Tratamento do câncer de próstata resistente à castração não metastático:

Caso Clínico

Lucas Nogueira
Fernando Maluf

Conflitos de interesse

De acordo com a Resolução 1595/2000 do Conselho Federal de Medicina e RDC 102/2000 da ANVISA, declaro que:

1. Participo de estudos clínicos patrocinados pelas empresas:

GSK, Janssen, Astellas, Bayer

2. Atuo como *speaker* de eventos das empresas:

Janssen, Bayer, Astra Zeneca, Astellas, Roche

3. Participo como membro do *advisory board* das empresas:

Janssen, Bayer, Astellas, Health Genomics

4. Não possuo ações de quaisquer destas companhias farmacêuticas.

Conflitos de interesse

De acordo com a Resolução 1595/2000 do Conselho Federal de Medicina e RDC 102/2000 da ANVISA, declaro que:

1. Participo de estudos clínicos patrocinados pelas empresas:

Sanofi-aventis, Janssen, Astrazeneca, Roche, Astellas, MSD, BMS, Novartis

2. Atuo como *speaker* de eventos das empresas:

Sanofi-aventis, Janssen, Astrazeneca, Roche, Astellas, MSD, BMS, Novartis, Amgen, Ferring

3. Participo como membro do *advisory board* das empresas:

Sanofi-aventis, Janssen, Astrazeneca, Roche, Astellas, MSD, BMS, Novartis, Amgen, Ferring

4. Não possuo ações de quaisquer destas companhias farmacêuticas.

Disclaimer

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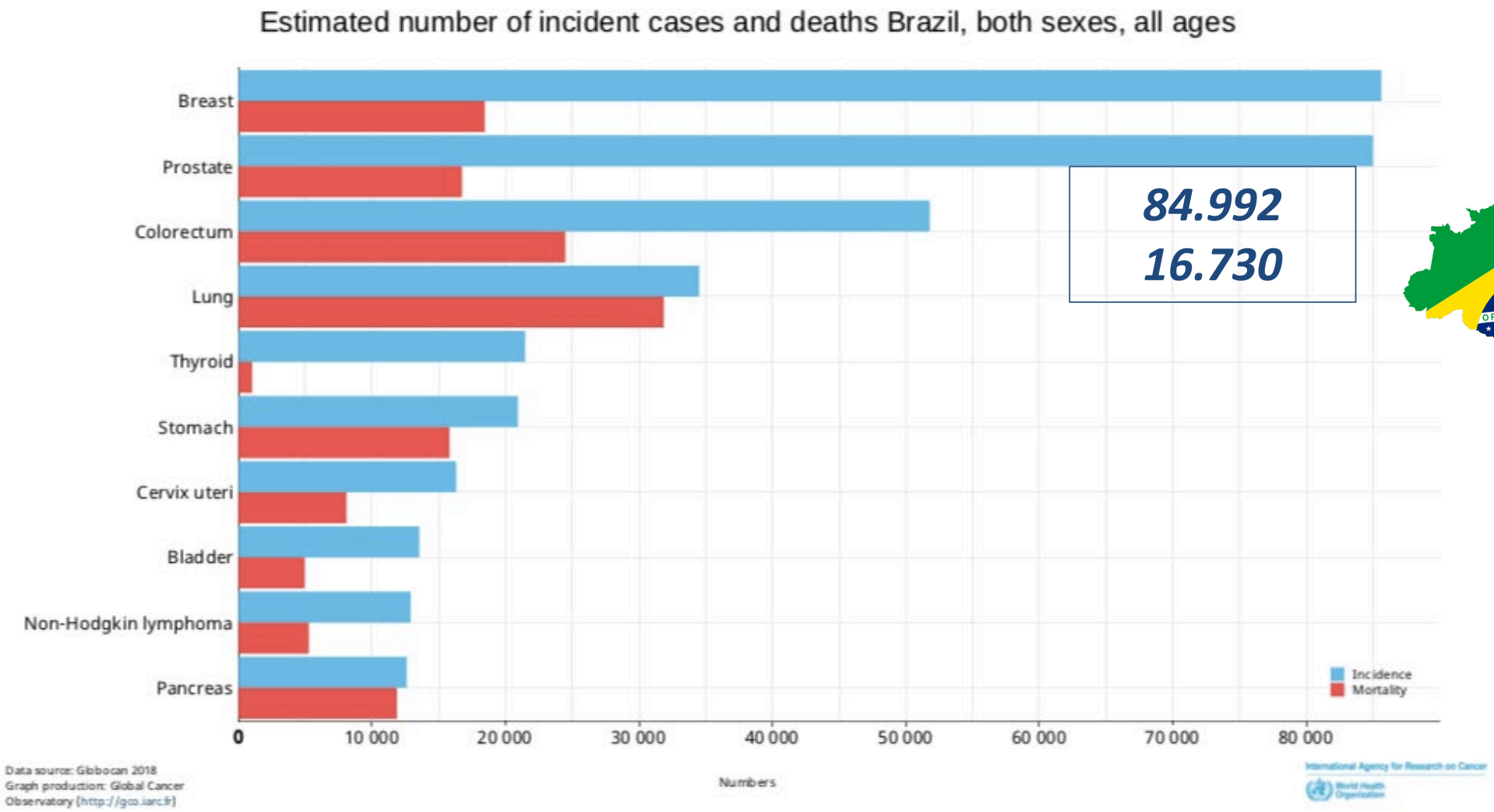
- Informações de outras indicações potenciais e utilizações futuras destinam-se apenas à discussão e não devem ser interpretadas como uma intenção de promover usos não aprovados.
- O conteúdo deste conjunto de slides não deve ser usado de qualquer forma, direta ou indiretamente, para promover ou vender o produto para uso não aprovado.
- A Astellas proíbe estritamente a promoção de uso não registrado no país e está em conformidade com todas as leis, regulamentos e políticas da empresa.

Prostate Cancer Epidemiology



84.992
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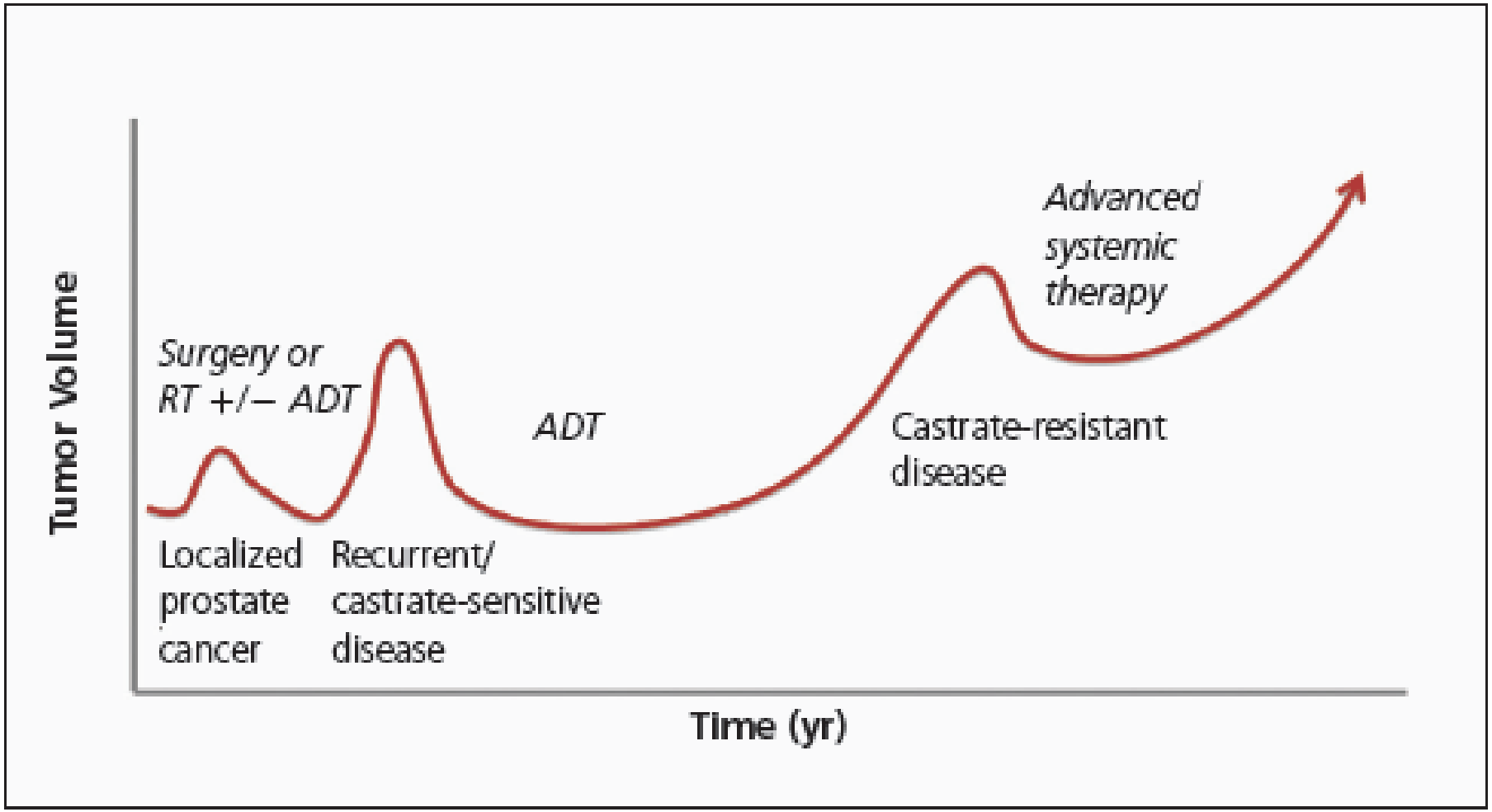
https://gco.iarc.fr/today/home


Tumor Volume
Surgery or
RT +/– ADT
ADT
Advanced
systemic
therapy
Castrate-resistant
disease
Localized
prostate
cancer
Recurrent/
castrate-sensitive
disease
Time (yr)

JLC, 58 anos

- Paciente sem comorbidades, raça negra, HF neg para CaP;
- PSA elevado em exame de rotina – 16,0 ng/ml, cT2a;
- Biópsia – G 4+4 – 3/14 fragmentos, 10 a 40%;
- CO e TC sem alterações.

JLC, 58 anos

Prostatectomia Radical e LND estendida:

- adenocarcinoma de próstata comprometendo ambos os lobos Gleason 8 (4 + 4).
- Margens livres.
- Linfonodos (24) e vesículas seminais sem comprometimento.
- Ausência de Invasão angiolinfática e perineural
- pT2c N0 Mx

PSA 3 meses após PR – 0,01 ng/ml, continente

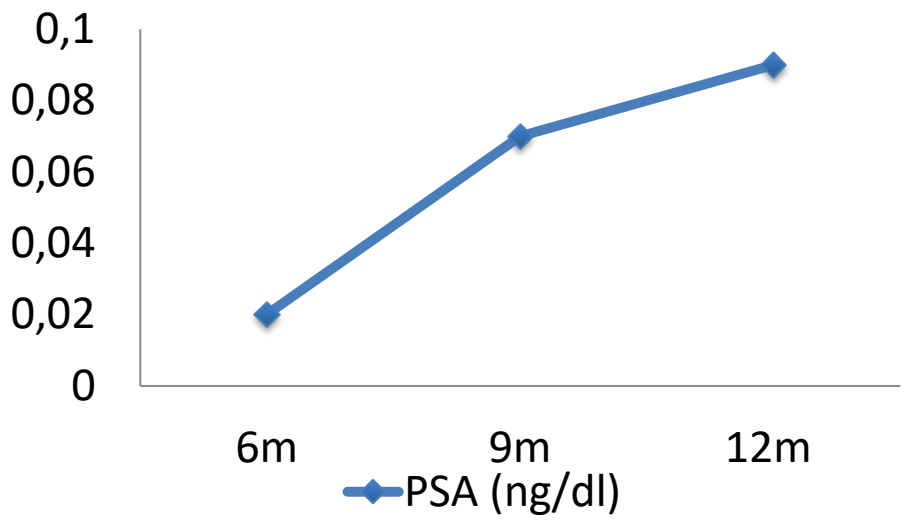
JLC, 58-59 anos

6m : PSA = 0,02 ng/mL

9 m: PSA = 0,07 ng/mL

12m : PSA = 0,09 ng/mL

Perdeu seguimento...

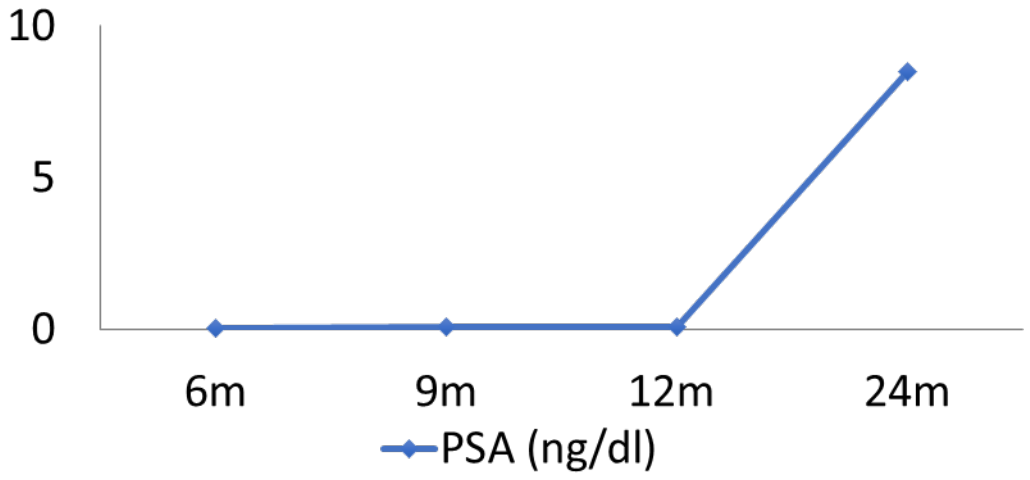


JLC, 60 anos

24m: assintomático, pedido novo PSA = 8,5

Cintilografia óssea : Sem alterações

Outro exame imagem? TC / RNM / PET ???



- Evaluation of Gallium-68 PSMA PET/CT Imaging in Individuals with Biochemical Recurrence Following Radical Prostatectomy
  - ✓ 391 patients from a single institution.

Table 1. Detection rates of PSMA PET following radical prostatectomy based on PSA banding

PSA level	Sample size	Number of positive patients	Detection rate (%)
<0.2ng/ml	97	41	42%
0.2-<0.5ng/ml	101	48	48%
0.5-<1.0ng/ml	54	36	67%
1.0-<2.0ng/ml	39	33	85%
>2.0ng/ml	100	92	92%
Total (overall)	391	250	64%

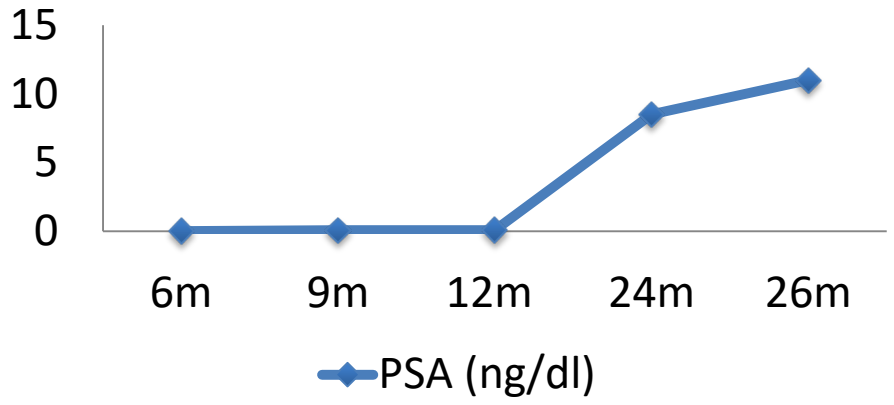
Yuigi Yuminaga, Kingswood, Australia, AUA 2018

JLC, 60 anos

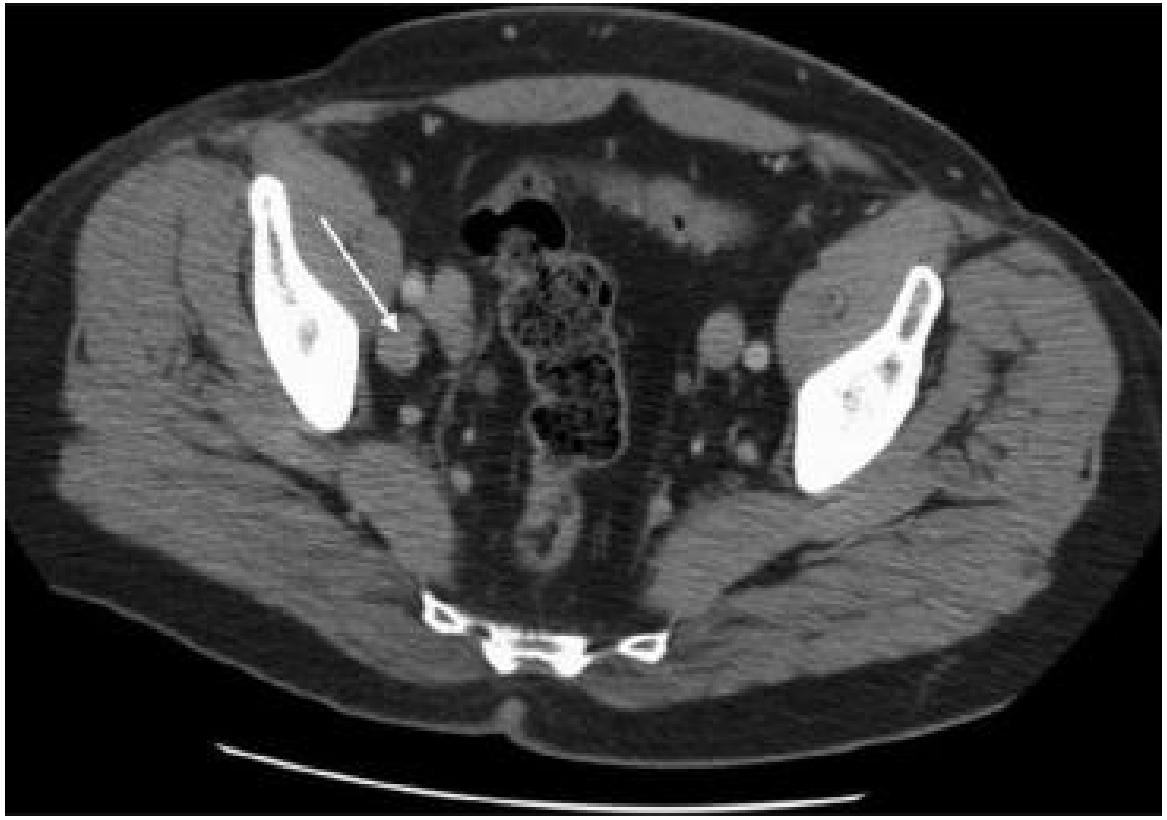
TC – aumento linfonodal a direita 2,5 cm

PET PSMA – captação em área linfonodal

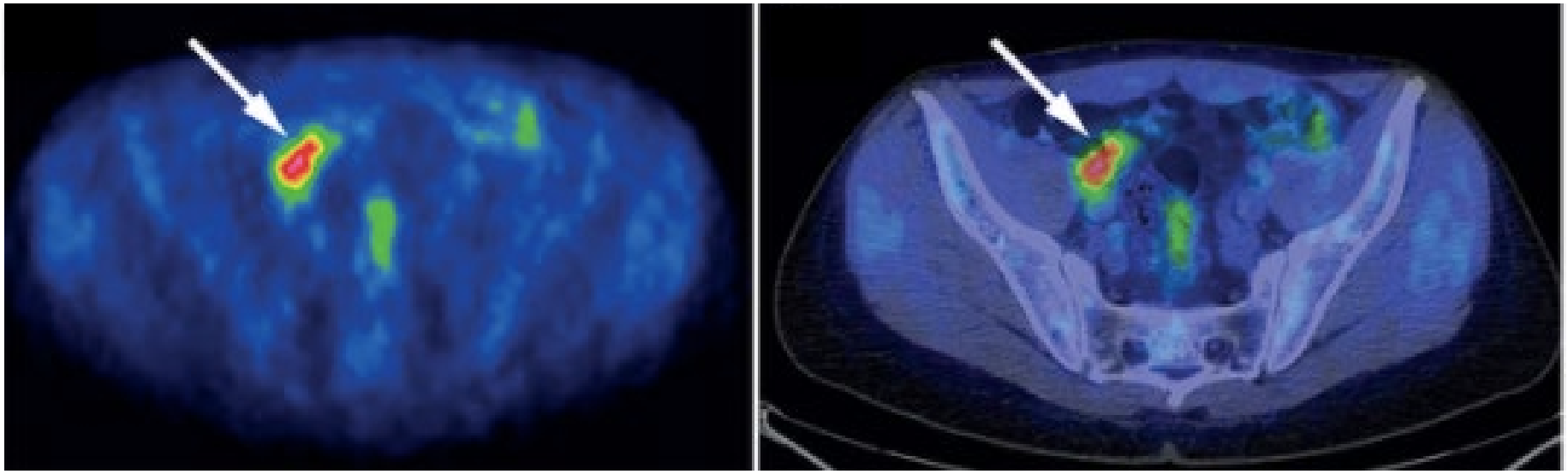
PSA – 11,0



JLC, 60 anos, CT



JLC, 60 anos, PET-CT PSMA

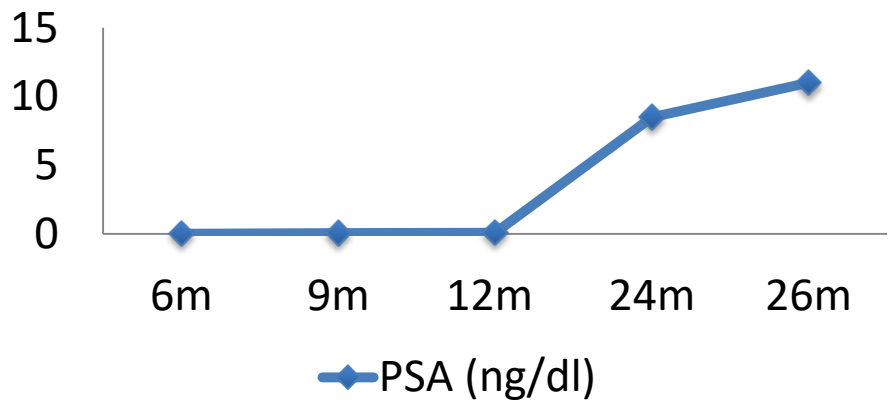


JLC, 60 anos

1) Observação com PSA / Imagem
2) ADT
3) Radioterapia (ADT ?) restrita ao leito
4) Radioterapia (ADT ?) leito e pelve
5) Linfadenectomia de resgate
6) Quimioterapia + ADT
7) Antiandrogênico 2ª geração ou Inibidor CYP 17 + ADT

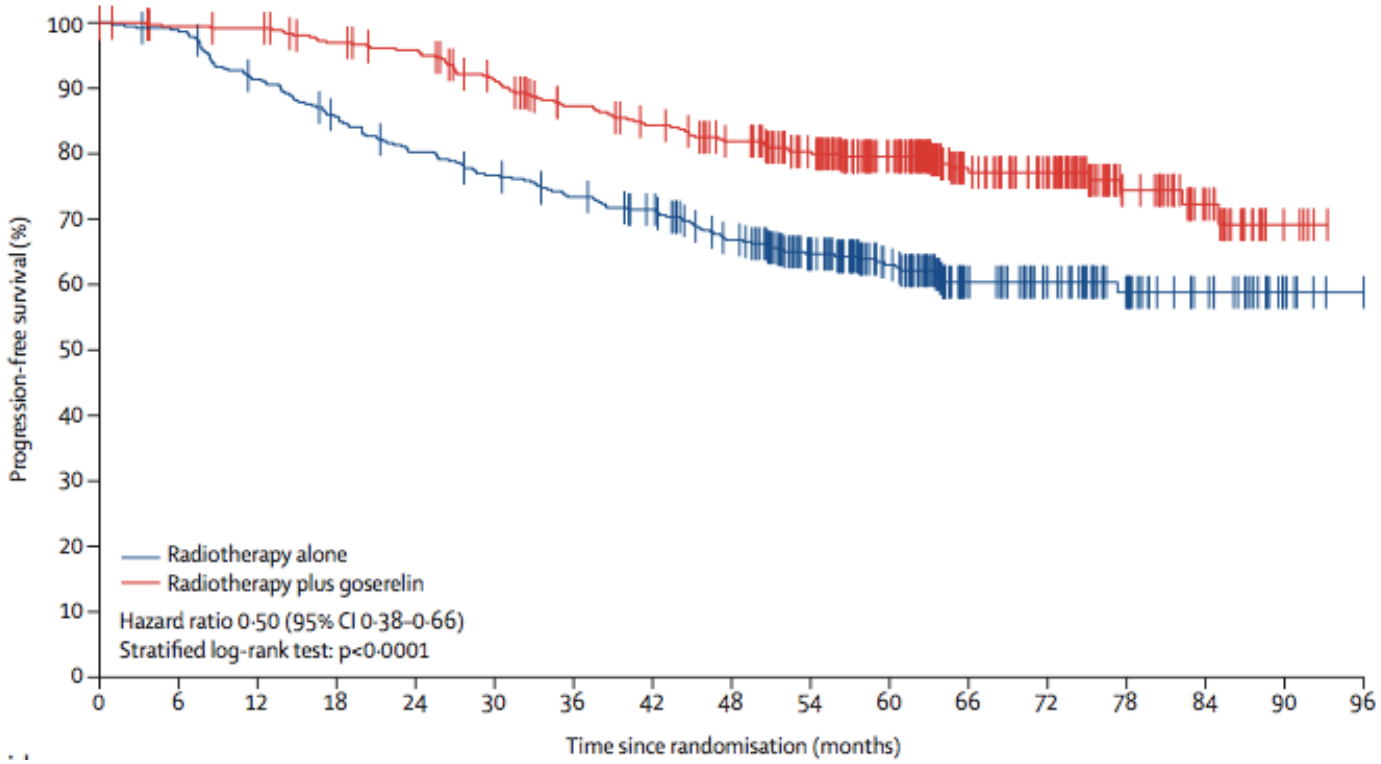
JLC, 60 anos

Submetido a radioterapia de resgate, com extensão para toda pelve, sem ADT associada



Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial

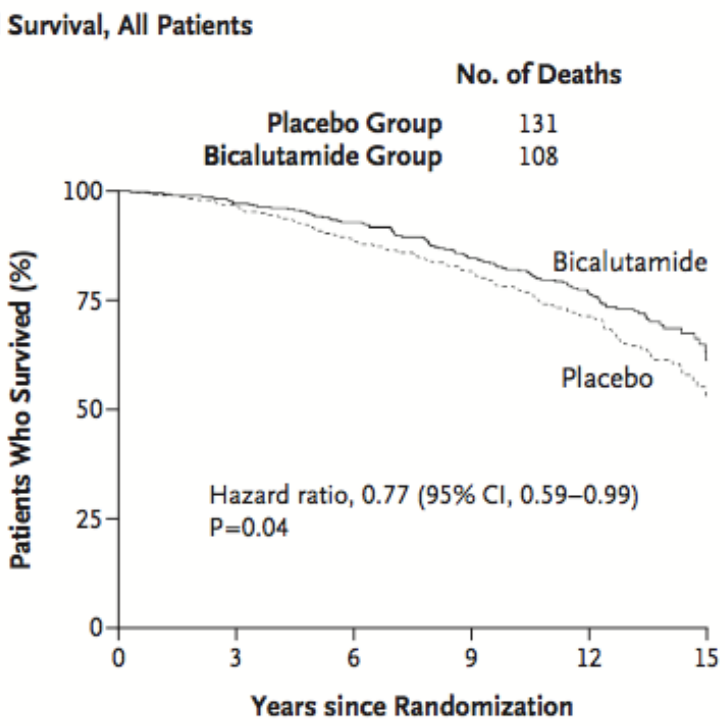
Christian Carrie, Ali Hasbini, Guy de Laroche, Pierre Richaud, Stéphane Guerif, Igor Latorzeff, Stéphane Supiot, Mathieu Bosset, Jean-Léon Lagrange, Véronique Beckendorf, François Lesaunier, Bernard Dubray, Jean-Philippe Wagner, Tan Dat N'Guyen, Jean-Philippe Suchaud, Gilles Créhange, Nicolas Barbier, Muriel Habibian, Céline Ferlay, Philippe Fourneret, Alain Ruffion, Sophie Dussart

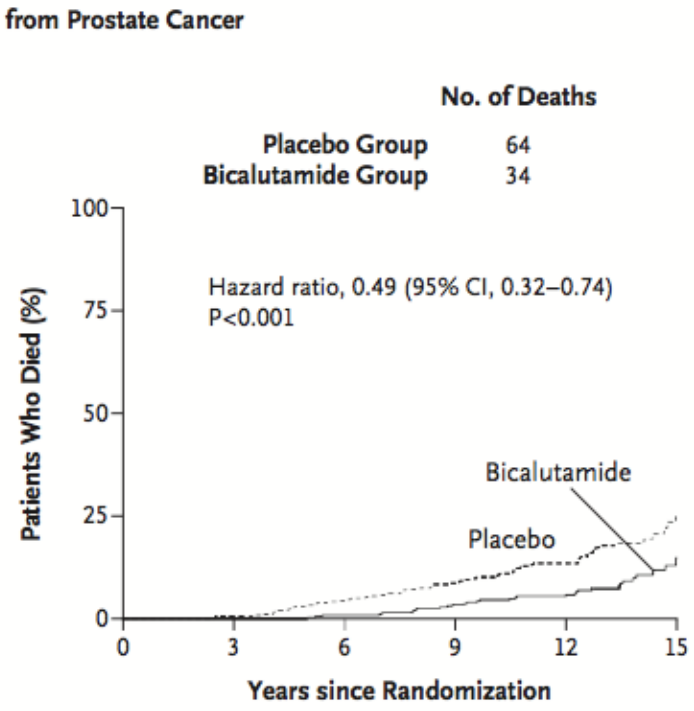


Lancet Oncol 2016; 17: 747–56

Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer

W.U. Shipley, W. Seiferheld, H.R. Lukka, P.P. Major, N.M. Heney, D.J. Grignon, O. Sartor, M.P. Patel, J.-P. Bahary, A.L. Zietman, T.M. Pisansky, K.L. Zeitzer, C.A.F. Lawton, F.Y. Feng, R.D. Lovett, A.G. Balogh, L. Souhami, S.A. Rosenthal, K.J. Kerlin, J.J. Dignam, S.L. Pugh, and H.M. Sandler, for the NRG Oncology RTOG*

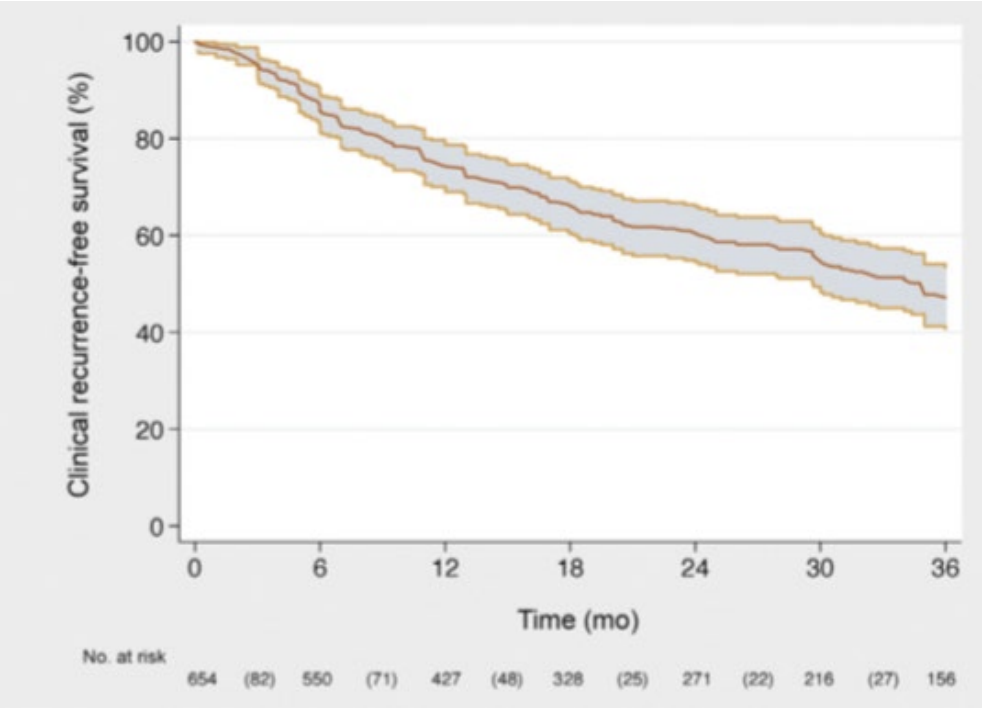


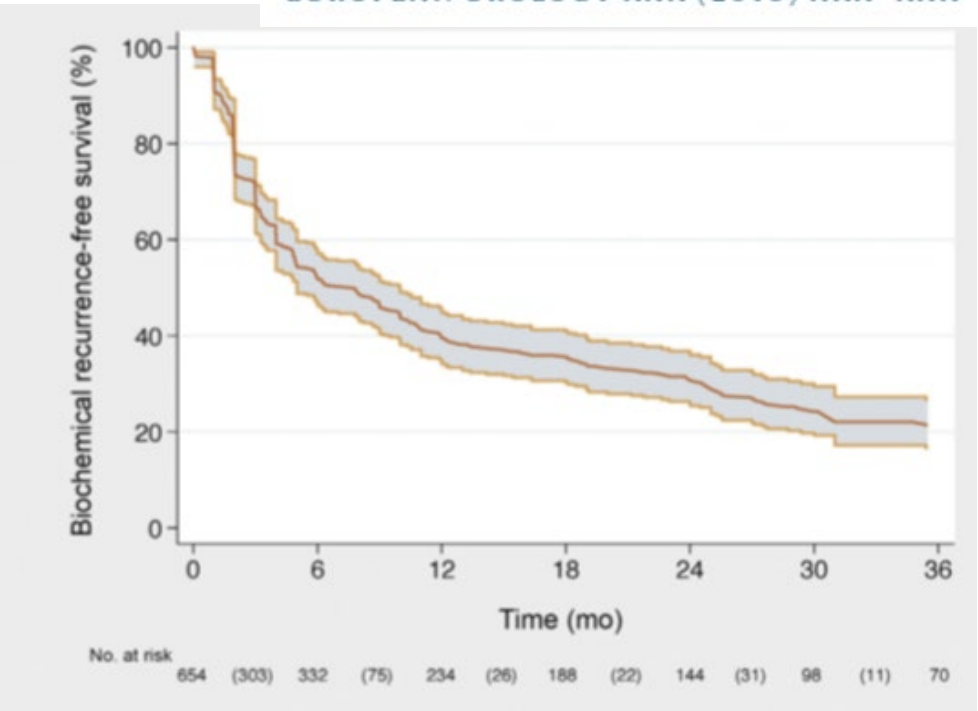


N Engl J Med 2017; 376:417-428

Identifying the Optimal Candidate for Salvage Lymph Node Dissection for Nodal Recurrence of Prostate Cancer: Results from a Large, Multi-institutional Analysis

EUROPEAN UROLOGY XXX (2018) XXX–XXX





Identifying the Optimal Candidate for Salvage Lymph Node Dissection for Nodal Recurrence of Prostate Cancer: Results from a Large, Multi-institutional Analysis

EUROPEAN UROLOGY XXX (2018) XXX–XXX

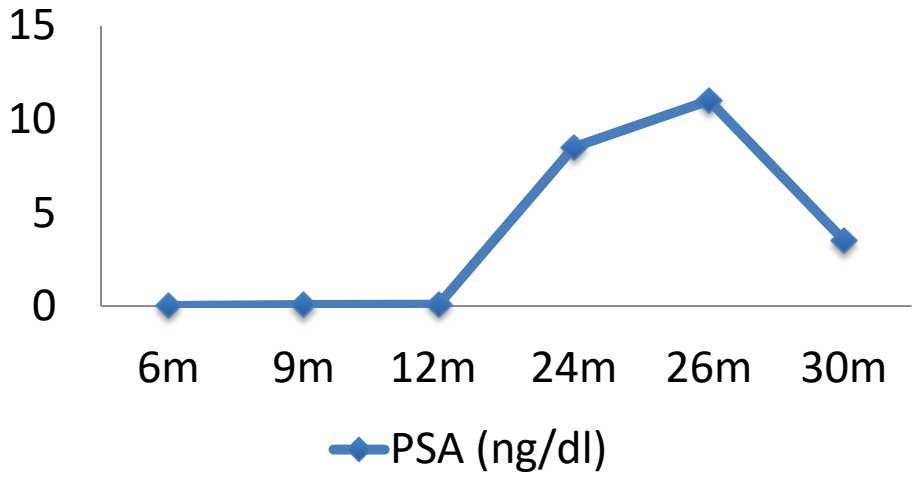
Predictor	HR	95% CI	*p* value
Gleason grade group			
≤4	1.00	Ref.	–
5	2.04	1.66–2.50	<0.0001
Time from RP to PSA rising, per 6 mo	0.98	0.96–0.99	0.025
HT administration at the time of PET/CT scan			
No	1.00	Ref.	–
Yes	1.47	1.19–1.82	0.0005
Retroperitoneum involvement at PET/CT scan			
No	1.00	Ref.	–
Yes	1.24	1.01–1.52	0.038
Positive spots at PET/CT scan			
≤2	1.00	Ref.	–
≥3	1.26	1.05–1.61	0.019
PSA at SLND, ng/ml	1.05	1.04–1.07	<0.0001

JLC, 60 anos

3 m – 3,5 ng/mL

CO sem alterações

TC diminuição LN



JLC, 61 anos

1) ADT

2) Quimioterapia + ADT

3) Observação com PSA / imagem

4) Antiandrogênico 2ª geração ou Inibidor CYP 17 + ADT

JLC, 60 anos

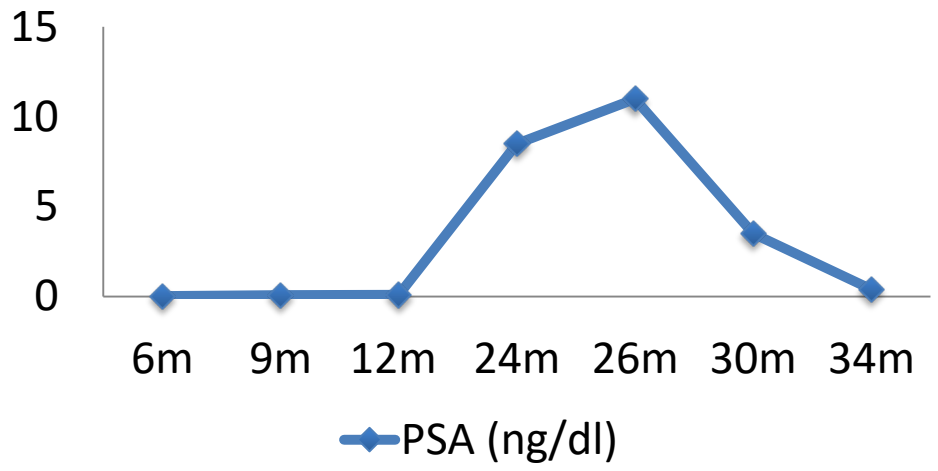
- Iniciado agonista - LHRH

JLC, 61 anos

2m - PSA = 0,4 ng/mL (anterior PSA = 3,5 ng/mL)

Paciente reclamando de:

- ✓ Fogachos intensos
- ✓ Impotência importante
- ✓ Fraqueza muscular leve



JLC, 61-62 anos

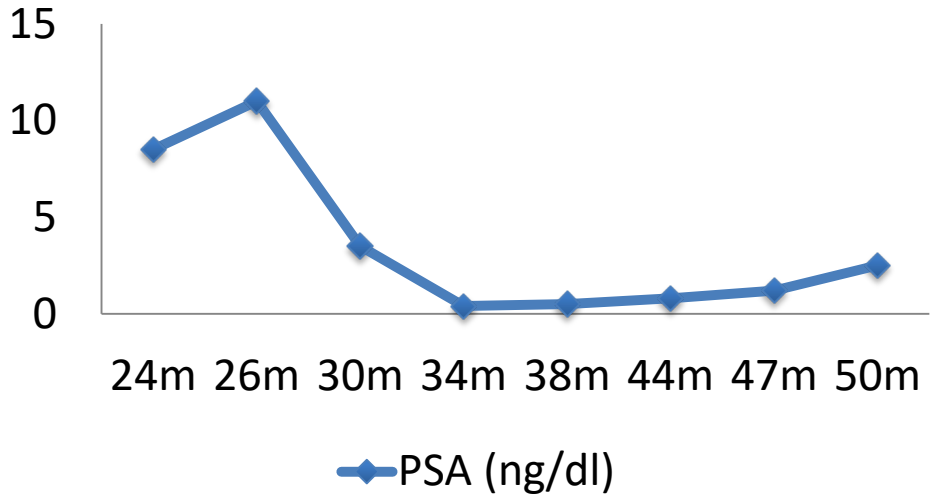
4m : PSA = 0,5 ng/mL

6 m: PSA = 0,8 ng/mL

9 m : PSA = 1,2 ng/mL

12 m: PSA = 2,5 ng/mL

Testosterona total - 22

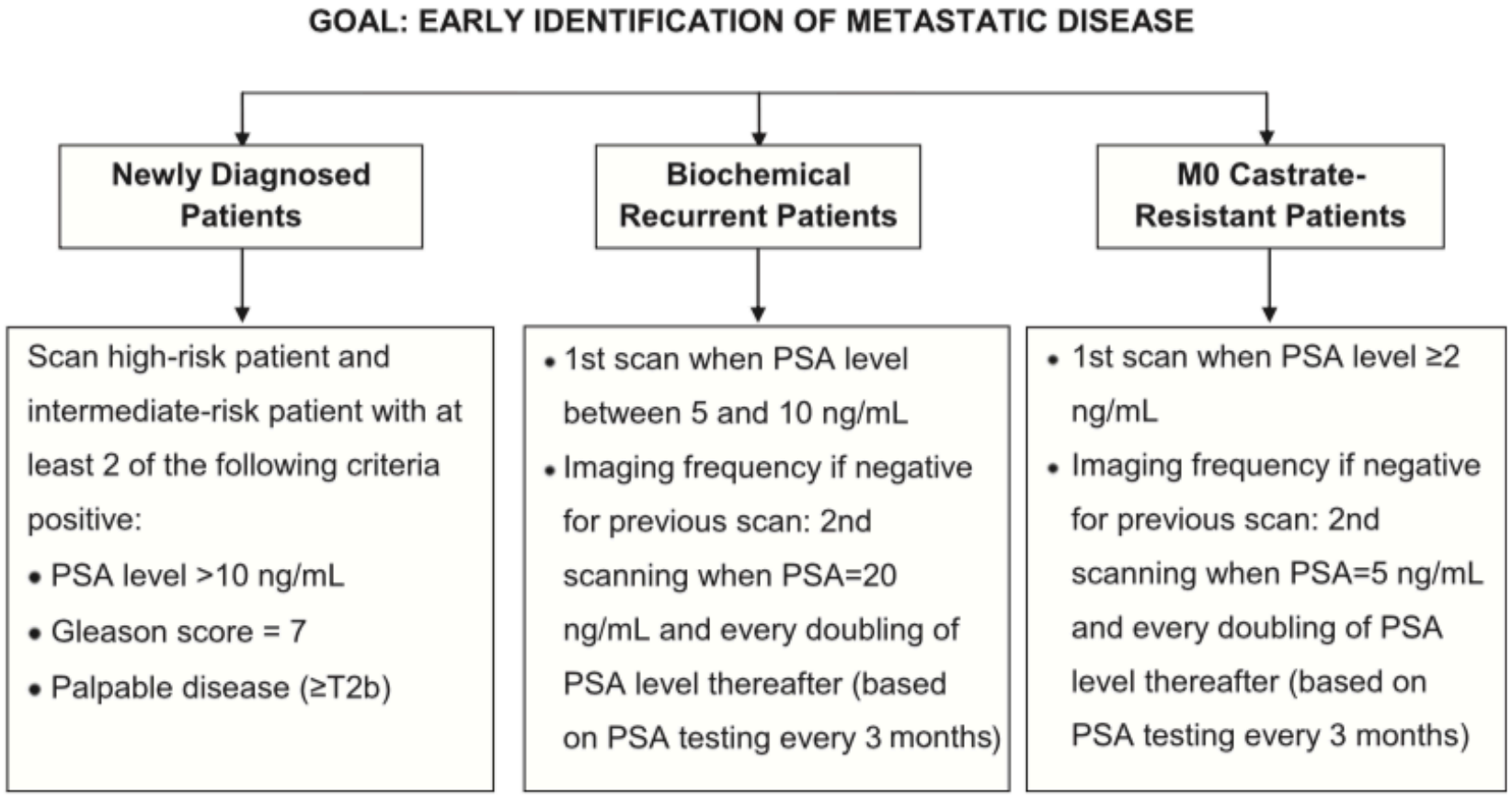


Qual a periodicidade da avaliação
Quando nova imagem ?

CO/TC

PSMA ?

Challenges and Recommendations for Early Identification of Metastatic Disease in Prostate Cancer



UROLOGY 83 (3), 2014

A Clinician's Guide to Next Generation Imaging in Patients With Advanced Prostate Cancer (Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence [RADAR] III)

Biochemical Recurrent Patients

1st conventional scan when PSA level between 5 and 10 ng/ml

Imaging frequency if negative for previous conventional scan: 2nd scanning when PSA=20 ng/ml and every doubling of PSA level thereafter (based on PSA testing every 3 months)

Consider NGI for PSA ≥0.5

PSA <0.5 can be considered based on specific performance of various NGI techniques

DOI: 10.1016/j.juro.2018.05.164

A Clinician's Guide to Next Generation Imaging in Patients With Advanced Prostate Cancer (Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence [RADAR] III)

M0 Castrate-Resistant Patients

1st conventional scan when PSA level ≥2 ng/ml

Imaging frequency if negative for previous conventional scan:

2nd conventional scan when PSA=5 ng/ml and every doubling of PSA level thereafter (based on PSA testing every 3 months)

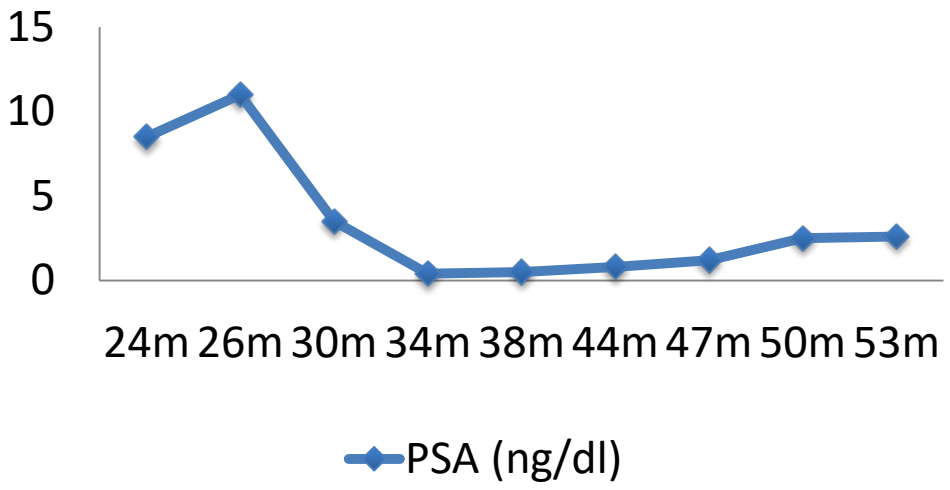
Only consider NGI in the setting of PSADT <6 months, when M1 therapies would be appropriate

DOI: 10.1016/j.juro.2018.05.164

JLC, 61-62 anos

15 m - PSA 2,6

TC e CO sem alterações



JLC, 61-62 anos

4m : PSA = 0,5 ng/mL

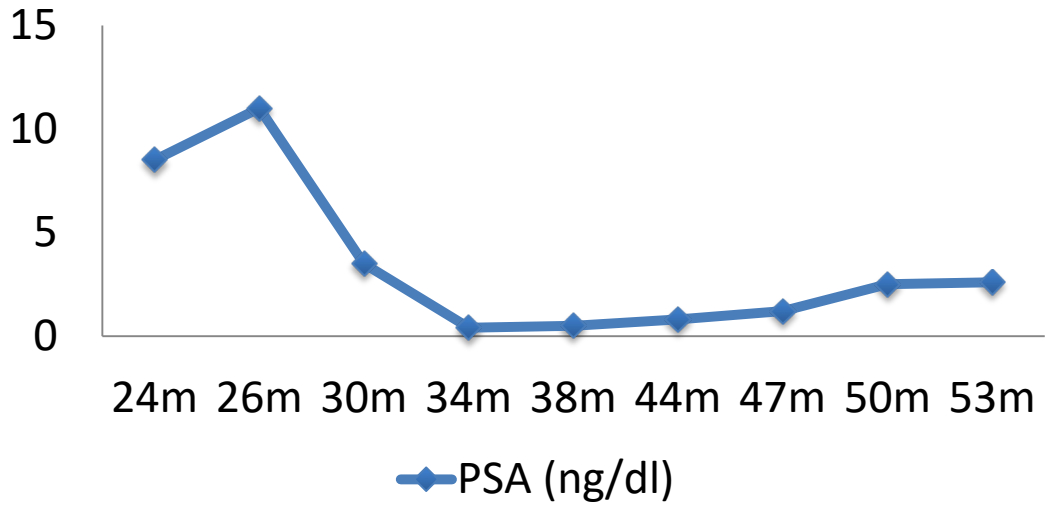
6 m: PSA = 0,8 ng/mL

9 m : PSA = 1,2 ng/mL

12 m: PSA = 2,5 ng/mL

15 m: PSA = 2,6 ng/mL

Testosterona total - 25



JLC, 62-63 anos

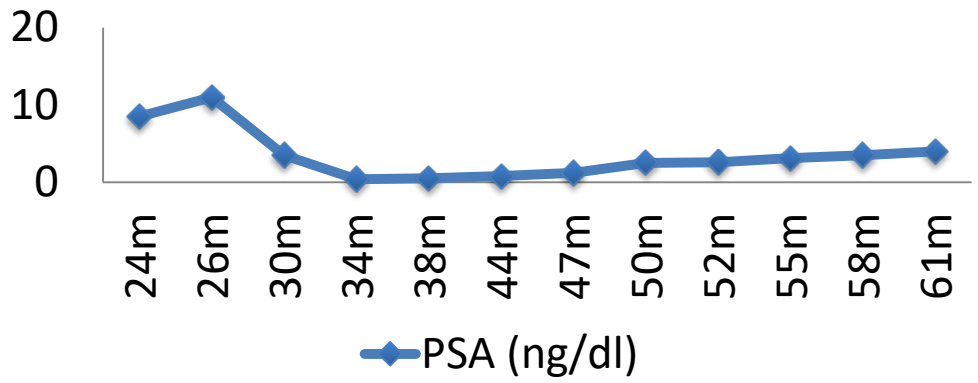
15 m : PSA = 2,6 ng/mL

18 m: PSA = 3,1 ng/mL

21 m : PSA = 3,5 ng/mL

24 m: PSA = 4,0 ng/mL

PSADT = 6,9



Ainda há indicação para o uso de AA de primeira geração no cenário atual?

Papel da Bicalutamida em CPRC ?

STRIVE trial

- M0 or M1 CRPC
- Asym/Minimally Sym.
- PSADT <10 mos
- 396 men total (1:1 RCT)
  - M0= 139
  - M1= 257
- Primary outcome: progression-free survival (defined as PSA progression, clinical event or death

TERRAIN trial

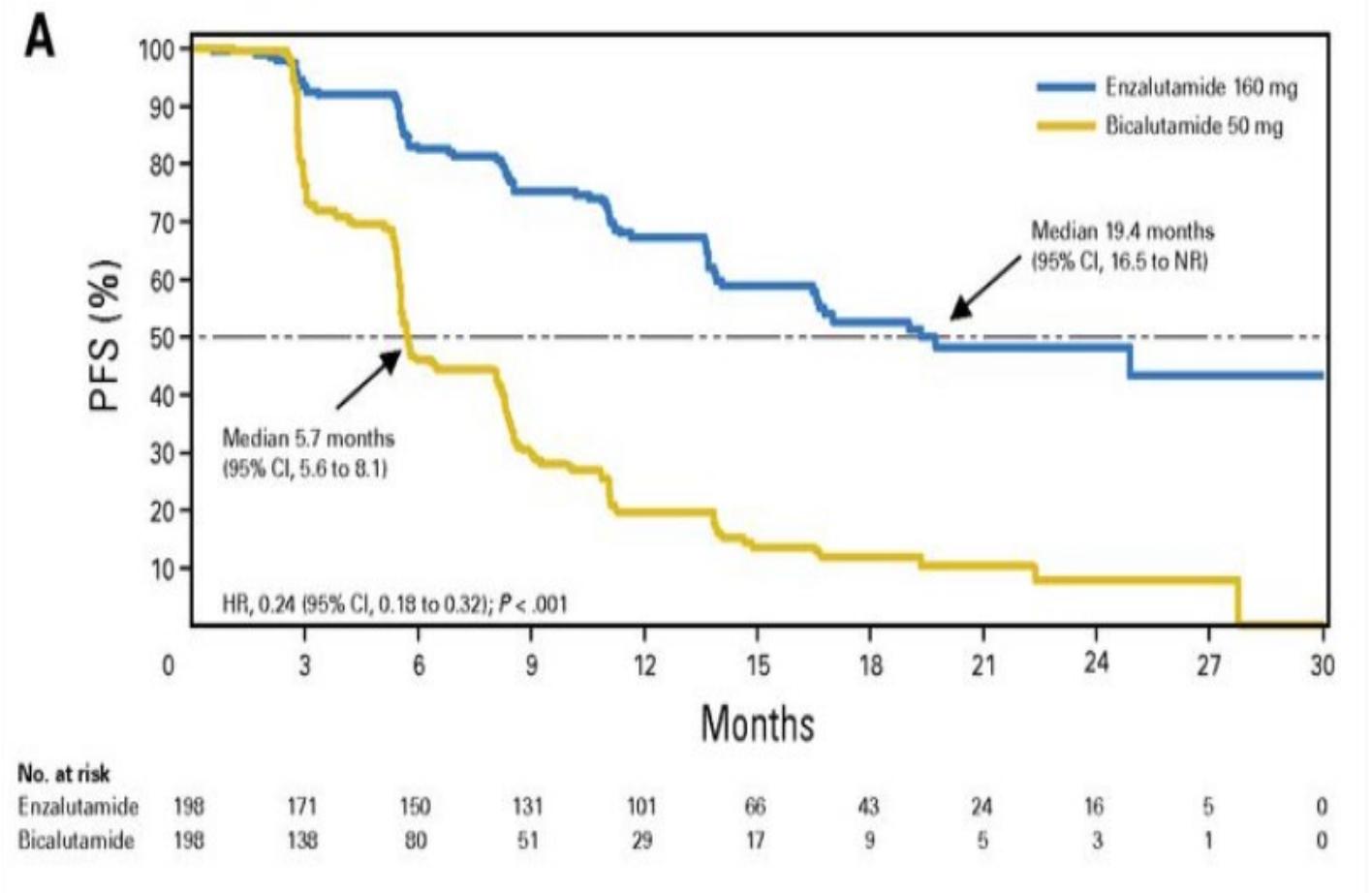
- M1 CRPC
- Asym/Minimally Sym.
  PSA <50 ng/ml
- 375 men total (1:1 RCT)
  - Median f/u time
  - 20mos in Enza group
  - 16.7 in bicalutamide group
- Primary outcome: progression-free survival (defined as clinical event or death)

Penson et al. J Clin Oncol, 2016
Shore et al. Lancet Oncol. 2016

Enzalutamide Versus Bicalutamide in Castration-Resistant Prostate Cancer: The STRIVE Trial

David F. Penson, Andrew J. Armstrong, Raoul Concepcion, Neeraj Agarwal, Carl Olsson, Lawrence Karsh, Curtis Dunshee, Fong Wang, Kenneth Wu, Andrew Krivoshik, De Phung, and Celestia S. Higano

J Clin Oncol 34:2098-2106.



nmCRPC

- Rising PSA and castrate testosterone levels
- No radiological findings of metastatic disease on CT and BS.

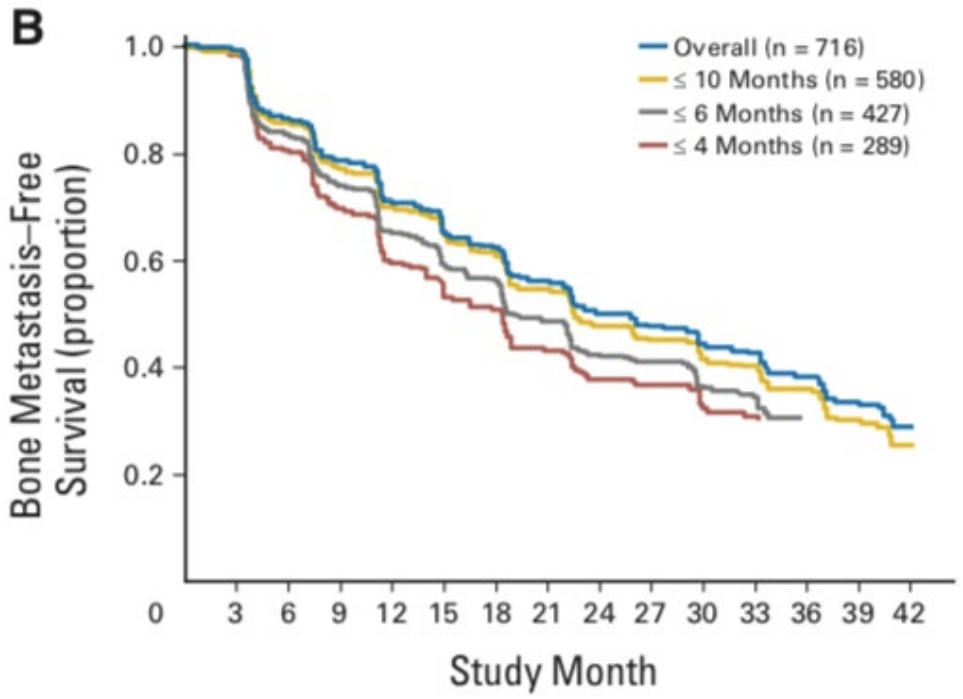
- Patients with nmCRPC are asymptomatic and have variable life expectancy.

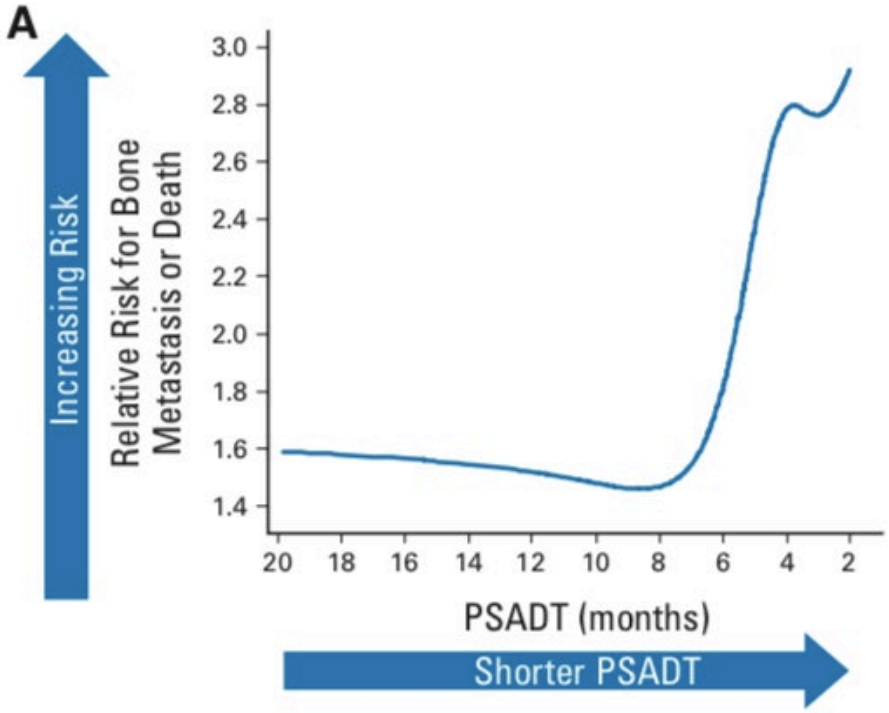
- One in three develop metastasis within 2 years, with baseline PSA and PSA rise kinetics independently predicting the risk of detection of metastasis.

Smith MR et al, J Clin Oncol 2005

Qual a Importância do PSADT na conduta dos pacientes com nmCRPC ?

Denosumab and Bone Metastasis–Free Survival in Men With Nonmetastatic Castration-Resistant Prostate Cancer: Exploratory Analyses by Baseline Prostate-Specific Antigen Doubling Time





J Clin Oncol 31:3800-3806.

www.mskcc.org/nomograms/prostate/psa_doubling_time

www.rtog.org/ClinicalTrials/CalculationofPSADoublingTimePSADT.aspx

www.doubling-time.com/compute-PSA-doubling-time.php

Qual é a sua conduta ?

RB pós PR – G 4+4 – MG neg

RTX resgate incluindo linfonodos

ADT com análogo

PSA em ascensão – PSADT 6,9 m

TC e CO sem alterações

Assintomático

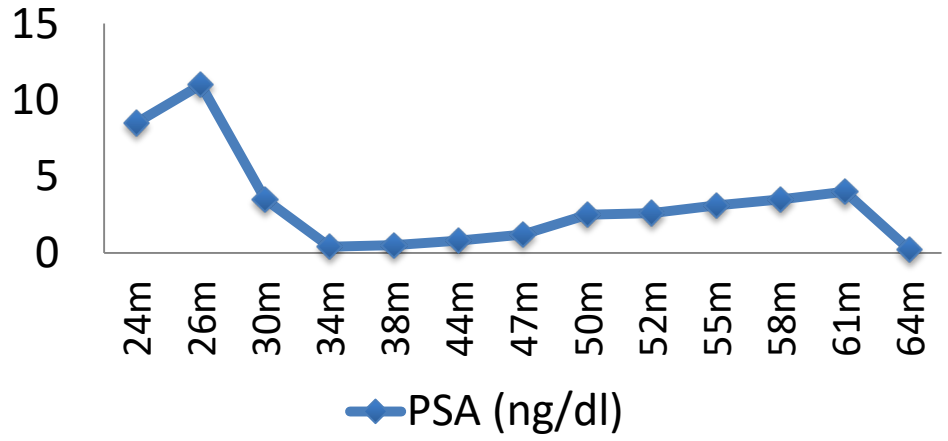
JCL, 62 anos

1) Adicionar Bicalutamida 50 mg/d
2) Suspender análogo e iniciar Bicalutamida 150 mg/d
3) Quimioterapia - Docetaxel
4) Manter Agonista – LHRH e observação
5) Inibidor CYP 17
6) AA de 2ª geração

JLC, 63 anos

Iniciado enzalutamida 160 mg - optado por orquiectomia

- PSA 3m = 0,2
- TEST – 8 ng/dL
- Cintilografia óssea – sem alterações



The NEW ENGLAND JOURNAL of MEDICINE

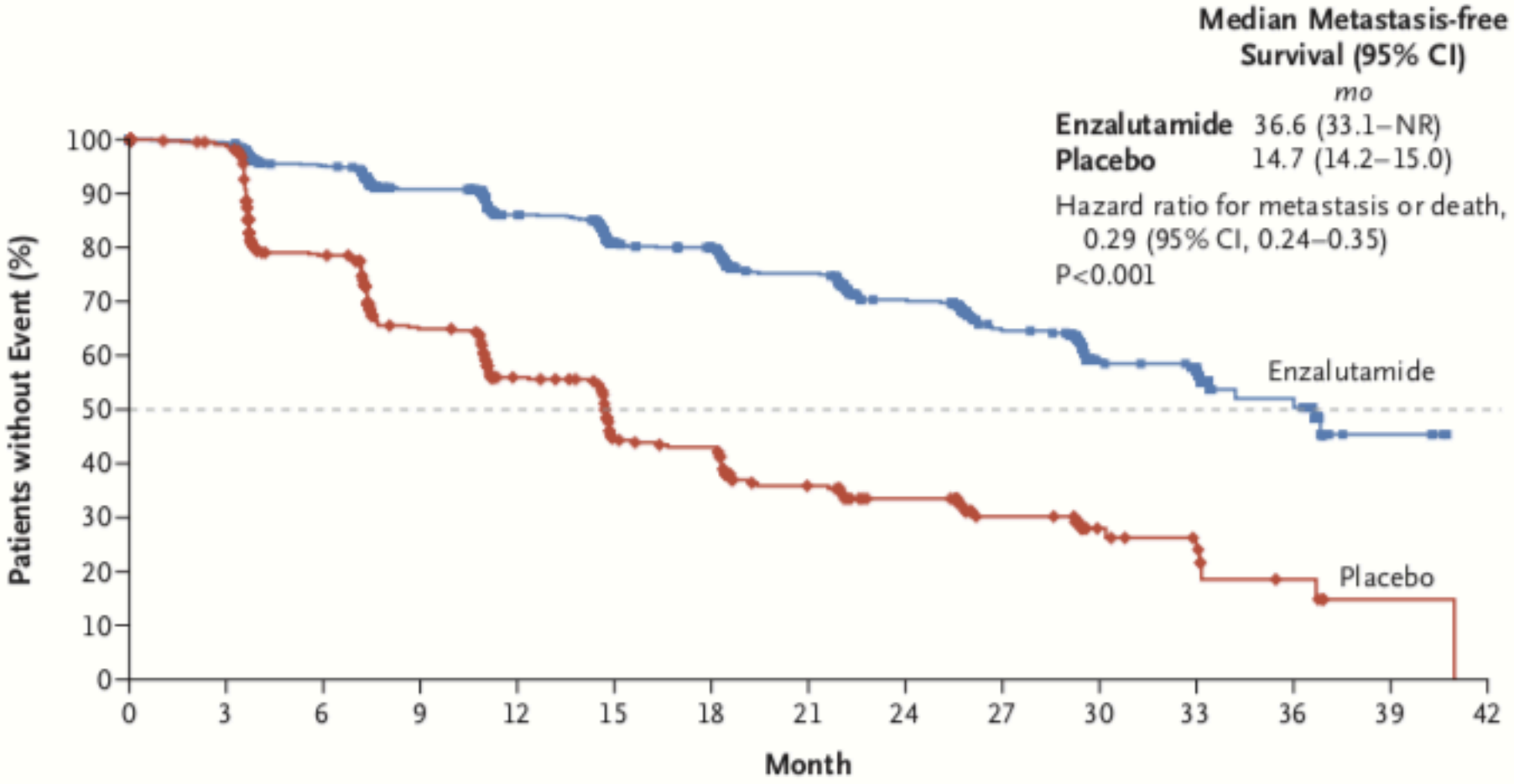
ESTABLISHED IN 1812 JUNE 28, 2018 VOL. 378 NO. 26

Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer

Maha Hussain, M.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Per Rathenborg, M.D., Neal Shore, M.D., Ubirajara Ferreira, M.D., Ph.D., Petro Ivashchenko, M.D., Eren Demirhan, Ph.D., Katharina Modelska, M.D., Ph.D., De Phung, B.S., Andrew Krivoshik, M.D., Ph.D., and Cora N. Sternberg, M.D.

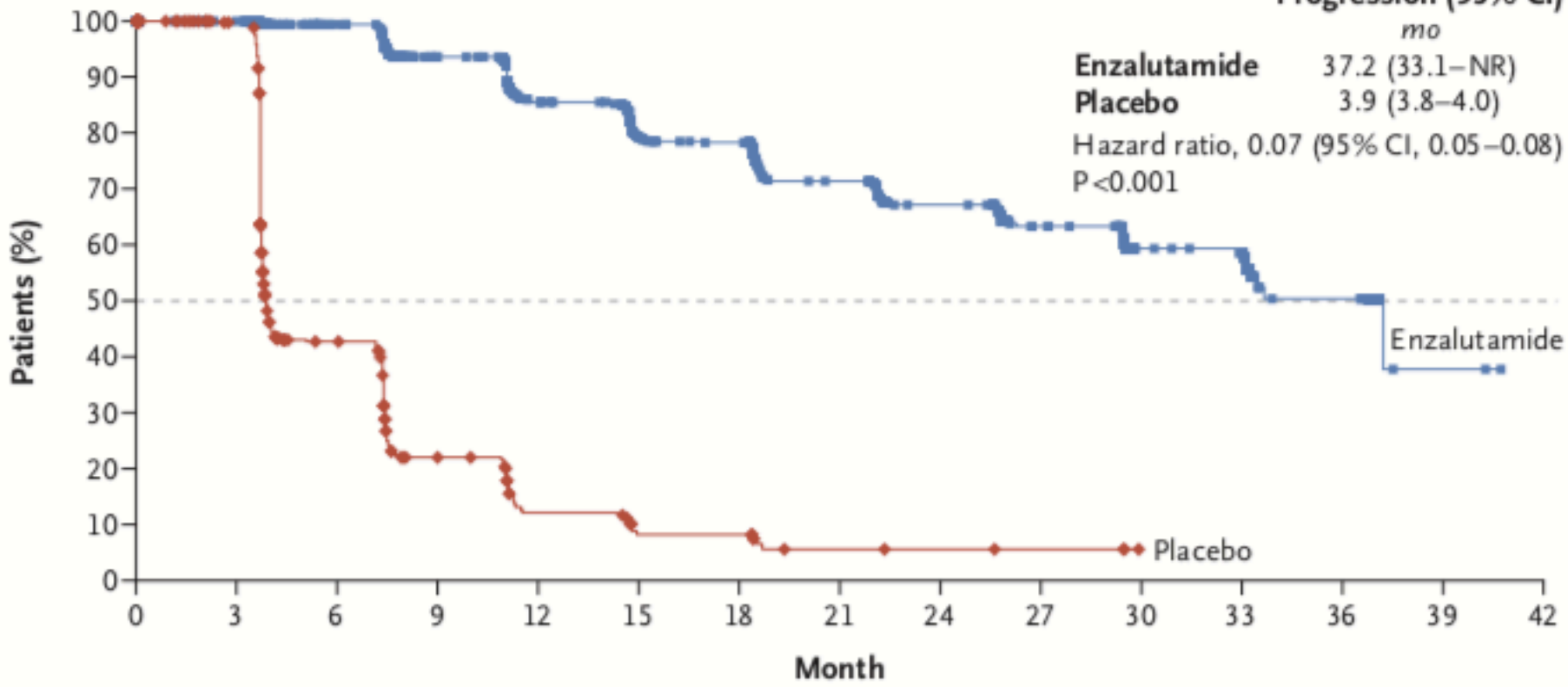
		PROSPER
Population	Experimental arm	Enzalutamide + continued ADT ($n = 933$) Median PSA-DT 3.8 mo
	Control arm	Placebo + continued ADT ($n = 468$) Median PSA-DT 3.6 mo
Efficacy	Primary endpoint—MFS exper. vs placebo	36.6 vs 14.7 mo HR 0.29 (95% CI 0.24–0.35), $p < 0.001$
	Time to PSA progression	37.2 vs 3.9 mo HR 0.07 (95% CI 0.05–0.08), $p < 0.0001$
	Progression-free survival	Not reported
	Interim analysis Overall survival	Median not reached for either group after median follow-up time of 22 mo HR 0.80 (95% CI 0.58–1.09), $p = 0.15$

Mateo J, et al. Eur Urol (2018)



No. at Risk															
Enzalutamide	933	865	759	637	528	431	418	328	237	159	87	77	31	4	0
Placebo	468	420	296	212	157	105	98	64	49	31	16	11	5	1	0

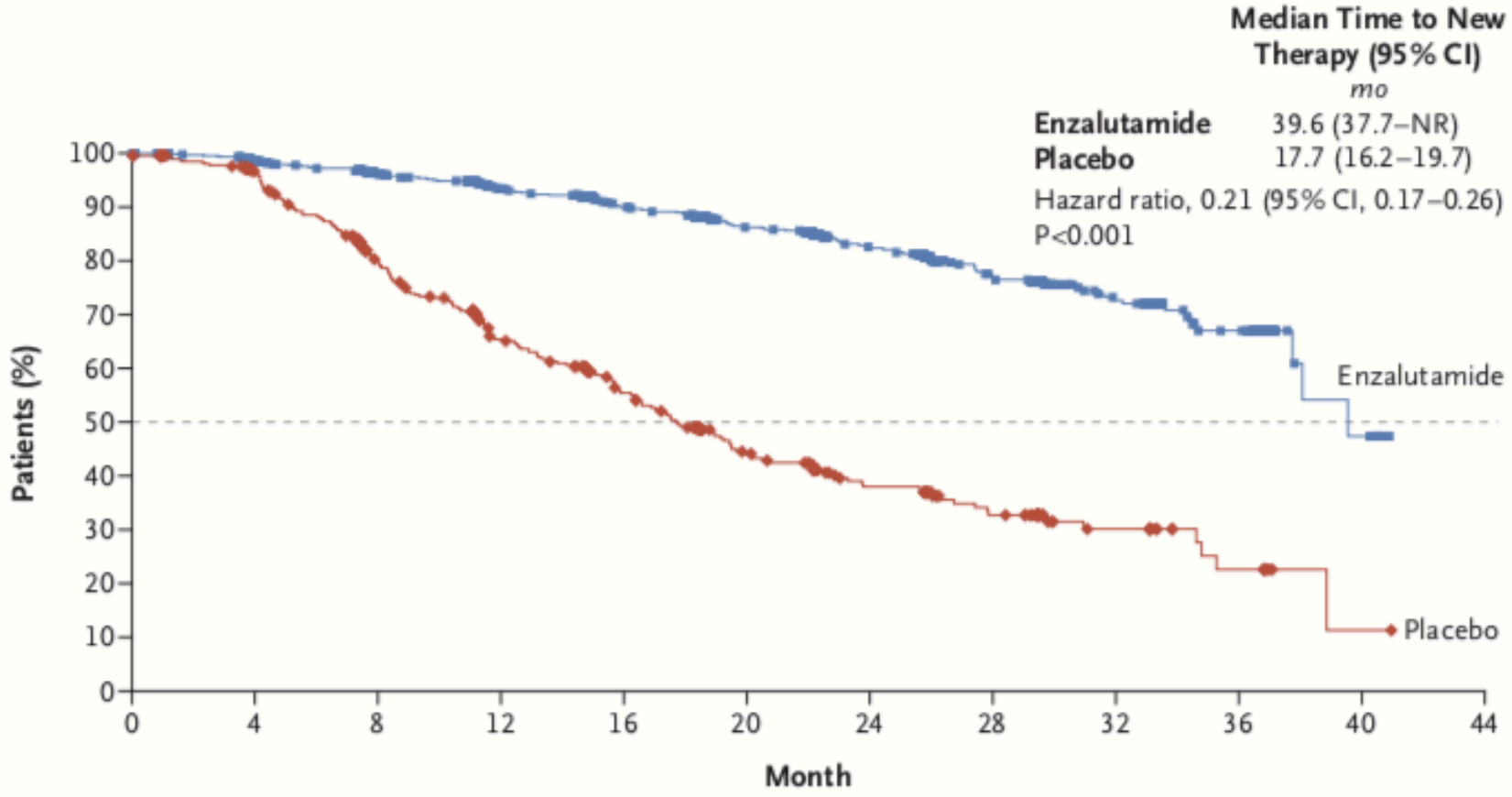
Hussain, et al. NEJM (2018)



No. at Risk															
Enzalutamide	933	879	771	635	500	401	386	288	203	137	76	71	24	2	0
Placebo	468	427	138	56	25	13	13	5	4	3	0	0	0	0	0

Hussain, et al. NEJM (2018)

B First Use of Subsequent Antineoplastic Therapy



No. at Risk

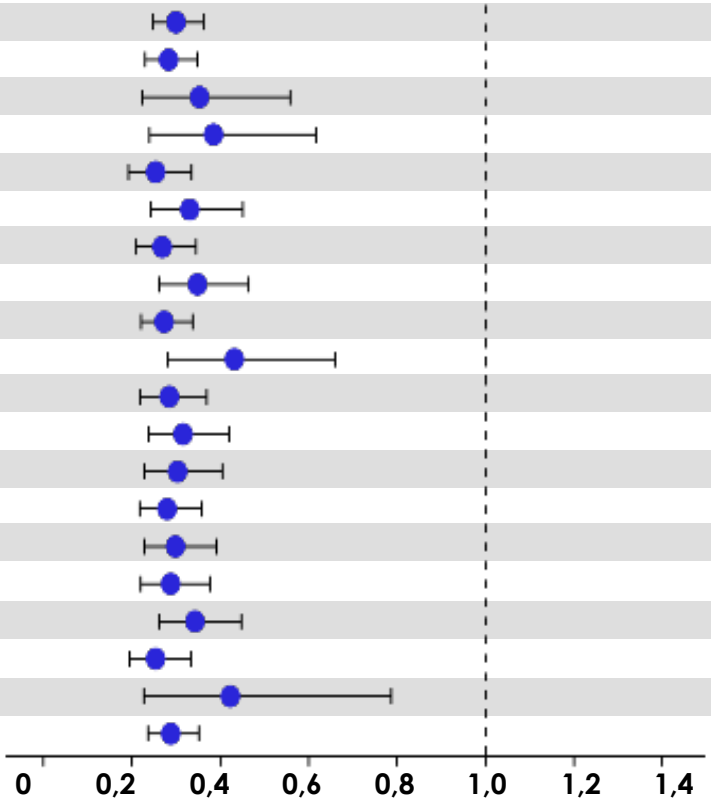
Enzalutamide	933	829	729	625	526	418	313	213	121	49	7	0
Placebo	468	406	299	221	186	107	72	46	21	9	1	0

Hussain, et al. NEJM (2018)

Desfecho primário:

SLM – Sobrevida Livre de Metástase – Análise de subgrupos

Subgrupo	HR (IC de 95%)
Todos os pacientes	0,30 (0,25-0,36)
Tempo de duplicação de PSA < 6 meses	0,28 (0,23-0.35)
Tempo de duplicação de PSA ≥ 6 meses	0,35 (0,22-0,56)
Região geográfica – América do Norte	0,38 (0,24-0,62)
Região geográfica – União Europeia	0,25 (0,19-0,34)
Região geográfica – resto do mundo	0,33 (0,24-0,45)
Idade na visita basal ≤ mediana (74 anos)	0,27 (0,21-0,35)
Idade na visita basal > mediana (74 anos)	0,35 (0,26-0,46)
ECOG PS na visita basal = 0	0,27 (0,22-0,34)
ECOG PS na visita basal = 1	0,43 (0,28-0,66)
Escore total de Gleason no diagnóstico ≤ 7	0,28 (0,22-0,37)
Escore total de Gleason no diagnóstico ≥ 8	0,32 (0,24-0,42)
Valor basal de PSA (ng/mL) ≤ mediana (10,73)	0,30 (0,23-0,40)
Valor basal de PSA (ng/mL) > mediana (10,73)	0,28 (0,22-0,36)
Valor basal de LDH (U/L) ≤ mediana (178)	0,30 (0,23-0,39)
Valor basal de LDH (U/L) > mediana (178)	0,29 (0,22-0,38)
Valor basal de hemoglobina (g/L) ≤ mediana (134)	0,34 (0,26-0,45)
Valor basal de hemoglobina (g/L) > mediana (134)	0,25 (0,19-0,33)
Uso basal de agente direcionado ao osso – sim	0,42 (0,23-0,79)
Uso basal de agente direcionado ao osso – não	0,29 (0,24-0,35)



Favorece enzalutamida + ADT

Favorece placebo+ ADT

Hussain, et al. NEJM (2018)

		PROSPER
Population	Experimental arm	Enzalutamide + continued ADT ($n = 933$) Median PSA-DT 3.8 mo
	Control arm	Placebo + continued ADT ($n = 468$) Median PSA-DT 3.6 mo
Efficacy	Primary endpoint—MFS exper. vs placebo	36.6 vs 14.7 mo HR 0.29 (95% CI 0.24–0.35), $p < 0.001$
	Time to PSA progression	37.2 vs 3.9 mo HR 0.07 (95% CI 0.05–0.08), $p < 0.0001$
	Progression-free survival	Not reported
	Interim analysis Overall survival	Median not reached for either group after median follow-up time of 22 mo HR 0.80 (95% CI 0.58–1.09), $p = 0.15$

Mateo J, et al. Eur Urol (2018)

Adverse Events*

Event, No. (%)	Enzalutamide + ADT (n = 930)	Placebo + ADT (n = 465)
Any adverse event	808 (87%)	360 (77%)
Any grade ≥ 3 adverse event	292 (31%)	109 (23%)
Grade ≥ 3 adverse events occurring in ≥ 1% of patients in the enzalutamide group		
Hypertension	43 (5%)	10 (2%)
Fatigue	27 (3%)	3 (1%)
Hematuria	16 (2%)	13 (3%)
Fall	12 (1%)	3 (1%)
Asthenia	11 (1%)	1 (< 1%)
Pneumonia	10 (1%)	2 (< 1%)
Syncope	10 (1%)	2 (< 1%)
Anemia	9 (1%)	6 (1%)
Urinary tract infection	7 (1%)	3 (1%)
Cataract	7 (1%)	2 (< 1%)
Cardiac failure	7 (1%)	1 (< 1%)
Acute myocardial infarction	6 (1%)	2 (< 1%)
Adenocarcinoma of the colon	5 (1%)	2 (< 1%)
Hyperglycemia	5 (1%)	1 (< 1%)
Hyponatremia	5 (1%)	1 (< 1%)
Coronary artery disease	5 (1%)	0

Adverse events as the primary reason for treatment discontinuation:

- Enzalutamide, n = 87 (9%)
- Placebo, n = 28 (6%)

Deaths due to adverse event on trial irrespective of attribution:

- Enzalutamide, n = 32 (3%)
- Placebo, n = 3 (1%)

*Adverse events were collected up to 30 days after the last dose of study drug.

Adverse Events of Special Interest*

Any Grade Event, No. (%)	Enzalutamide + ADT (n = 930)	Placebo + ADT (n = 465)
Hypertension†	114 (12%)	25 (5%)
Major adverse cardiovascular event‡	48 (5%)	13 (3%)
Mental impairment disorders§	48 (5%)	9 (2%)
Hepatic impairment	11 (1%)	9 (2%)
Neutropenia	9 (1%)	1 (< 1%)
Convulsion	3 (< 1%)	0
Posterior reversible encephalopathy syndrome	0	0

In both arms the incidence of major adverse cardiovascular events was higher in patients with:

- Baseline history of cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia, or age ≥75 years

*Adverse events were collected up to 30 days after the last dose of study drug.
†Includes increased blood pressure.
‡Includes acute myocardial infarction, hemorrhagic cerebrovascular conditions, ischemic cerebrovascular conditions, and heart failure.
§Includes memory impairment, disturbance in attention, cognitive disorders, amnesia, dementia Alzheimer's type, senile dementia, mental impairment, and vascular dementia.

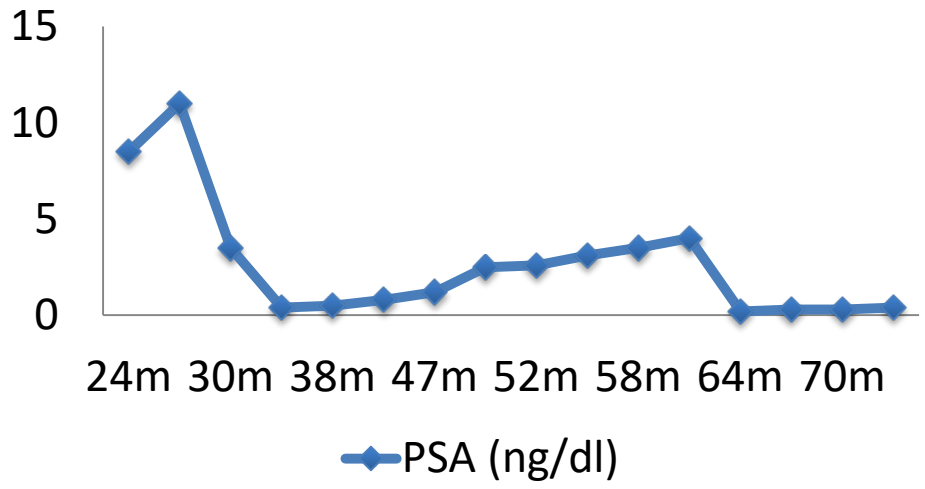
JLC, 63-64 anos

03 m : PSA = 0,2 ng/mL

06 m: PSA = 0,3 ng/mL

09 m : PSA = 0,3 ng/mL

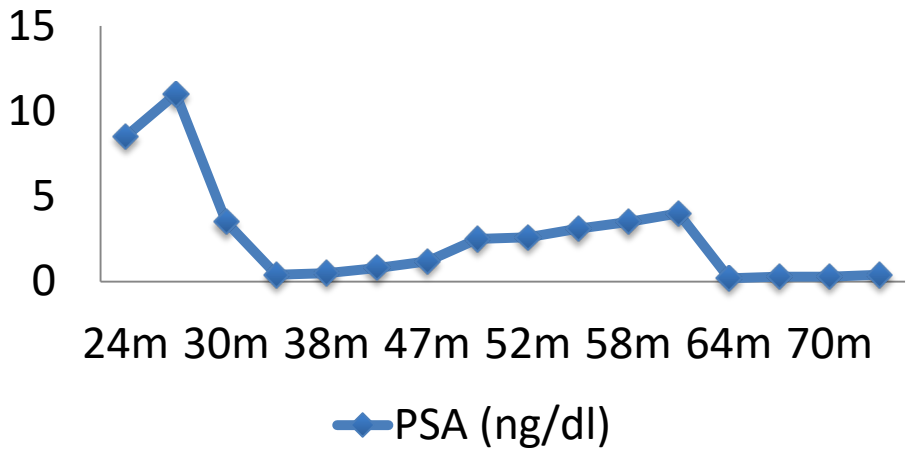
12 m: PSA = 0,4 ng/mL



JLC, 63-64 anos

12 m: PSA = 0,4 ng/mL

Clinicamente bem, fadiga leve, hipertensão controlada



Como definir falha do tratamento e qual o seguinte passo?

Obrigado!