II SIMPÓSIO INTERNACIONAL
GU - REVIEW 2018 - LACOG

Câncer de próstata / Doença de Risco Intermediário: Eu indico Radioterapia

Fernando Freire de Arruda

23 E 24 | NOVEMBRO 2018 | HOTEL INTERCONTINENTAL | SÃO PAULO

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2018 Prostate Cancer

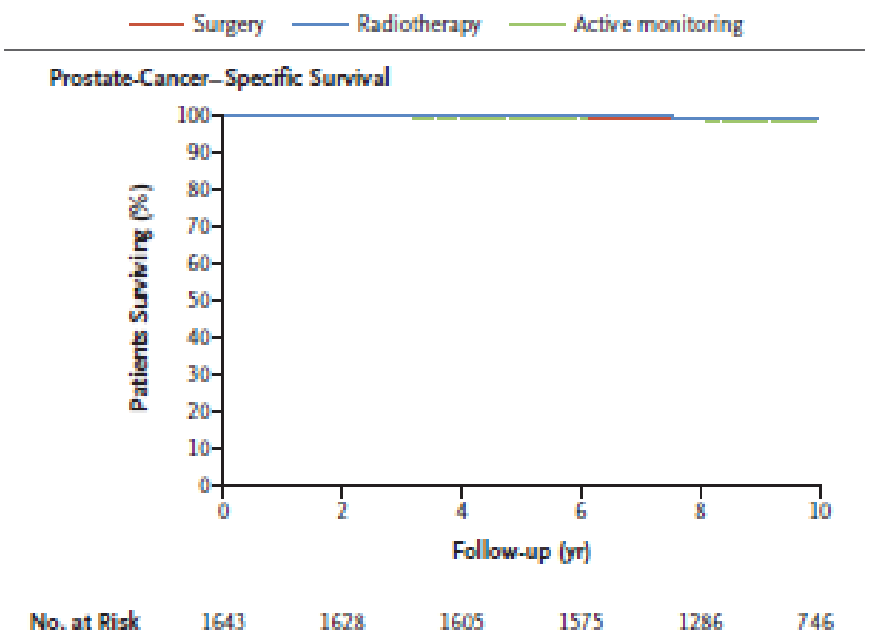
Risk group	Clinical/pathologic features
Very low[g]	• T1c AND • Gleason score ≤6/grade group 1 AND • PSA <10 ng/mL AND • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[h] AND • PSA density <0.15 ng/mL/g
Low[g]	• T1-T2a AND • Gleason score ≤6/grade group 1 AND • PSA <10 ng/mL
Favorable intermediate[g]	• T2b-T2c OR • Gleason score 3+4=7/grade group 2 OR • PSA 10–20 ng/mL AND • Percentage of positive biopsy cores <50%
Unfavorable intermediate[g]	• T2b-T2c OR • Gleason score 3+4=7/grade group 2 or Gleason score 4+3=7/grade group 3 OR • PSA 10–20 ng/mL
High	• T3a OR • Gleason score 8/grade group 4 or Gleason score 4+5=9/grade group 5 OR • PSA >20 ng/mL
Very high	• T3b-T4 OR • Primary Gleason pattern 5 OR • >4 cores with Gleason score 8–10/ grade group 4 or 5

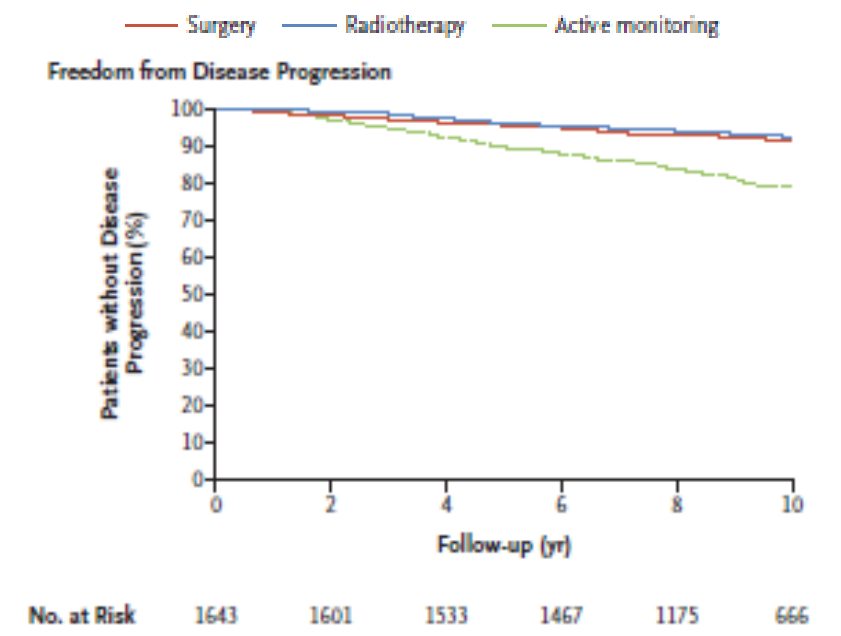
Cirurgia vs Radioterapia

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 13, 2016 VOL. 375 NO. 15

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*





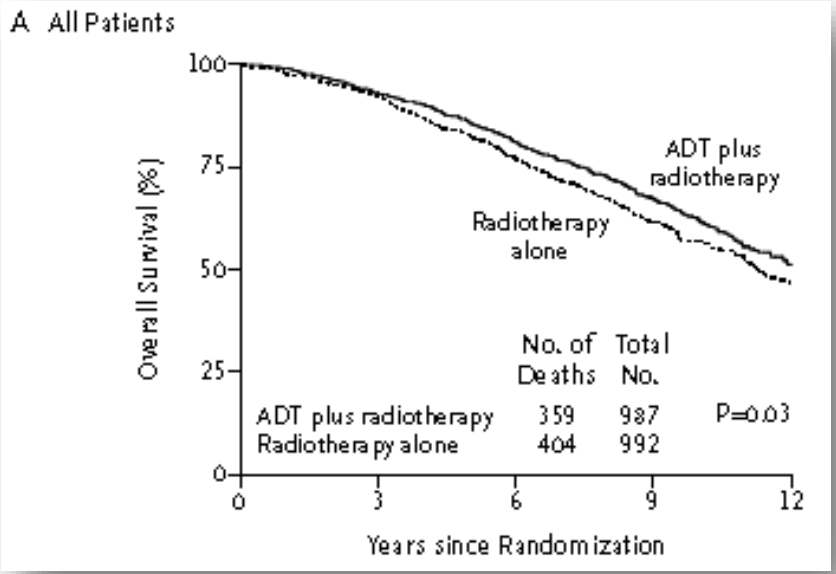
RT com HT curto Prazo
Tratamento do Risco Intermediário

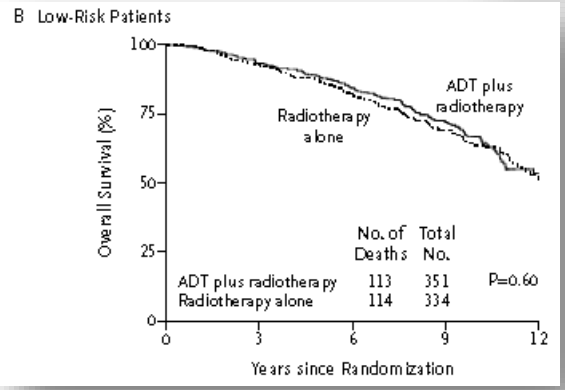
RT combinada a HT de curto prazo

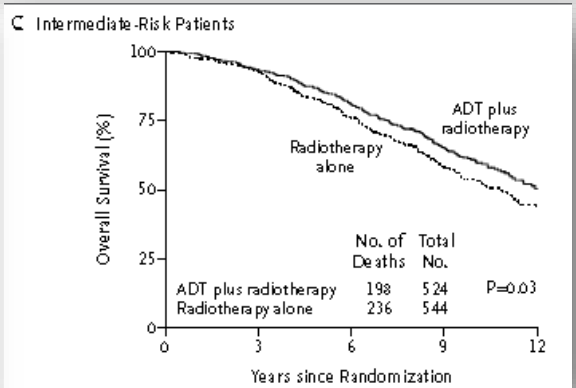
ESTUDO	RISCO	RT/HT	GANHO ABSOLUTO SV	P
RTOG 9408 (n=1979) 9.1 anos	Baixo 36% Int 53% Alto 11%	66Gy **66Gy HT 4 m**	**5%** 10 anos	0.03
DFCI 95096 (n=206) 7.6 anos	Int 77% Alto 23%	70Gy **70Gy HT 6m**	**13%** 8 anos	0.01

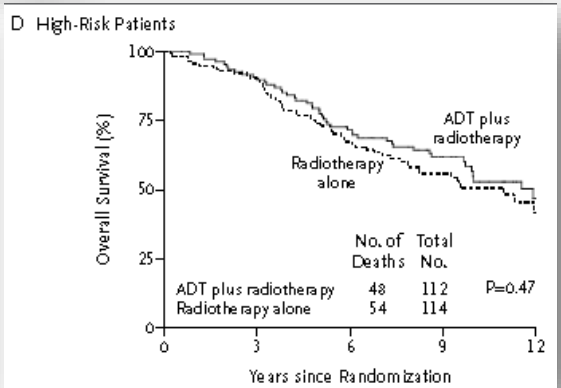
RT combinada a HT de curto prazo

RTOG 9408









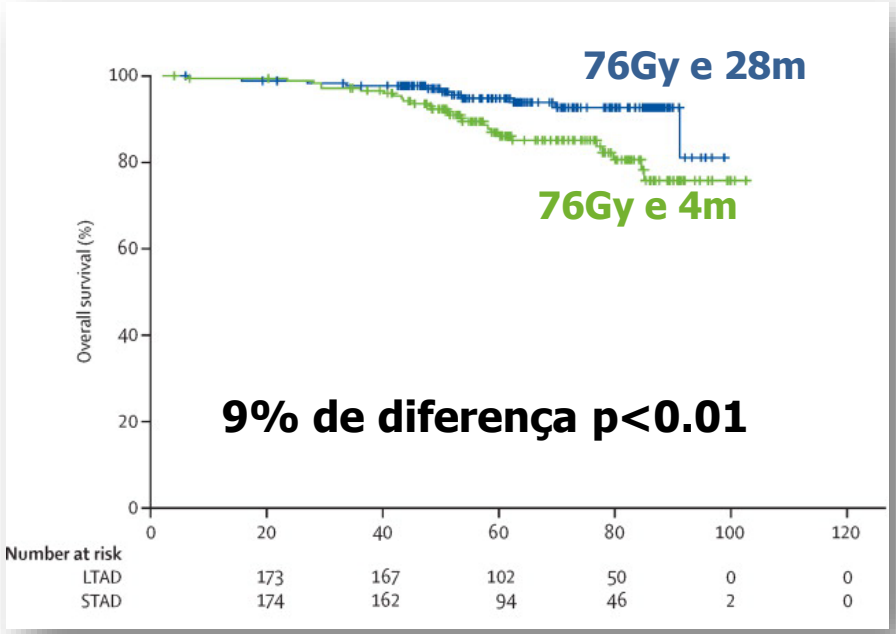
NEJM 2011; 365:107-18

Estudos Fase III
Escalonamento de dose / HT curto e longo

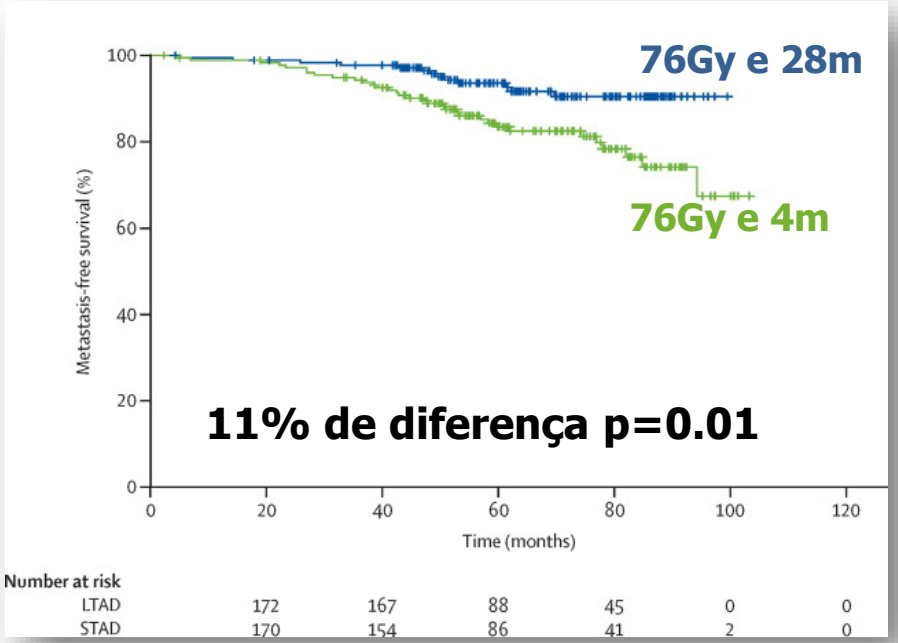
ESTUDO	RISCO	RT/HT	Falha PSA 5 anos	p	DFS 5 anos	p
Canadá (ASCO GU 2015) N=600 6.3 anos	100% int	**70Gy HT 6m** **76Gy HT 6m** 76Gy	**12.5%** **8%** 21%	0.023 <0.0001	**93%** **97.5%** 86%	0.01 <0.001
GETUG 14 (ASCO 2016) N=375/450* fechado precocemente 7 anos	100% int	**80Gy HT 4m** 80Gy	**10%** 21%	<0.01	**84%** 76%	0.02
DART01/05GICOR N=355 6.3 anos	Int 45% Alto 55%	**76Gy HT 28m** 76Gy HT 4m	**10%** 19%	0.01		

DART01/05GICOR

SV Global



SV Livre de Metástases



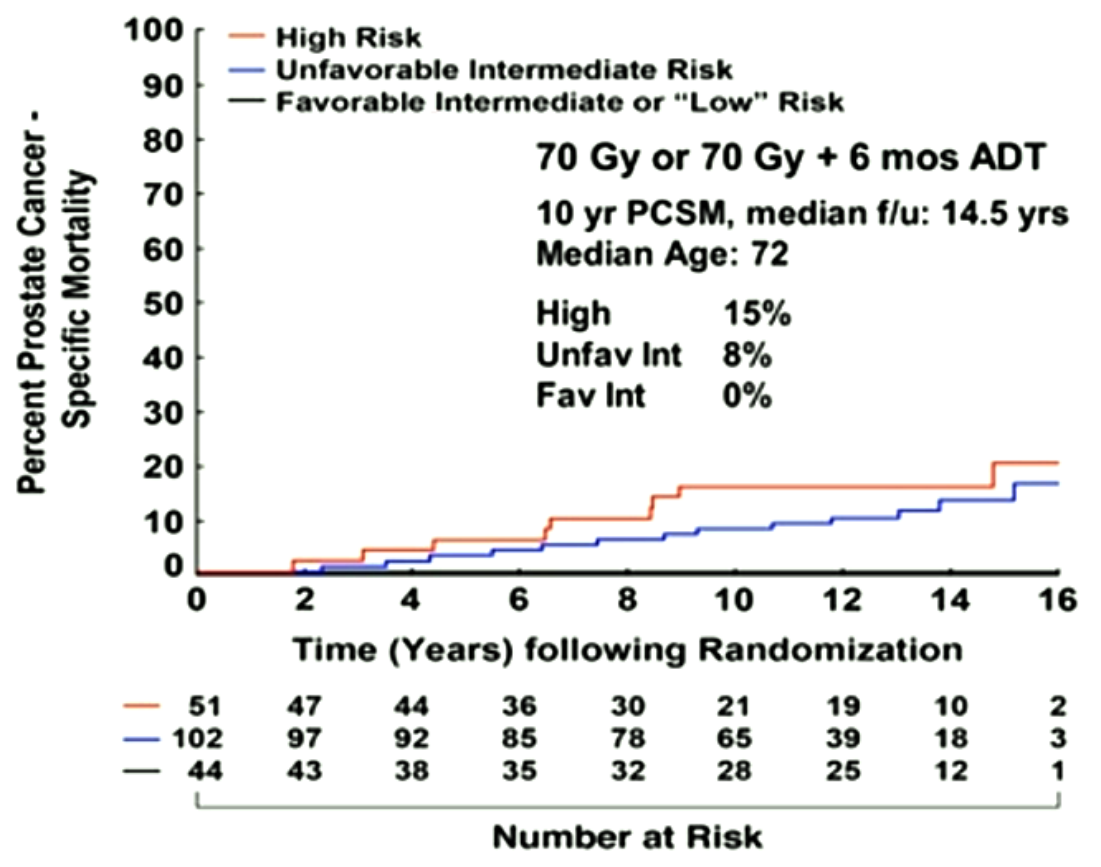
RTOG 0815: estudo aberto 79.2Gy ± HT6m

Lancet Oncol 2015; 16:320-27

Heterogeneidade do Risco Intermediário

Análise Estudo DFCI 95096

Risco de morte por Câncer de acordo com o risco Intermediário Favorável: 1 fator NCCN, ≤3+4, <50% Fr+

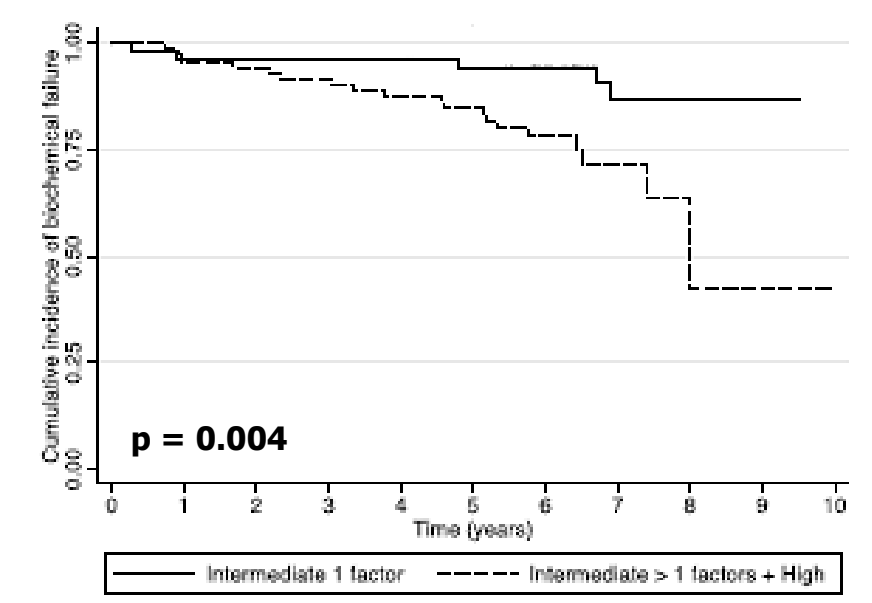


D'Amico, ASCO GU 2015

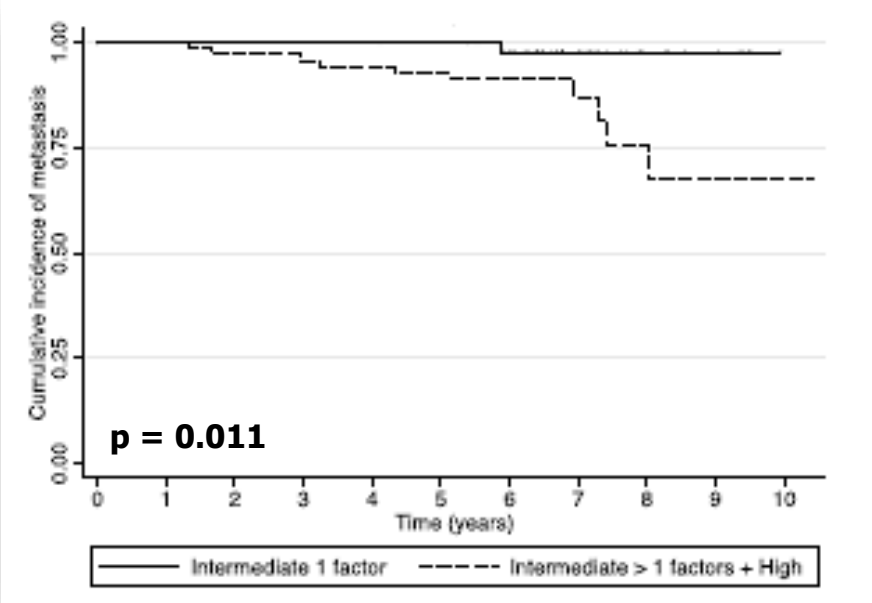
Experiência HSL 2001-2010 RT exclusiva

≥ 74Gy (90% ≥ 78Gy)
N = 127 (59% int, 41% alto risco)
Seguimento mediano 6.7 anos

SV livre de falha bioquímica



SV livre de metástases



Gadia, Adv Radiat Oncol. 2016 Oct-Dec; 1(4): 300–309

Impressões: Risco Intermediário

Risco intermediário: RTHT e 4-6 meses de HT

Se RT 66-70Gy, HT dá ganho em SV

Se RT >76Gy, ganho em SV livre de falha (ganho em SV?)

Minha Tendência:

Risco Intermediário favorável: **RT exclusiva ≥ 78Gy**

Risco Intermediário desfavorável: **RT ≥ 78 Gy com HT 4-6 meses**

RT novos fracionamentos

Estudos Hipofracionamento em CA de Próstata

ESTUDO	RISCO	ESQUEMA	EFICÁCIA 5 ANOS SLFB	TOX TARDIA	PROs
CHHiP N=3216	Baixo 15% **Int 73%** Alto 12%	37 x 2Gy **20 x 3Gy** *HT 3-6m 100%	**=** **88% vs 90%**	**=**	**=**
PROFIT N=1200	**Int 100%** G3+4: 63% T1C: 54%	39 x 2Gy **20 x 3Gy** *HT	**=** **85% vs 85%**	**=**	**=**
NRG 0415 N=1115	**Baixo 100%** T1 80%	41 x 1.8Gy **28 x 2.5Gy**	**=** **DFS 85%**	**GU/GI Grau 2**	**=**

HYPO-RT-PC Trial (Ultra-Hipofracionamento)

Material and methods – trial design

- Open, randomised, phase III trial
  - Intermediate/high prostate can
  - 1200 patie
    - July 20
  - No androgen therapy

Designed as superiority trial with 10% improvement in BF/CF from 70-80%

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)

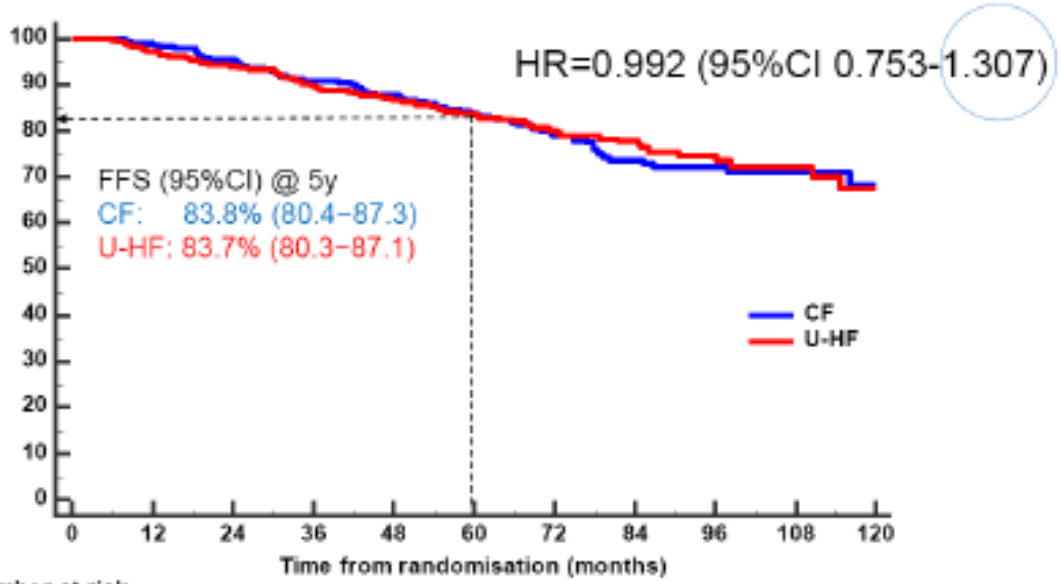
[a]T1c-T3a, PSA ≤20 with one or two of the following risk factors; T3a or Gleason ≥7 or PSA >10

	CF (n=591)	U-HF (n=589)	Total (n=1180)
Age			
Median (IQR)	69 (65–72)	68 (64–72)	**68 (65–72)**
T stage			
T1c	289 (49%)	313 (53%)	**602 (51%)**
T2	275 (47%)	252 (43%)	**527 (45%)**
T3a	27 (5%)	24 (4%)	**51 (4%)**
Gleason score			
≤6	108 (18%)	104 (18%)	**212 (18%)**
7	444 (75%)	447 (76%)	**891 (76%)**
3+4	310	325	**635**
4+3	134	122	**256**
≥8	39 (7%)	38 (6%)	**77 (7%)**
Pre-treatment PSA (ng/ml)			
Median (IQR)	8.6 (5.7–12.0)	8.7 (6.0–12.2)	**8.6 (5.9–12.0)**
Risk group			
Intermediate	527 (89%)	527 (89%)	**1054 (89%)**
High[a]	64 (11%)	62 (11%)	**126 (11%)**

Widmark, et al

HYPO-RT-PC Trial (Ultra-Hipofracionamento)

Results – primary endpoint

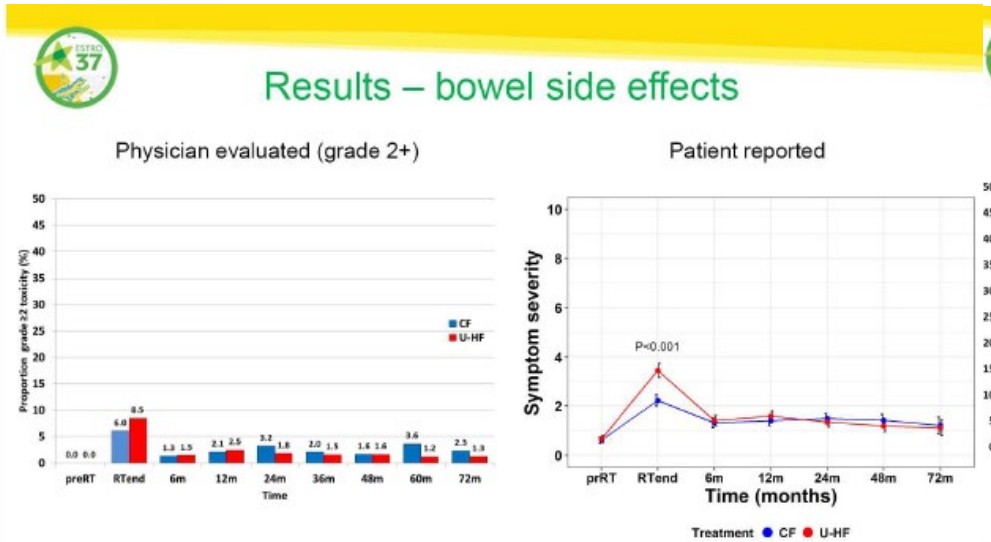


Number at risk

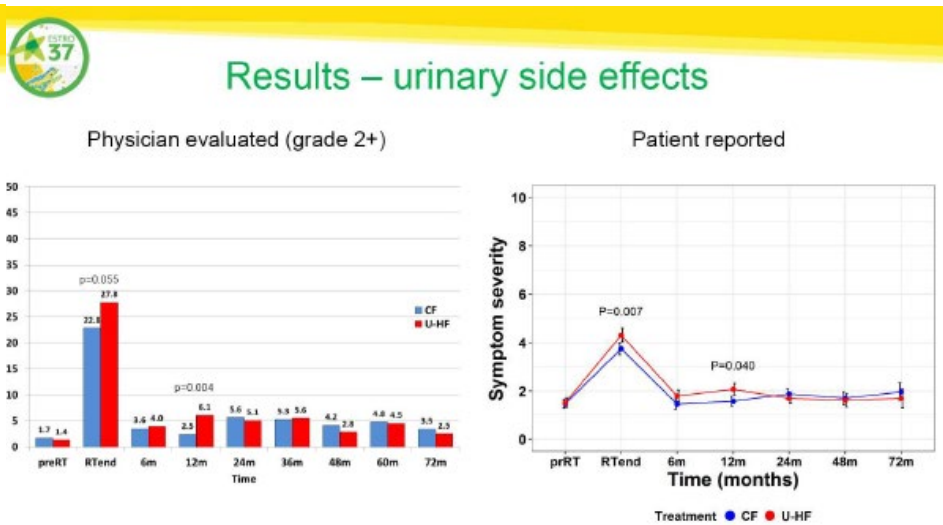
Group: CF	591	580	540	433	332	242	171	108	67	37	23
Group: U-HF	589	569	527	408	325	242	160	113	71	38	20

Widmark, et al

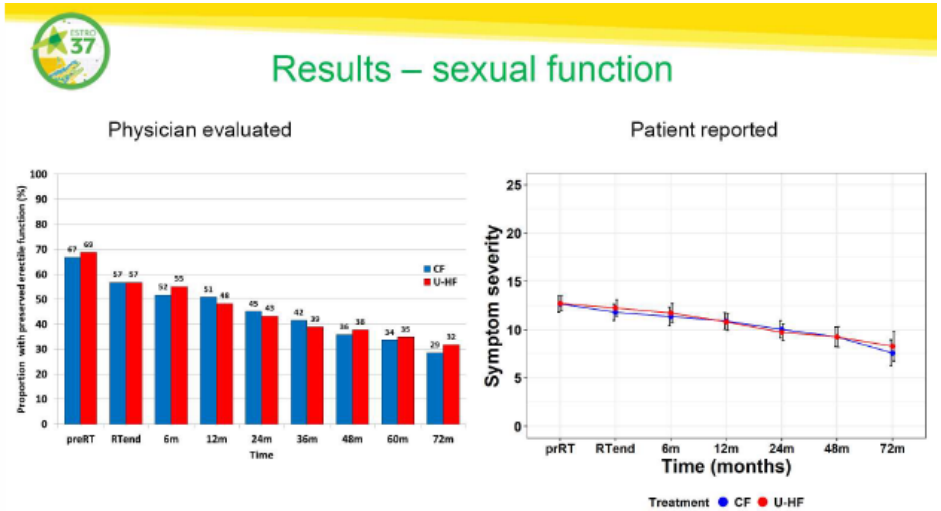
HYPO-RT-PC Trial (Ultra Hipofracionamento)



8.5% vs 6% Final da RT



28% vs 23% Final da RT
6% vs 2.5% 12m pós-RT



Widmark, et al

RT Hipofracionada

Hipofracionamento moderado (20 x 3Gy; 28 x 2.5Gy) validado em estudos fase III de não-inferioridade

Ultra-hipofracionamento: esquema promissor com um estudo fase III mostrando equivalência terapêutica

RT / Braquiterapia

ASCENDE-RT Trial

N=398
122 risco intermediário
276 Alto risco

Neo HT 8 meses
RT externa 78Gy+ HT 4 meses

Neo HT 8 meses
Braqui I-125+ RT externa 46Gy
+ HT 4 meses

Int J Radiation Oncol Biol Phys, Vol. 98, No. 2, pp. 275e285, 2017

ASCENDE-RT Trial

SV livre de falha no PSA em 9 anos

RT+BT: 83% RT: 62% (p=0.001)

SV livre de falha Metástases em 9 anos

RT+BT: 89% RT: 85% (p=ns)

SV Global em 9 anos

RT+BT: 78% RT: 74% (p=ns)

Toxicidade Urinária Grau 3

RT+BT: 8.6% RT: 2.2% (p=0.001)

Int J Radiation Oncol Biol Phys, Vol. 98, No. 2, pp. 275e285, 2017

RTOG 0232

N=579 risco intermediário

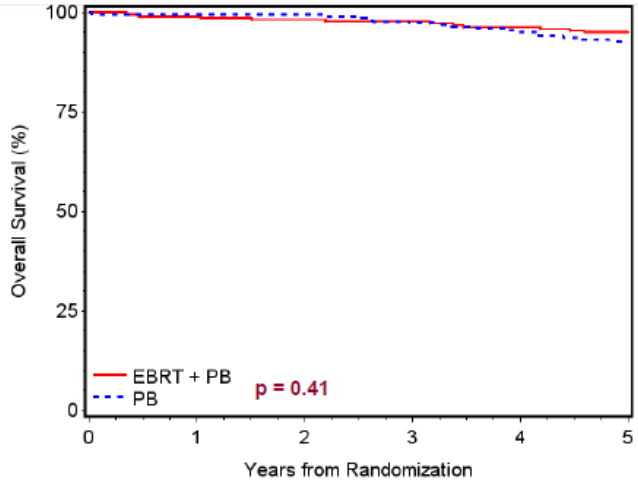
70% T1; 90% Gleason 7 e PSA <10

RT ext 45Gy +BT (I-125; Pd103)

BT (I-125; Pd103)

Prestidge et al, ASTRO 2016

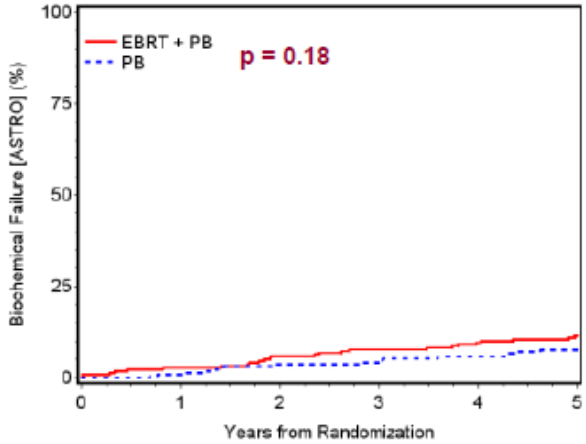
Overall Survival



Patients at Risk						
EBRT + PB	220	217	215	214	210	203
PB	223	222	222	217	212	201

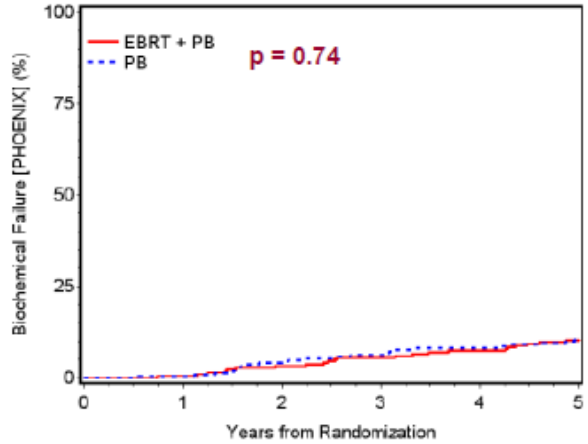
Biochemical Failure

ASTRO Definition



Patients at Risk						
EBRT + PB	220	212	203	198	192	183
PB	223	219	213	208	199	187

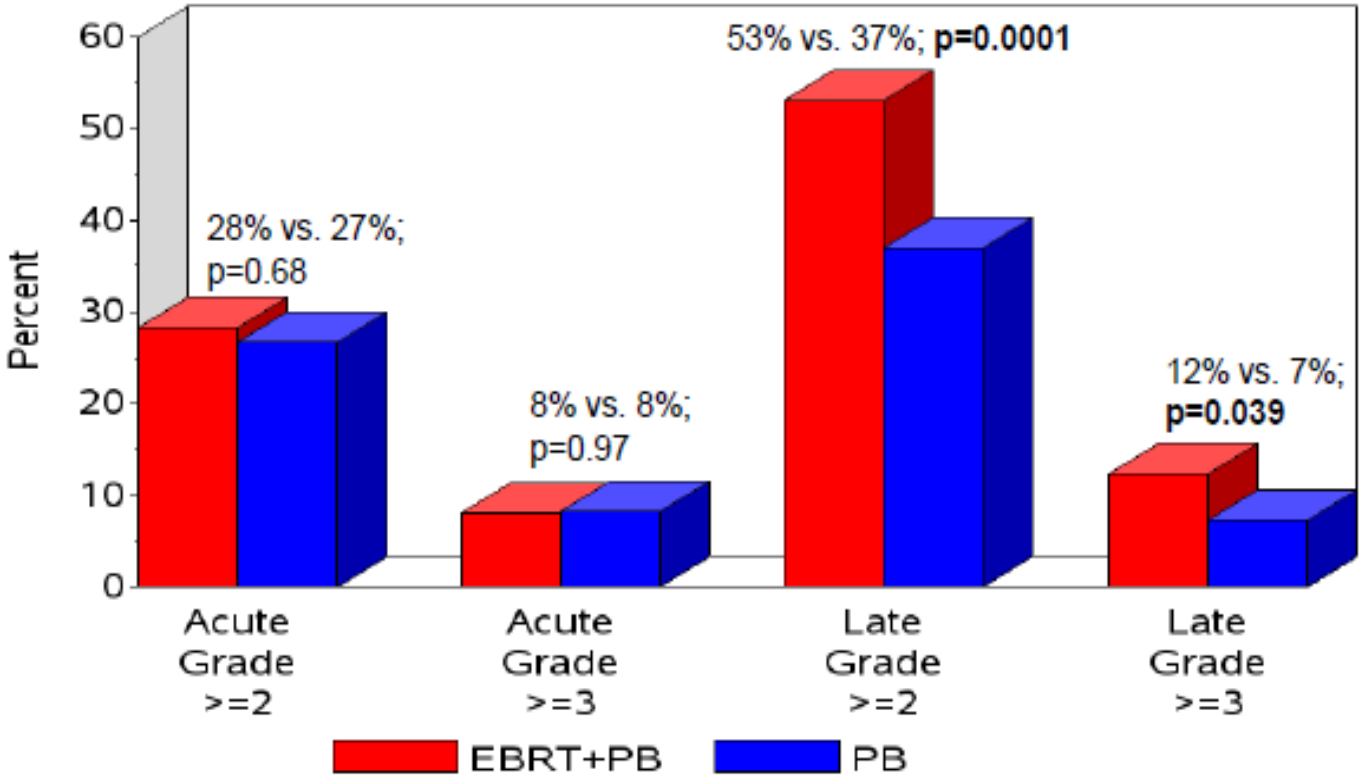
Phoenix Definition



Patients at Risk						
EBRT + PB	220	213	204	198	191	178
PB	223	220	211	203	195	182

Prestidge et al, ASTRO 2016

Adverse Events



NRG ONCOLOGY™

Prestidge et al, ASTRO 2016

Braquiterapia no Risco Intemediário

Pode ser usada associada a RT externa (sugestão de mais controle de PSA com mais toxicidade urinária)

Pode ser usada como tratamento exclusivo no risco intermediário favorável