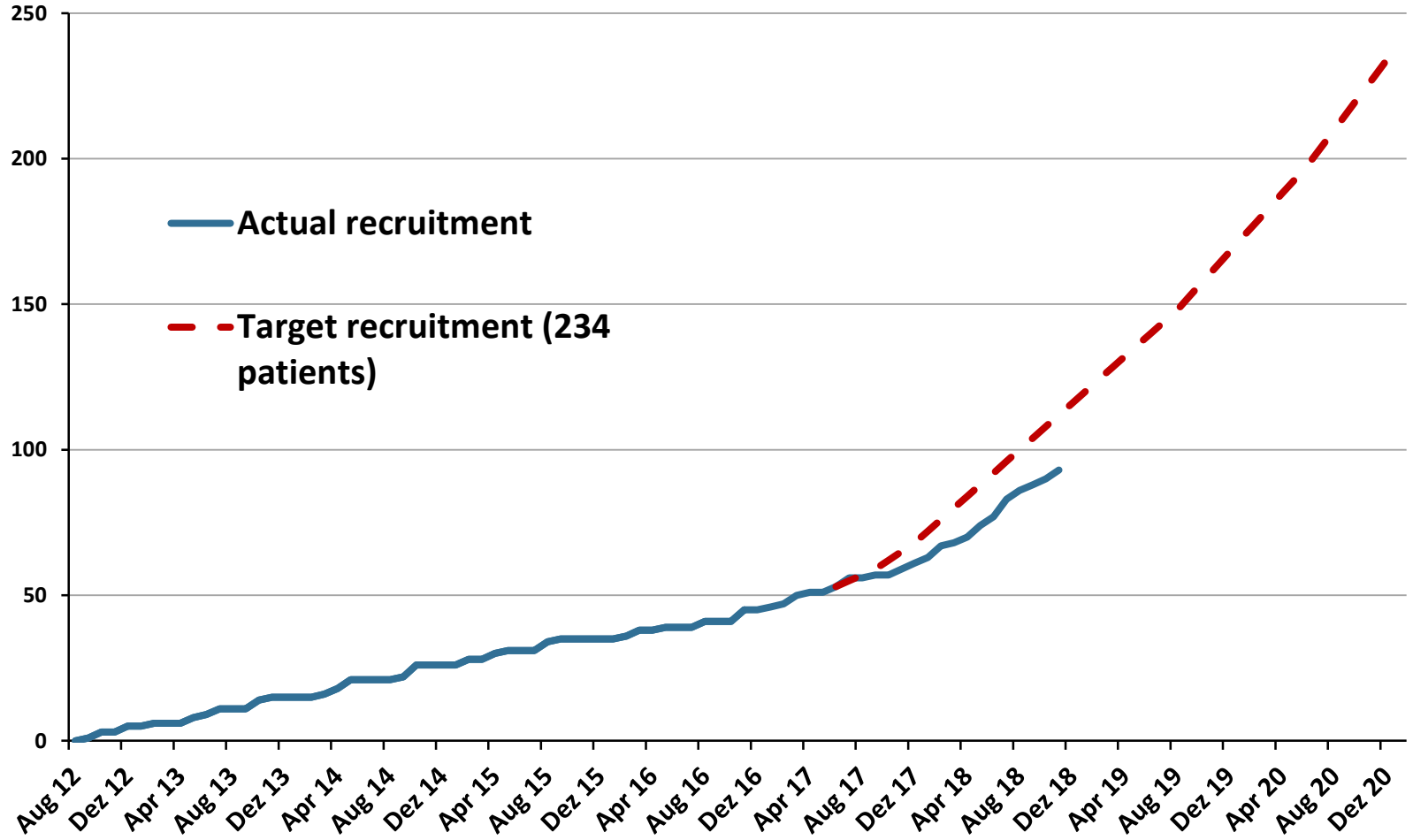
PACE-C

- Funding agreed
- Protocol in development
- Aim to start accrual at the start of 2019

PACE-A: Accrual

PACE-A: Actual and target cumulative recruitment

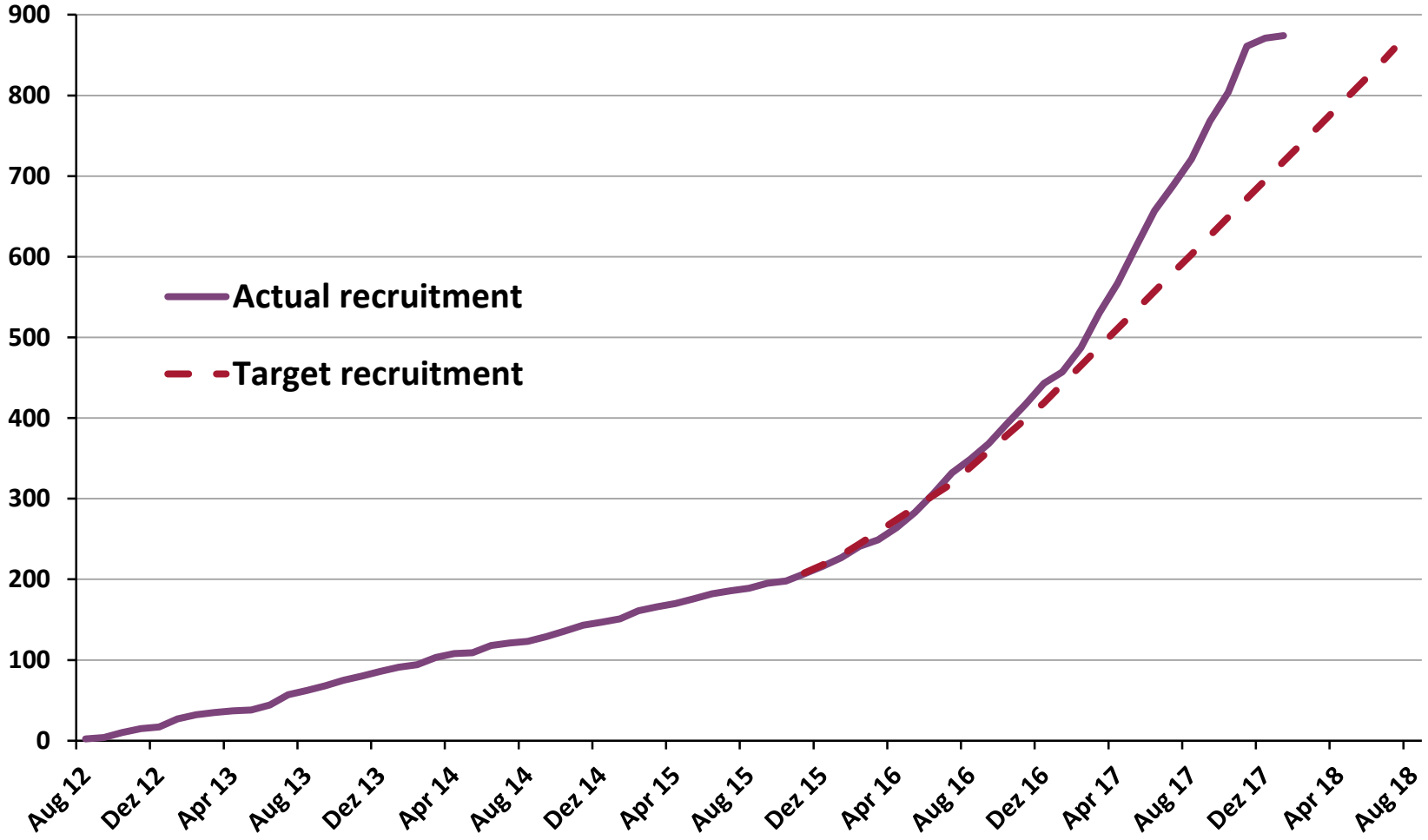
Accrual to 15 November 2018



PACE-B: Accrual

PACE-B: Actual and target cumulative recruitment

Accrual to 05 January 2018 (Closed to recruitment)



Genitourinary Cancers Symposium

February 14-16, 2019
Moscone West Building
San Francisco, CA
#GU19

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
ASTRO TARGETING CANCER CARE
SUO Society of Urologic Oncology

PACE B acute toxicity submitted as a late breaking abstract

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Thank you