Novinky v léčbě karcinomu prostaty

T. Svoboda, ORAK FN Plzeň

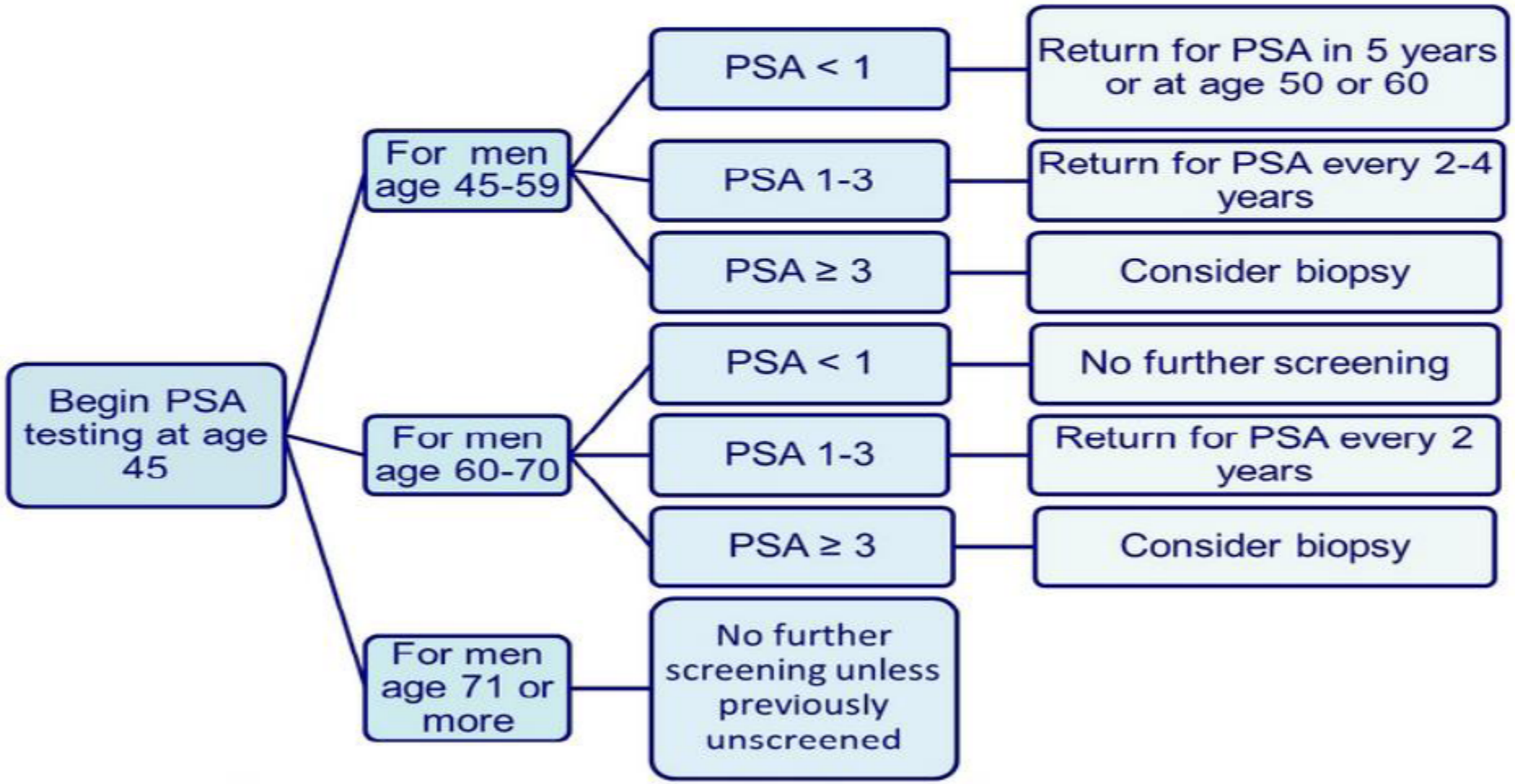
Souhrn

- 1. otázka screeningu
- 2. diagnostika
- 3. systémová léčba - výběr
- 4. Xofigo (dominantně meta ve skeletu)
- 5. radioterapie
- 6. ostatní a pohled do budoucnosti

- Sporné: imunoterapie (Sipuleucel-T), vakcinace

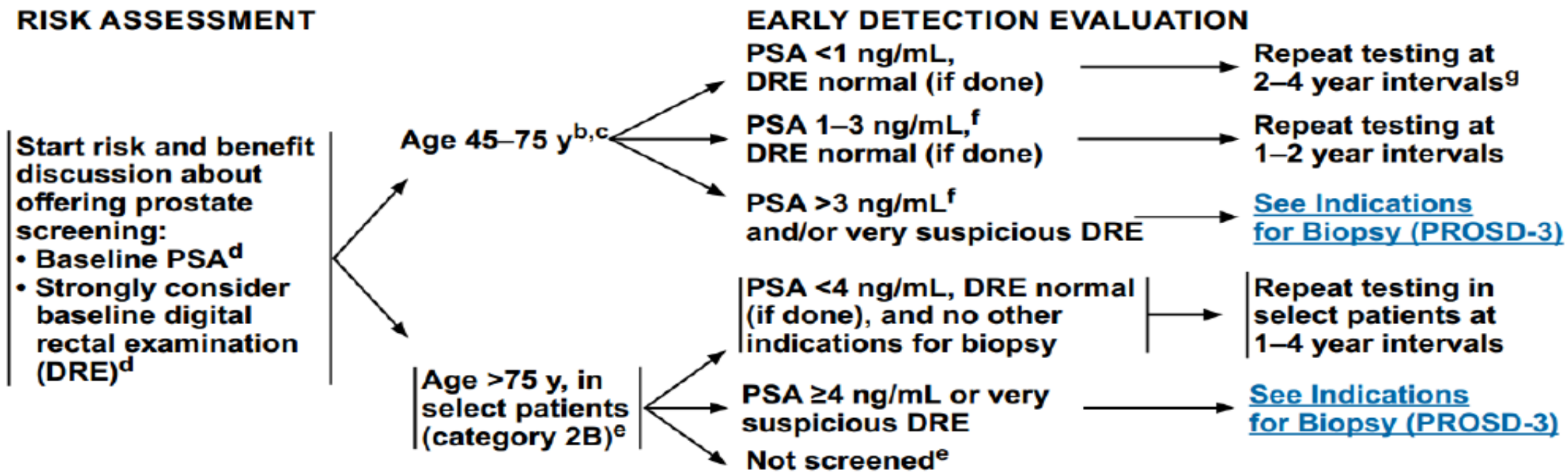
Doporučená praxe

- **MSKCC**



Doporučená praxe

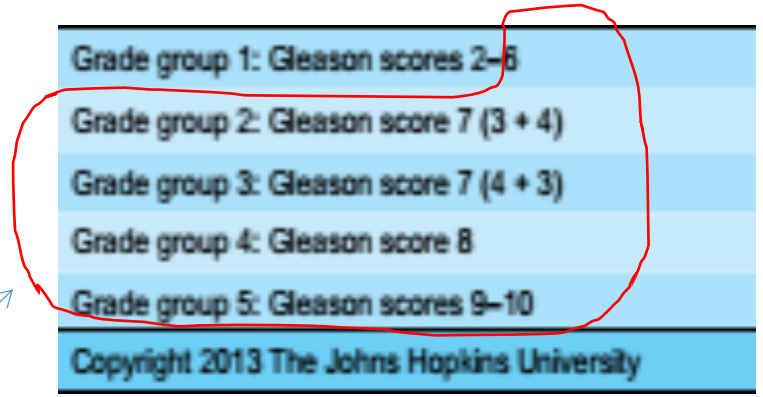
- **NCCN**



[g] Men ≥60 years with PSA <1.0 ng/mL and men >75 years of age with a PSA <3.0 ng/mL have a very low risk of prostate cancer metastases or death and may be counseled to consider stopping PSA testing. This low risk is especially true for those in the latter category.

„Nový“ gradingový systém, tzv. grade group system
Není součástí WHO, udává se/udávat lze

- Lepší stratifikace pacientů
- Jednodušší systém s 5 skupinami
- Nejnižší grade group je 1



Punkce

Diagnostika – aktuální doporučení

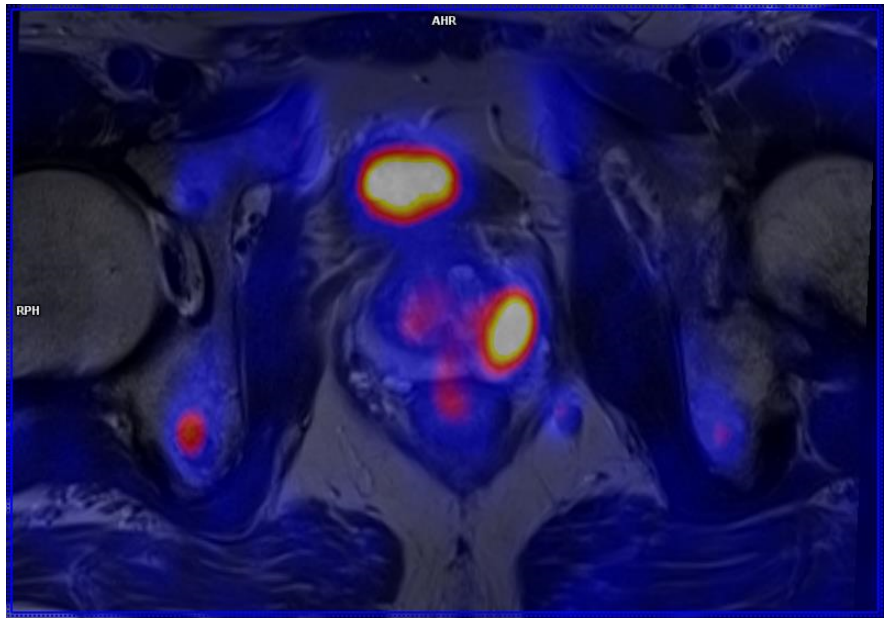
- **• pac. s nově dg. high risk Ca prostaty**
- •mpMR pánve
- •scinti skeletu
- •18F-cholin PET/CT (ostatní vyš. negativní nebo nejednoznačné)
- •(ev. NaF PET/CT pro nejasná kostní ložiska)

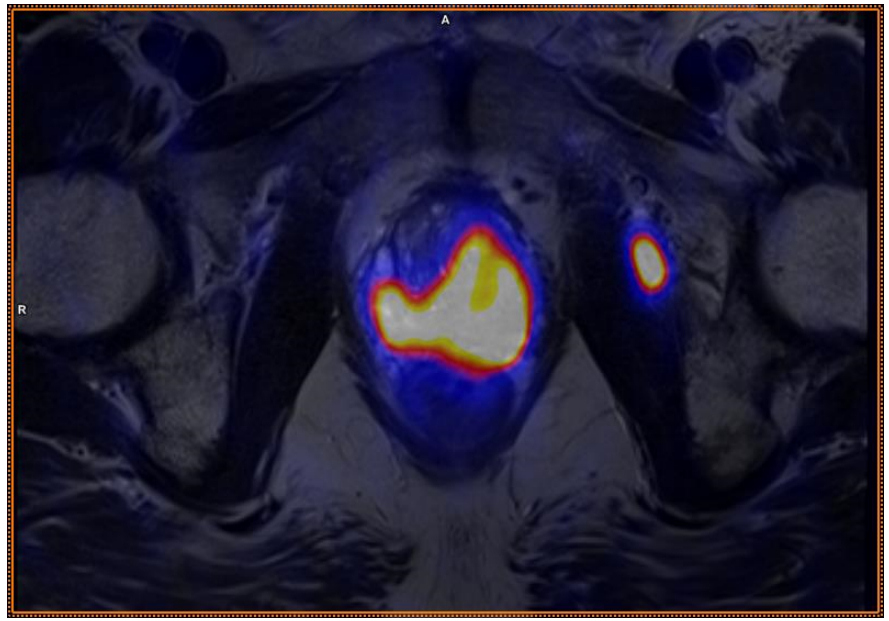
- **• pac. s biochem. relapsem**
- •scinti skeletu (ev. NaF PET/CT)
- •Axumin PET/CT – nižší PSA, susp. lokální relaps
- •18F-cholin PET/CT
- •(68Ga-PSMA PET/CT n. PET/MR)

PET radiofarmaka pro zobrazení CAP

- **Látky označené radioaktivním prvkem s β^+ rozpadem**
  - **^{18}F-fluorocholin**
  - **^{18}F-flucyclovin**
  - **^{18}F-natriumfluorid**
  - *^{18}F-fluorodeoxyglukóza*
  - **^{68}Ga-PSMA ligandy**

fluorocholin

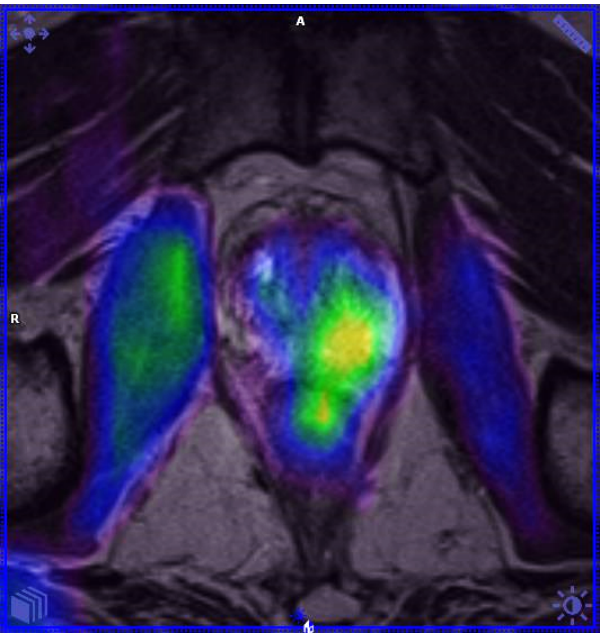


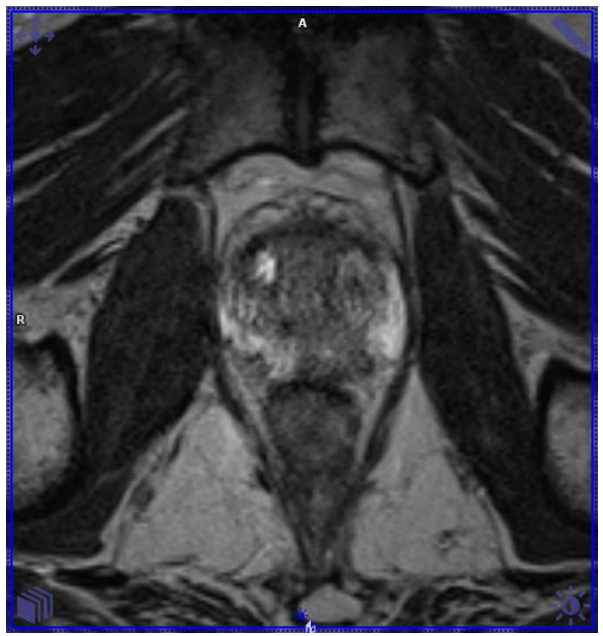


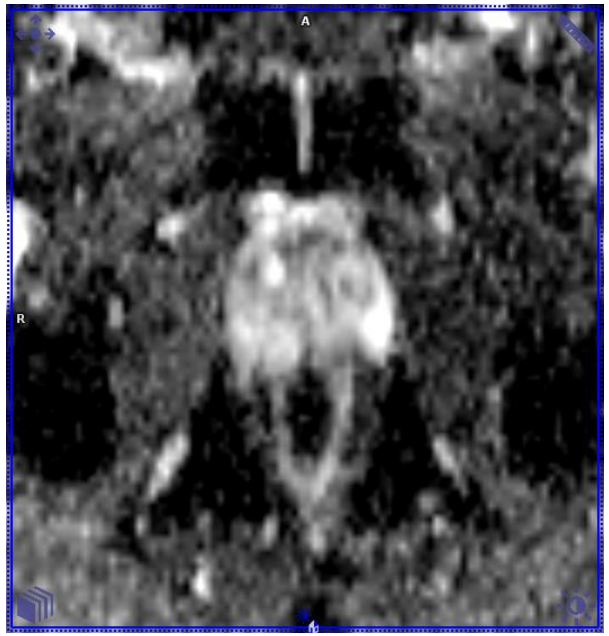
PSMA ligand

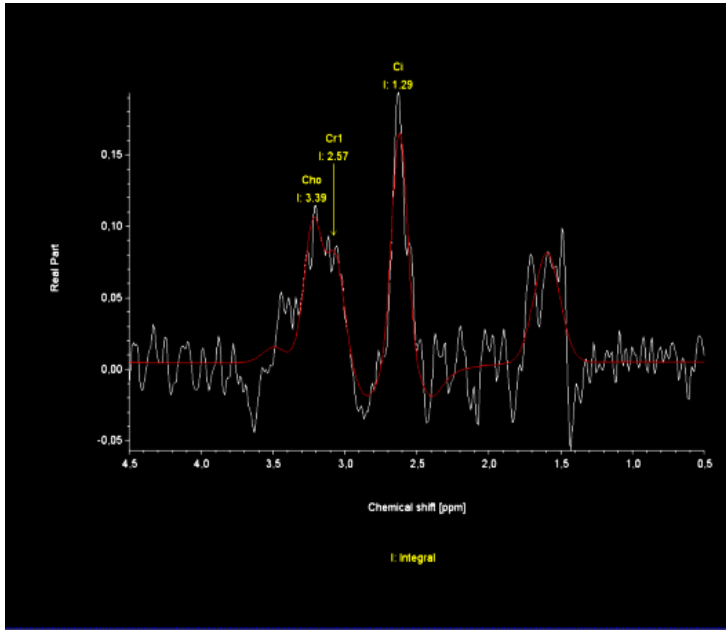
^{18}F-FCH-PET/MR

- Výstavba buněčných membrán
- Nespecifický marker
- Významný vliv distribuce s ohledem na perfuzi





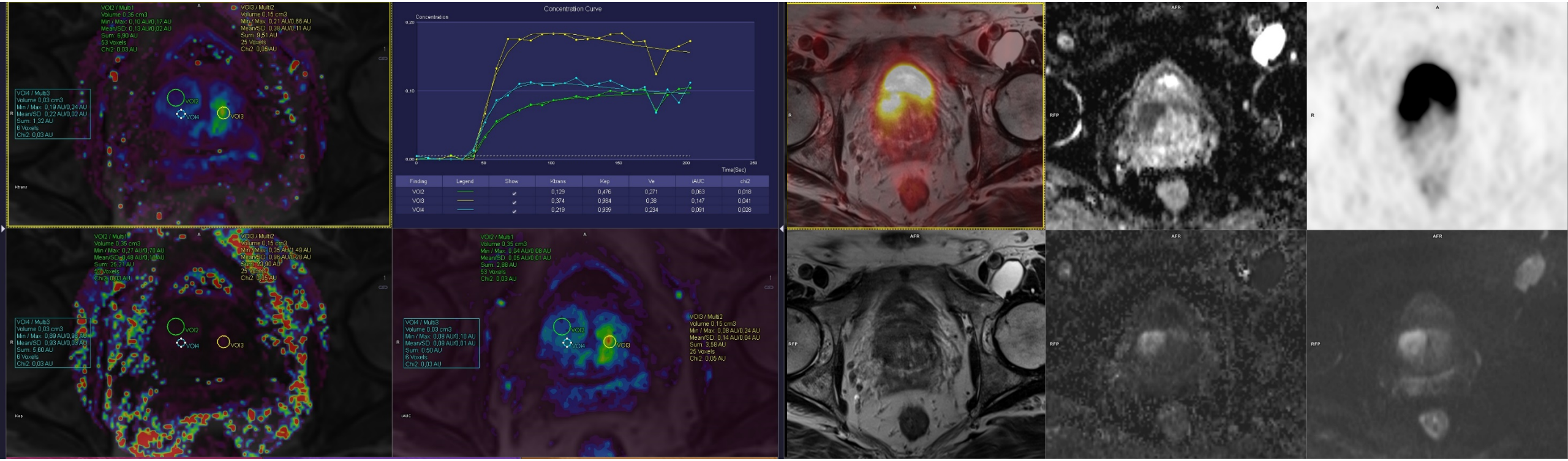




Karcinom prostaty – PET/MRI s fluorocholinem

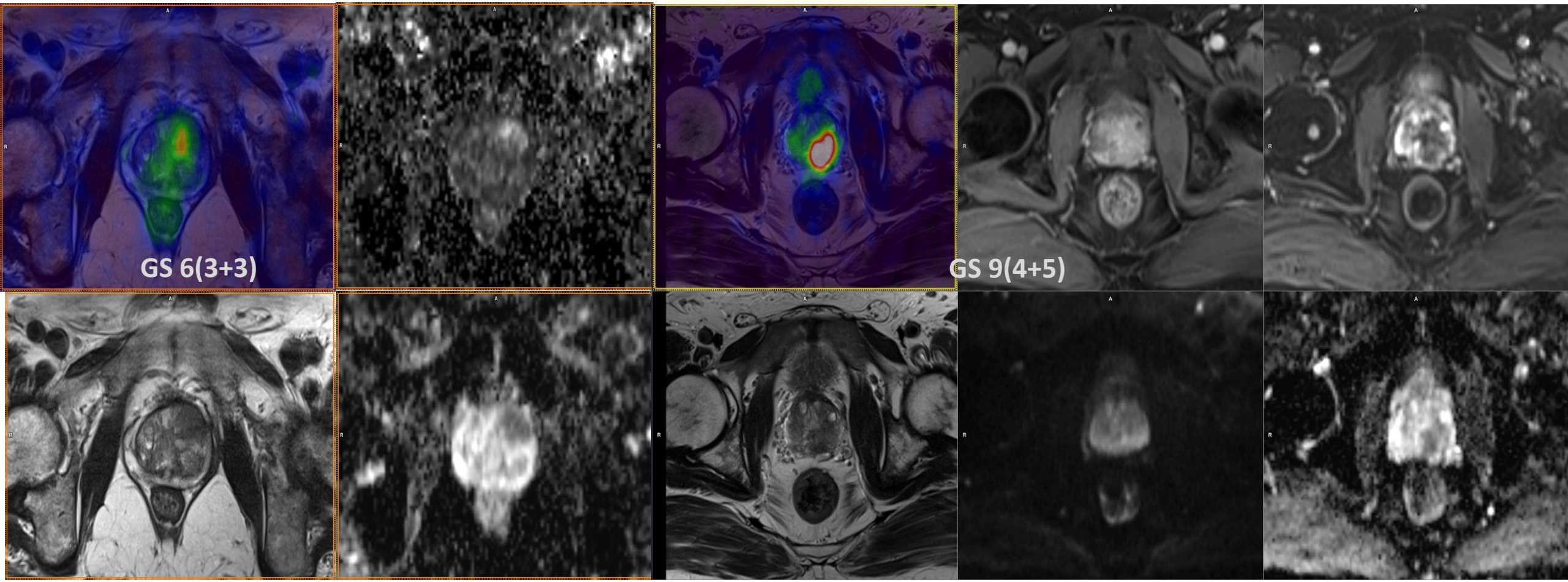
^{68}Ga-PSMA-11 a multiparametrická MR

- **Akumulace ^{68}Ga-PSMA rozsah a agresivita tumoru?**
  - *Shoda s mírou restrikce difuze - buněčnatost*
- **TSE T2 obrazy – morfologie a lokální staging – kapsula, nervověcévní svazek**



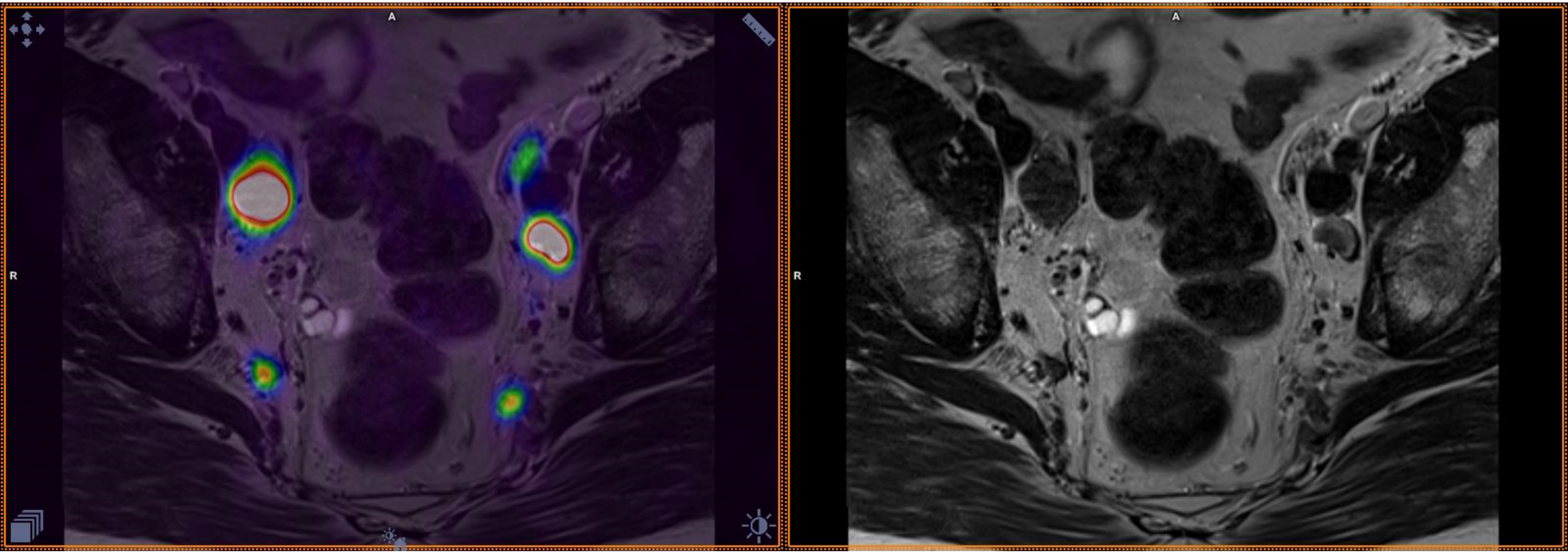
^{68}Ga-PSMA-11 a Gleason skóre

- Dosud není objasněn



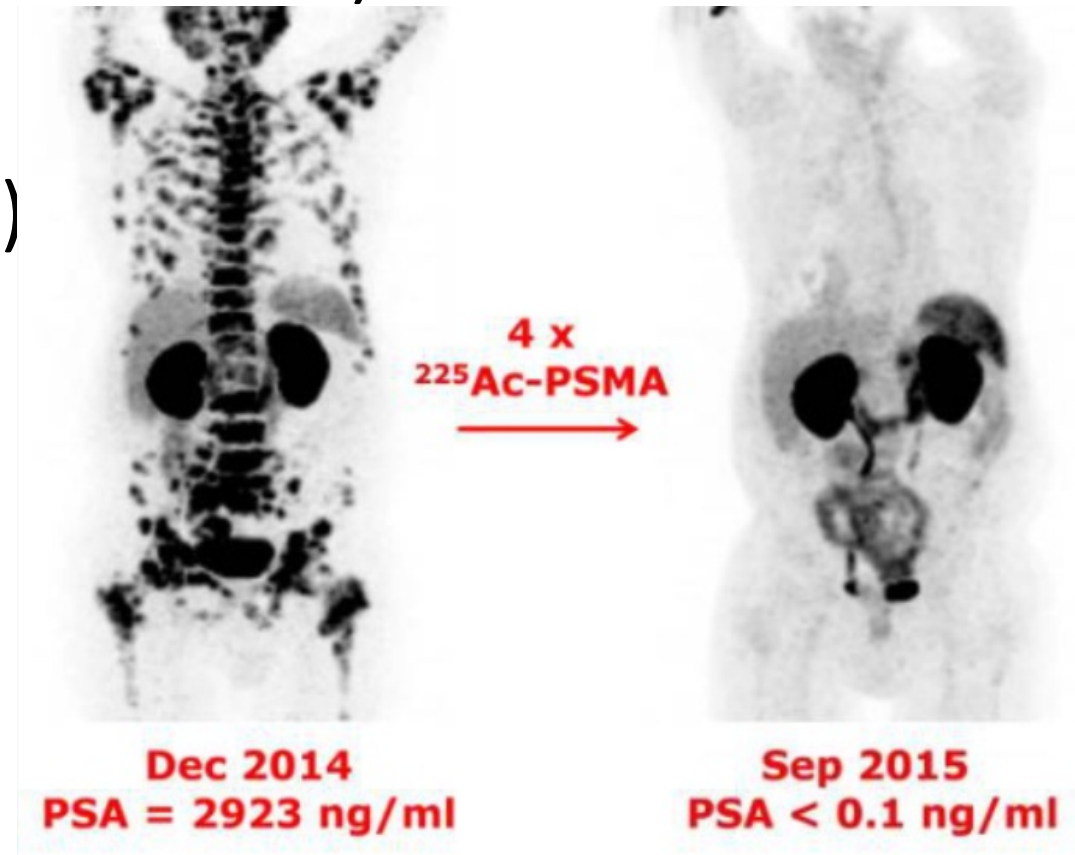
Uzlinové postižení a ^{68}Ga-PSMA-11

- **Nižší podíl falešně pozitivních nálezů ve srovnání s FCH**

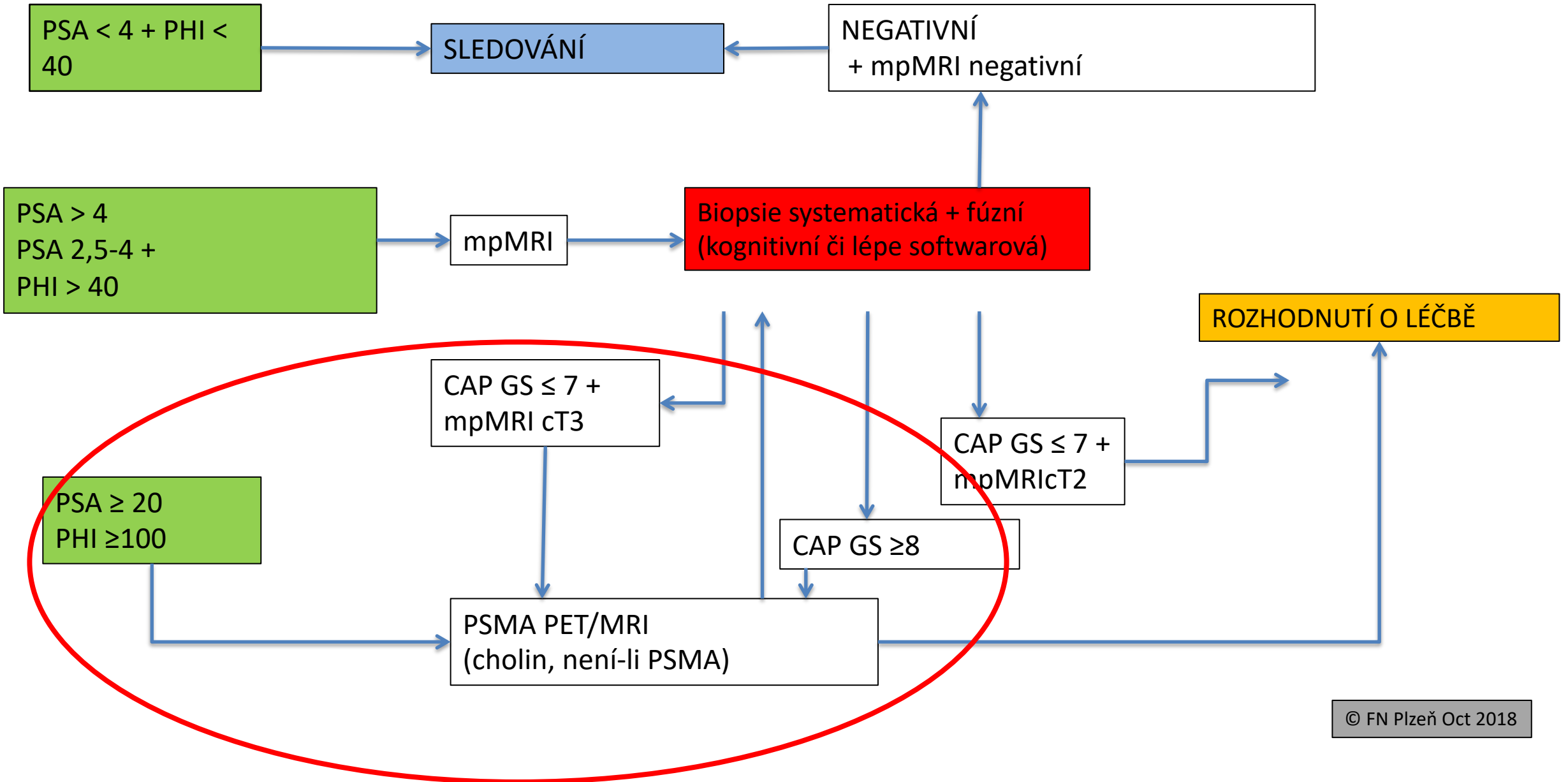


Terapeutické využití PSMA

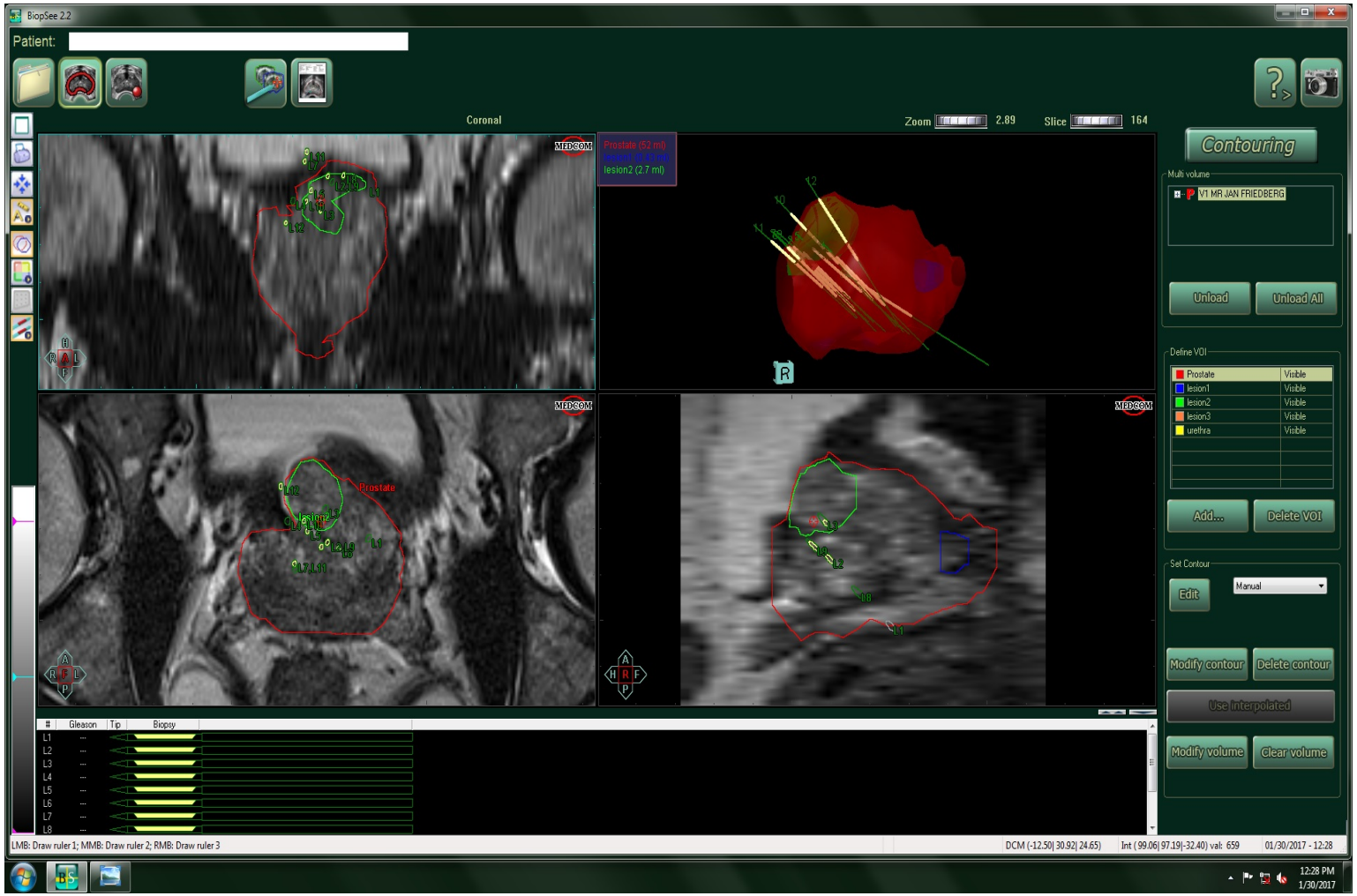
- Několik izotopů, nejdále PSMA-617 s beta zářením lutecia^{177} nebo Y^{90}, event. alfa zářením Bi^{213} nebo Ac^{225})
- Léčba na principu BRT
- Cca 500.000Kč (název Prostathera?)

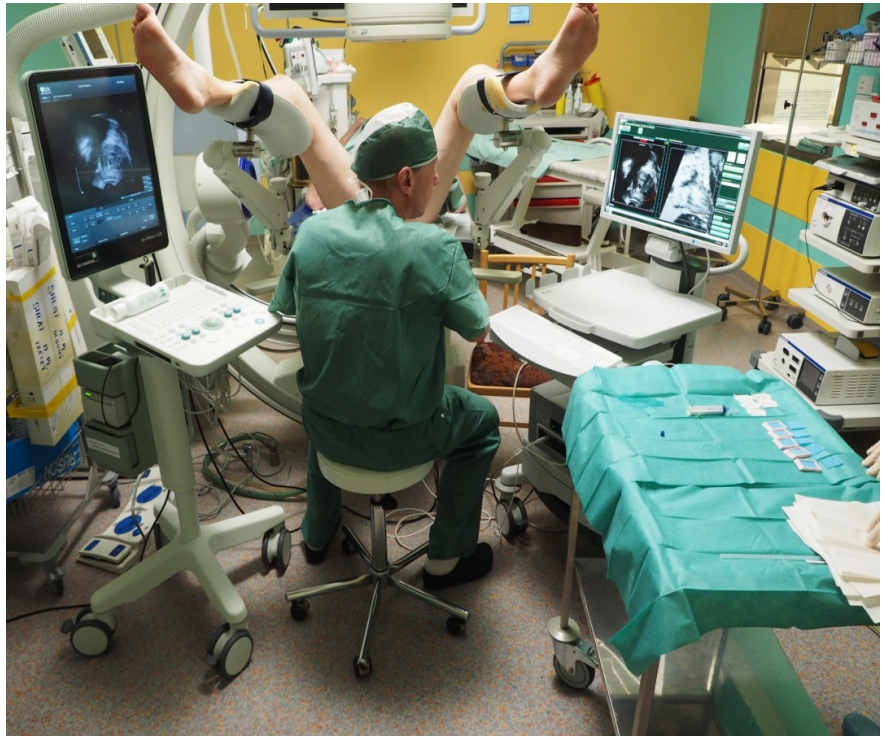


Benešová M., BOD 2019



MR/TRUS fúzní biopsie





Konturace

Registrace

Odběr prům. 10 vzorků

Léčba lokalizovaného CaP: WW vs AS

	Active survillance	Watchful waiting
záměr léčby	kurativní	paliativní
sledování	režim	podle pacienta
postup a hodnocení	PSA, DRE, reBx mpMRI (volitelné)	není definováno (PSA)
life-expectancy	> 10 (≤ 20) let	< 10 let
cíl	↓ NÚ léčby bez dopadu na přežití	↓ NÚ léčby
vhodný pacient	LR CaP	kdokoliv

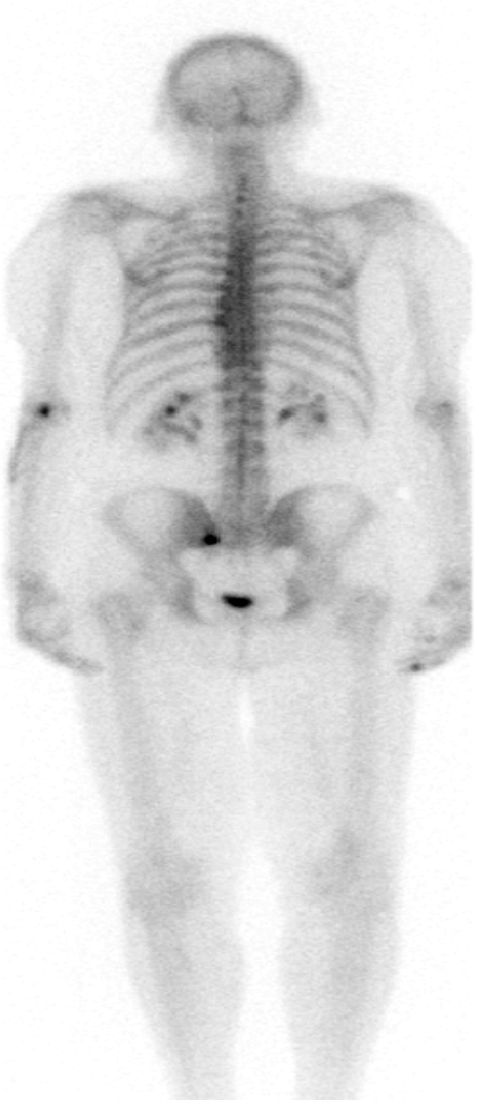
Léčba - kdo je vhodný pro AS?

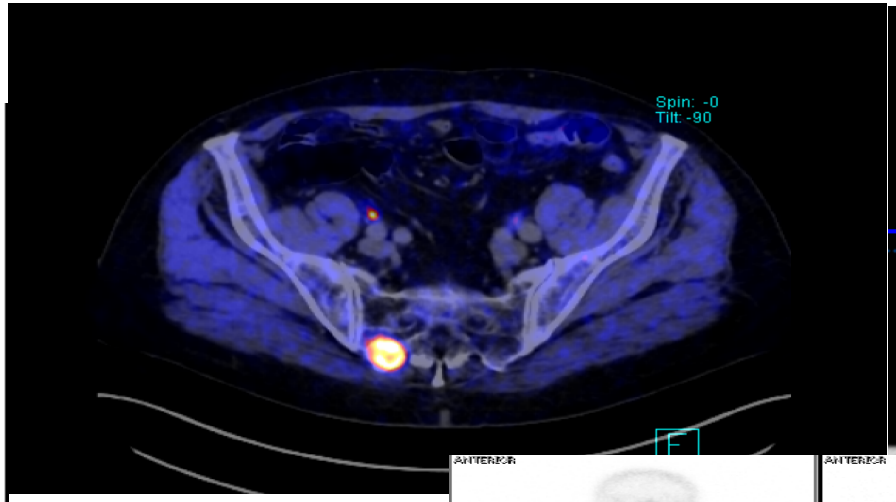
- pacienti s nízkým a velmi nízkým rizikem progrese
  - T1c
  - GS ≤ 6 GG 1
  - PSA < 10
  - ≤ 2 vzorky v bx + ≤ 50 % válečku
  - PSA denzita < 0.15 ug/l
- T1 – T2a
- GS ≤ 6 GG 1
- PSA < 10

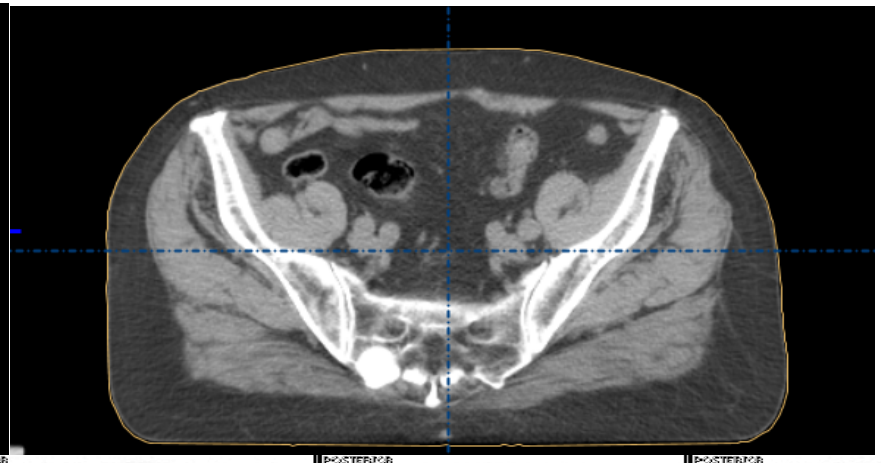
- **obvyklé schéma AS:**
- **PSA, DRE**
- **re-biopsie**
- PSA á 3 měsíce(NCCN á 6m)
- DRE á 6 měsíců (NCCN á 12m)
  - **1. rebiopsie za 1 rok**,
  - další á 1-3 roky

- **10-let CSS 96-100 %**

Oligometastázy vs. dif.meta ve skeletu – význam lok.léčby



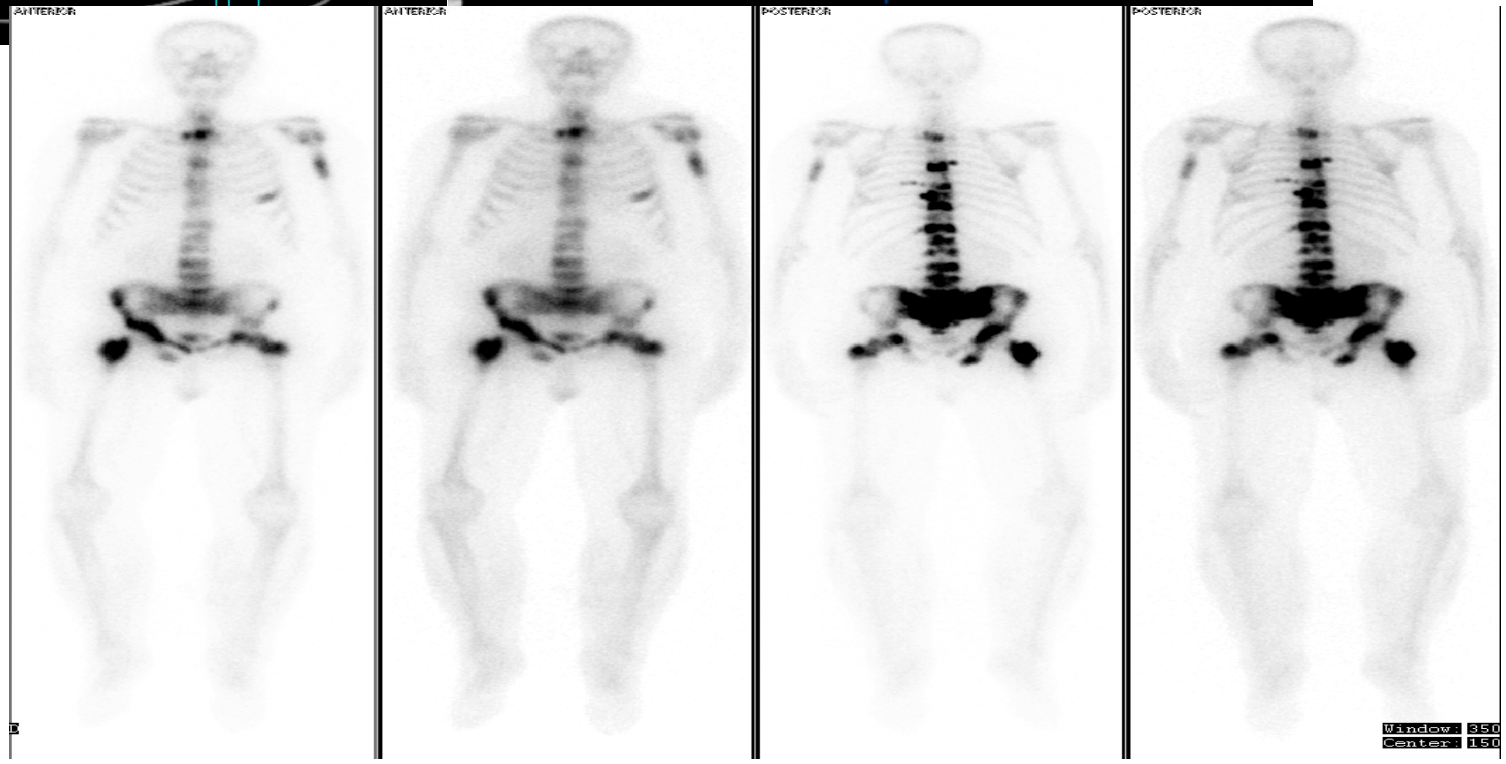




Pouze lok. léčba

vs.

Xofigo (ne v kombinaci)



HYPOFRAKCIONACE

- **RANDOMIZOVANÉ STUDIE**

RTOG 0415	73,8 Gy (1,8 Gy) vs. 70 Gy (2,5 Gy)		
	tumor + 15 %	=	zdravé tkáně ISO > GI/GU ≥ 2
CHHiP	74 Gy (2,0 Gy) vs. 60 Gy (3,0 Gy) vs. 57 Gy (3,0 Gy)		
	tumor ISO	=	zdravé tkáně ISO =
HYPRO	78 Gy (2,0 Gy) vs. 64,6 Gy (3,4 Gy)		
	tumor + 16 %	=	zdravé tkáně ISO > GU ≥ 3
PROFIT	78 Gy (2,0 Gy) vs. 60 Gy (3,0 Gy)		
	tumor ISO	=	zdravé tkáně ISO < GI ≥ 2

PROTONOVÁ RT

AUA-ASTRO-SUO 2018

Clinicians should inform localized prostate cancer patients who are considering proton beam therapy that it offers no clinical advantage over other forms of definitive treatment.

RANDOMIZOVANÁ STUDIE PBT vs. IMRT, MGH, 400 pacientů, QoL

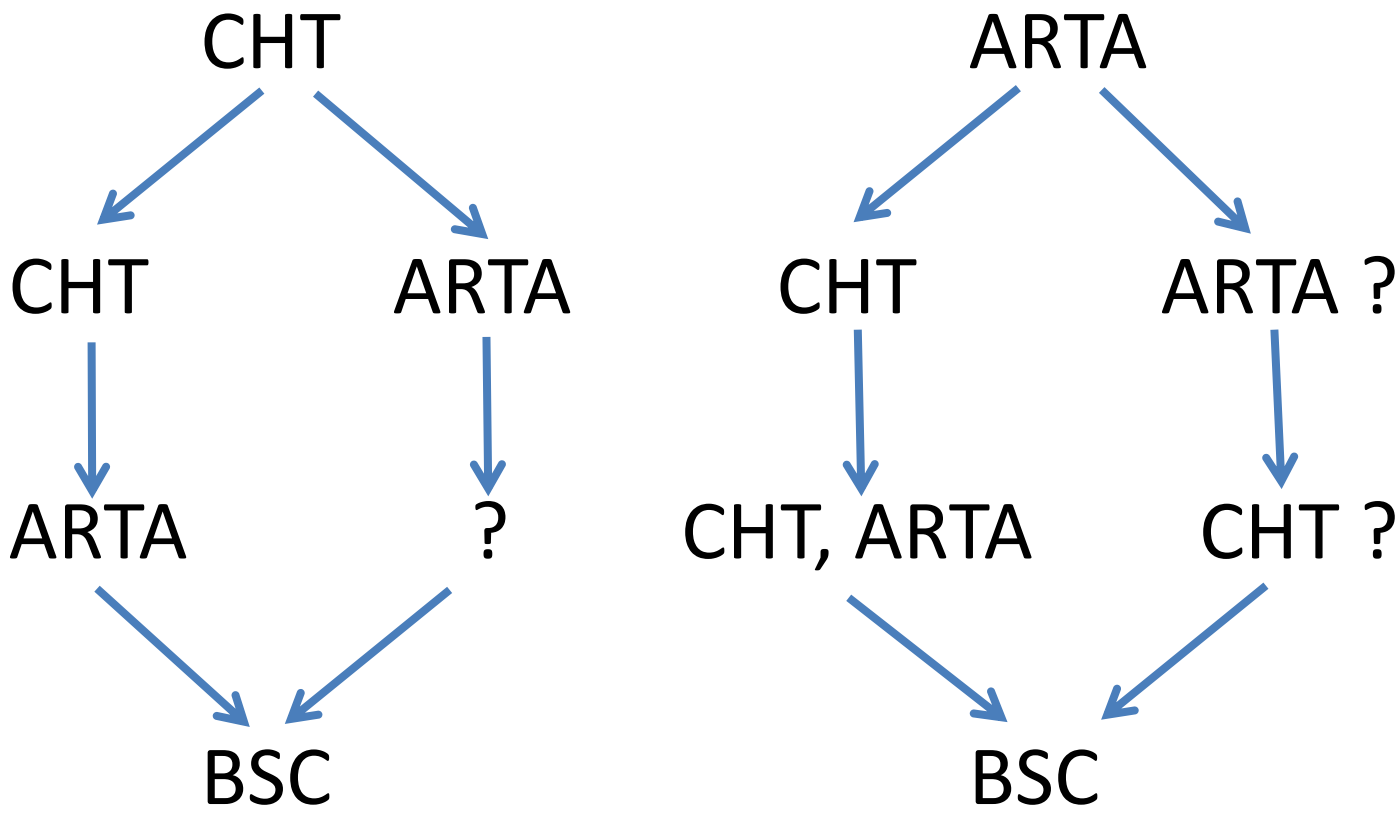
Zvažované charakteristiky pro sekvenci

- Celkový stav !!!
- Rozsah a lokalizace postižení
- Závažnost symptomatologie (omezení – úhradová vyhláška)
- Komorbidity, lab. hodnoty
- Očekávané přežití
- Přání pacienta

- Méně podstatné: výše PSA, PSA-DT

Možné linie

- 1. linie:
- 2. linie:
- 3. linie:
- 4. linie:



Pac. nevhodní k docetaxelu

- Velká kriteria (nejméně 1):
  - Hypersenzitivita
  - Leuko hladina < 1,5
  - Těžší hepatopatie (bili > ULN, AST, ALT >3,5 ULN, ALP > 6x ULN)
- Malá kriteria (alespoň 2):
  - Přítomná polyneuropatie
  - Věk > 75 let
  - PS ECOG >2
  - DM na PAD či insulinu
  - Jiné závažné komorbidity (kardiovaskul., hypertenze, plicní…)

Ad.2 - ARTA

- Abirateron acetát (Zytiga) + Prednison
  - P.o.podávaný analog pregnenolonu, irreverzibilně blokuje klíčový enzym biosyntézy androgenů CYP-17
  - Schválen po selhání ADT u onem. asymptomatického či mírně symptomatického
  - Po Doce+Pred ve studii COU-AA-301, do 1. linie dle výsledků studie III.fáze COU-AA-302
- Enzalutamid (Xtandi)
  - Cílen na řadu kroků v androgenezi, inhibitor androgenních receptorů
  - po selhání Doce (AFFIRM), již úhrada i prechemo indikace

The Prostate

Comparing Sequencing of Abiraterone and Enzalutamide in Men With Metastatic Castration-Resistant Prostate Cancer: A Retrospective Study

Benjamin L. Maughan, Brandon Luber, Rosa Nadal, and Emmanuel S. Antonarakis*

Department of Oncology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland

Maughan et al. Prostate. 2017 Jan;77(1):33-40.

Methods

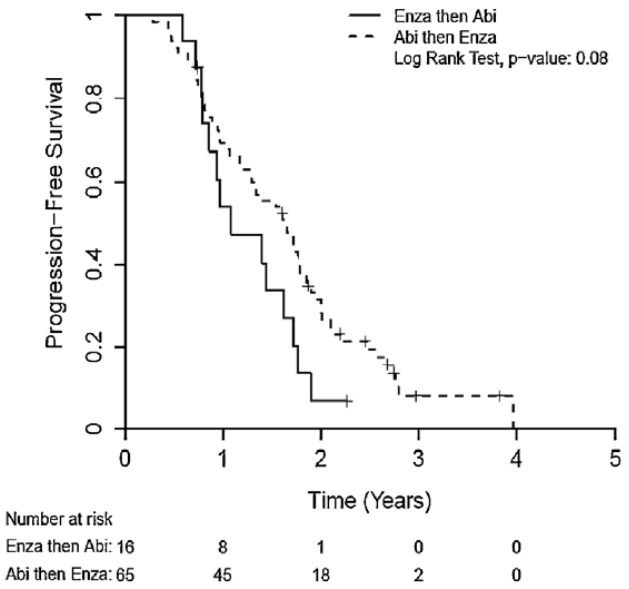
- **Retrospective analysis of consecutive mCRPC** patients treated with ENZ and AA+P conducted at Johns Hopkins.
- Patients treated with sequential ENZ and AA+P, in either order (no specification regarding pre- and post-chemotherapy)
  - **65 patients** received AA+P-then-ENZ
  - **16 patients** received ENZ-then-AA+P
- Primary endpoint:
  - Combined clinical/radiographic PFS (PFS: PFS1+PFS2) measured from the start of the first mCRPC therapy (i.e., ENZ or AA+P) until the time of radiographic or clinical progression
  - PFS1 and PFS2 are the progression-free intervals on the first and second agents, respectively.
- Secondary endpoints:
  - OS: defined from the start of the first therapy to death from any cause
  - Combined PSA–PFS: defined as the time from initiation of the first therapy until the time of PSA progression (25% increase from baseline or nadir) on the second therapy.
- Outcomes were adjusted using propensity score-weighted multivariable Cox analyses.

Results – Combined PFS

Maughan

- Unadjusted Kaplan–Meier analysis the median combined PFS was:
  - **AA+P-to-ENZ: 19.5 months (95%CI 15.5–22.3 months)**
  - **ENZ-to-AA+P: 13.0 months (95%CI 10.3–21.2 months)**
    (log-rank-0.08)
- Difference was statistically significant in the propensity score weighted univariate and multivariable analyses:
  - Univariate propensity-weighted model: AA+P-to-ENZ sequence was associated with superior combined PFS (HR 0.58, 95%CI 0.36–0.94; P=0.03) compared to the alternative sequence.
  - Multivariable propensity-weighted model also identified a significant difference in the sequences favoring AA+P-to-ENZ (HR 0.37, 95%CI 0.22–0.64; P<0.001)

Combined PFS



Multivariate Cox Model for PFS

	Hazard ratio	95%CI	*P*-value
Treatment sequence			
Enza-Abi	Ref		
Abi-Enza	0.37	0.22–0.64	<0.001
Prior docetaxel			
No	Ref		
Yes	1.58	0.95–2.63	0.08
Gleason			
<8	Ref		
8–10	1.49	0.92–2.40	0.10
Baseline PSA	1.001	1–1.001	0.13
Visceral disease			
No	Ref		
Yes	1.03	0.51–2.07	0.93
ECOG			
0–1	Ref		
>1	5.34	1.78–16.06	0.003

Propensity score model for treatment sequence was adjusted for age, Gleason score, ECOG, visceral disease, prior ketoconazole use, prior Docetaxel use, baseline PSA, prostatectomy, and bone pain.

Factors predicting poorer combined PFS:

⟸ Treatement sequence

⟸ ECOG PS >1

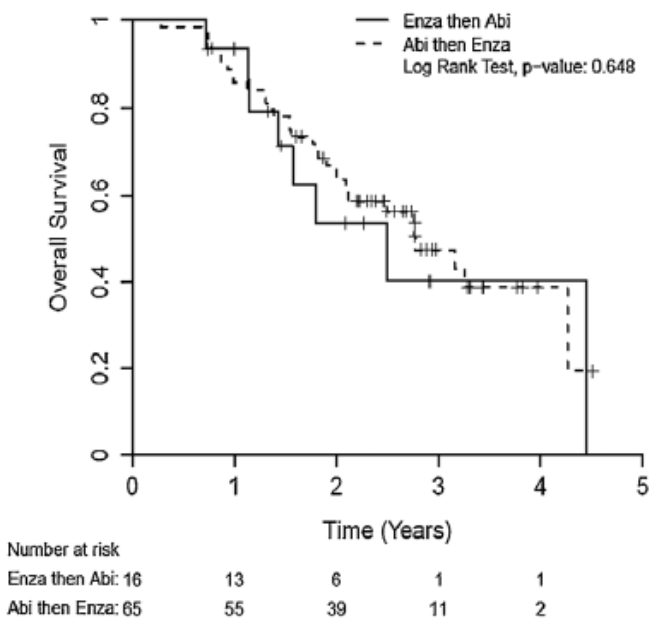
Maughan et al. Prostate. 2017 Jan;77(1):33-40.

Results – OS

Maughan

- Unadjusted Kaplan–Meier analysis the median OS was:
  - **AA+P-to-ENZ: 33.3 months (95%CI 25.4—not reached**
  - **ENZ-to-AA+P 29.9 months (95%CI 18.8–not reached**
    (log-rank P=0.65)
- No statistical differences were found in either the univariate or multivariable propensity score-weighted Cox models in evaluation of OS.
  - there was a trend towards superior OS with the AA+P-to-ENZ sequence (HR 0.57, 95%CI 0.29–1.11; P=0.098)

OS



Multivariate Cox Model for OS

	Hazard ratio	95%CI	*P*-value
Treatment sequence			
Enza-Abi	Ref		
Abi-Enza	0.57	0.29–1.11	0.098
Prior docetaxel			
No	Ref		
Yes	2.12	1.13–3.98	0.02
Gleason			
<8	Ref		
8–10	1.48	0.76–2.89	0.25
Baseline PSA	1.00	1–1.002	0.10
Visceral disease			
No	Ref		
Yes	0.52	0.16–1.72	0.29
ECOG			
0–1	Ref		
>1	3.26	0.91–11.66	0.07

Propensity score model for treatment sequence was adjusted for age, Gleason score, ECOG, visceral disease, prior ketoconazole use, prior Docetaxel use, baseline PSA, prostatectomy, and bone pain.

Factors predicting shorter OS:

Prior Docetaxel

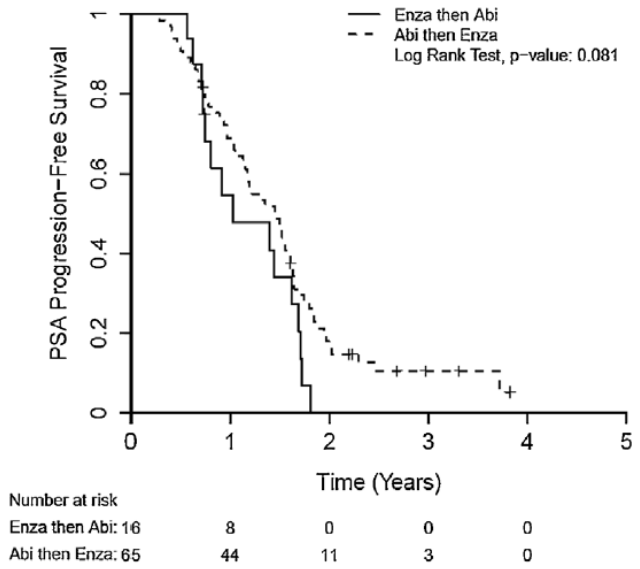
Maughan et al. Prostate. 2017 Jan;77(1):33-40.

Results – Combined PSA-PFS

Maughan

- Unadjusted Kaplan–Meier analysis the median combined PSA-PFS was:
  - **AA+P-to-ENZ: 17.5 months (95%CI 14.0–19.5 months)**
  - **ENZ-to-AA+P: 12.3 months (95%CI 8.9–20.5 months)**
    (log-rank P=0.08)
- Difference was statistically significant in the propensity score weighted univariate and multivariable analyses:
  - Univariate propensity-weighted model: AA+P-to-ENZ sequence was associated with a decreased risk of PSA progression (HR 0.56, 95%CI 0.35–0.90; P=0.02).
  - Multivariable propensity-weighted model also suggested a decreased risk of PSA progression with the AA+P-to-ENZ sequence (HR 0.44, 95%CI 0.26–0.74; P=0.002).

Combined PSA-PFS



Multivariate Cox Model for PSA_PFS

	Hazard ratio	95%CI	*P*-value
Treatment sequence			
Enza-Abi	Ref		
Abi-Enza	0.44	0.26–0.74	0.002
Prior docetaxel			
No	Ref		
Yes	1.54	0.93–2.55	0.097
Gleason			
<8	Ref		
8–10	1.58	0.99–2.52	0.054
Baseline PSA	1	1–1.001	0.22
Visceral disease			
No	Ref		
Yes	1.08	0.54–2.16	0.83
ECOG			
0–1	Ref		
>1	3.89	1.30–11.65	0.015

Propensity score model for treatment sequence was adjusted for age, Gleason score, ECOG, visceral disease, prior ketoconazole use, prior Docetaxel use, baseline PSA, prostatectomy, and bone pain.

Factors predicting increased risk of PSA progression:

⟸ Treatement sequence

⟸ ECOG PS >1

Doporučení: výsledky pouze hypotézu generující, OS neovlivněn)

Maughan et al. Prostate. 2017 Jan;77(1):33-40.

ARTICLE IN PRESS

Original Study

Comparative Assessment of Efficacies Between 2 Alternative Therapeutic Sequences With Novel Androgen Receptor-Axis-Targeted Agents in Patients With Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer

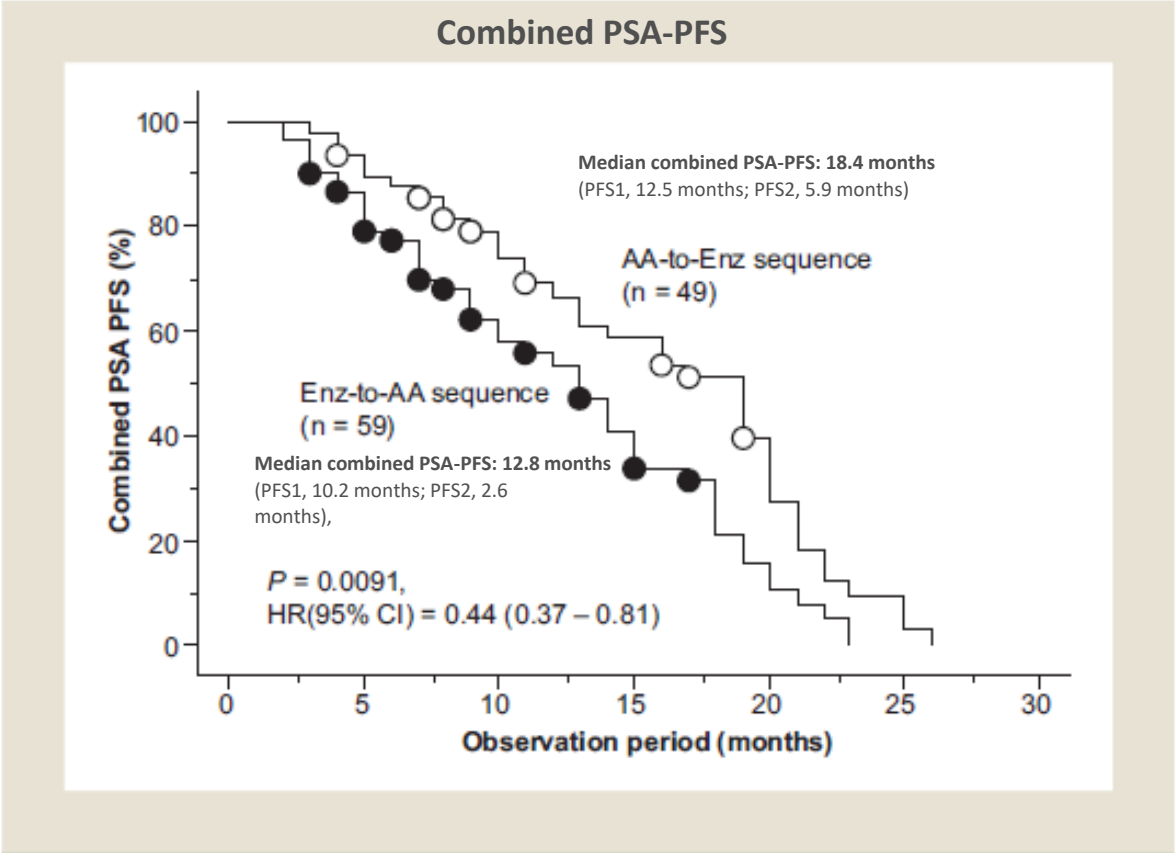
Hideaki Miyake,[1,2] Takuto Hara,[1] Keita Tamura,[2] Takayuki Sugiyama,[2] Hiroshi Furuse,[2] Seiichiro Ozono,[2] Masato Fujisawa[1]

Clinical Genitourinary Cancer, Vol. ■, No. ■, ■-■
Keywords: Abiraterone acetate, Cross-resistance, Enzalutamide, Sequential therapy

Miyake et al. Clin Genitourin Cancer. 2016 Dec 22. [Epub ahead of print]

Miyake

Results - Combined PSA-PFS

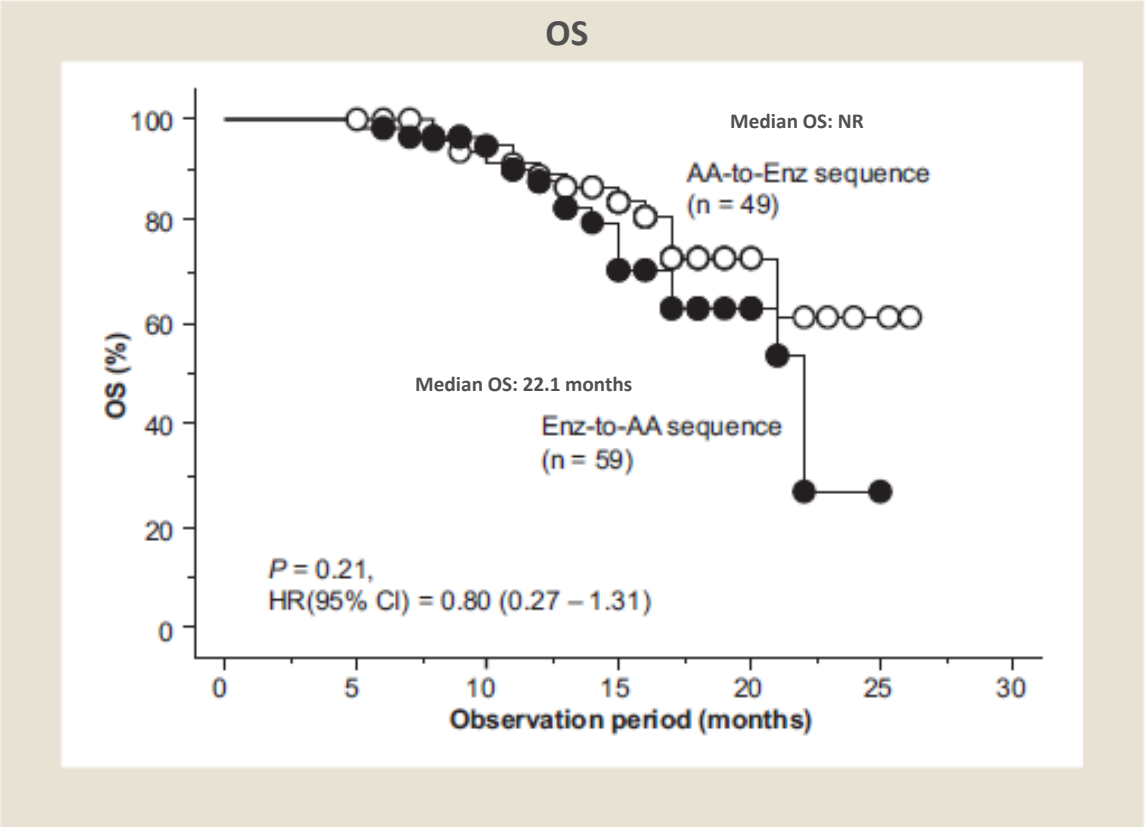


- **Combined PSA PFS in the AA-to-ENZ group was significantly more favorable** than that in the ENZ-to-AA group

Miyake et al. Clin Genitourin Cancer. 2016 Dec 22. [Epub ahead of print]

Miyake

OS During Sequential ARAT Therapy



- No significant difference in the OS between the 2 groups

Výsledky podobné, OS bez signifikantního rozdílu

Miyake et al. Clin Genitourin Cancer. 2016 Dec 22. [Epub ahead of print]

INTERNATIONAL JOURNAL OF UROLOGY
International Journal of Urology (2017) doi: 10.1111/iju.13346

Original Article

Exploring the optimal sequence of abiraterone and enzalutamide in patients with chemotherapy-naïve castration-resistant prostate cancer: The Kyoto-Baltimore collaboration

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Terada N, et al. J Clin Oncol 2017;35 (suppl 6S): Abstract 219.
Terada N et al. Int J Urology 2017; doi: 10.1111/iju.13346

Objective & Methods

Terada

Objective:

- To evaluate and compare the efficacy of sequential treatment with AA+P followed by ENZ or vice versa versus using combined data from two institutions.

Methods:

- Consecutive patients who received sequential AA+P and ENZ at Kyoto University Hospital and John Hopkins Sidney Kimmel Comprehensive Cancer Center were analysed.
- Only patients that received sequential therapy with AA+P-to-ENZ (n=113) or ENZ-to-AA+P (n=85) (without intervening treatments) **before CT** were included.

Endpoints:

- Combined PSA-PFS: measured from start of first novel hormonal therapy (AA+P or ENZ) until time of PSA progression in the subsequent (second) AR-targeted therapy
- OS: time from initiation of AA+P or ENZ treatment until death from any cause
- Univariate and multivariate Cox proportional hazard analyses were performed to evaluate optimal treatment sequence after adjusting for baseline clinical and demographic variables

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Results – PSA-PFS

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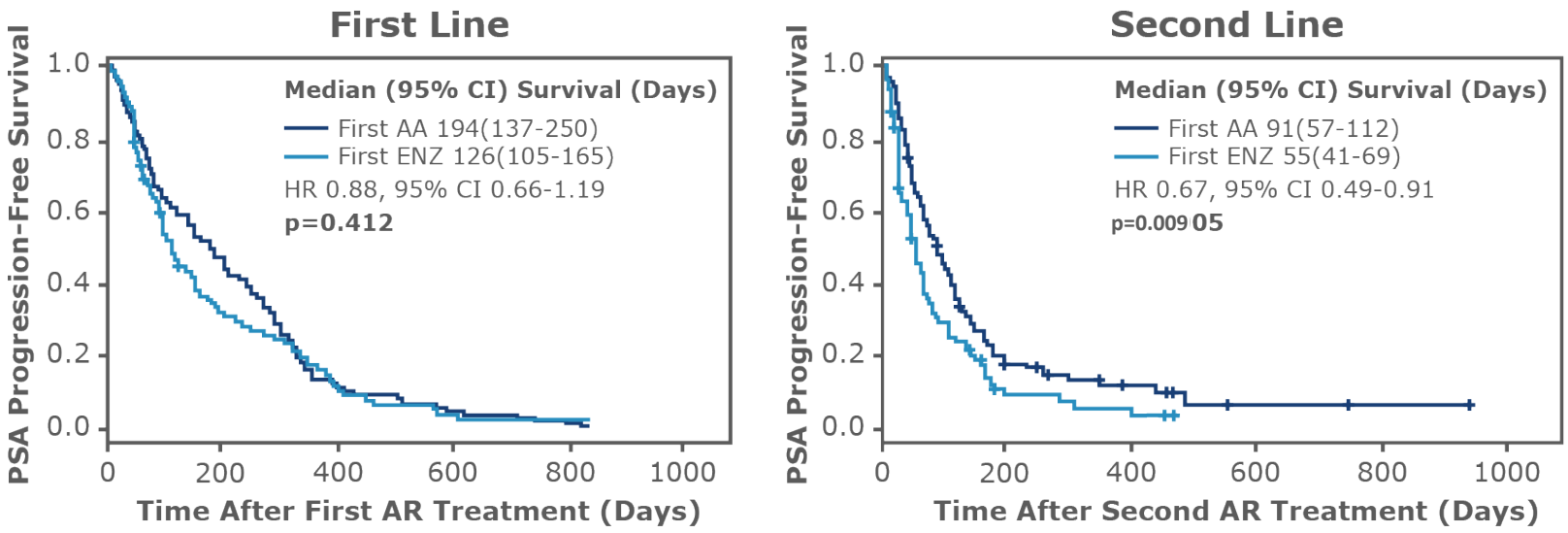
- Median PSA-PFS was not significantly different between AA+P and ENZ in the 1st line setting,
- There was an advantage favouring ENZ versus AA+P in the 2nd line setting (HR=0.67, 95% CI 0.49-0.91, p=0.009)

PSA PFS of AA+P and ENZ as first and 2nd line treatments



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Results – Combined PSA-PFS

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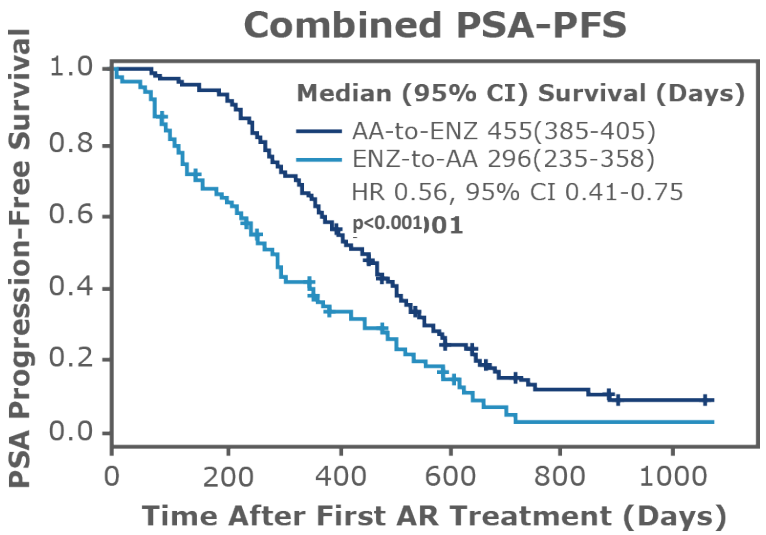
- **Combined PSA-PFS was significantly longer in AA+P-to-ENZ than in ENZ-to-AA+P (HR=0.56, 95% CI 0.41-0.76, p<0.001).**
- The difference was significant even in multivariate analysis (HR=0.56, 95% CI 0.35-0.90, p=0.017)



Cox Model for PSA-PFS

	Univariate			Multivariate		
	Hzard Ratio	95% CI	P-value	Hzard Ratio	95% CI	P-value
Treatment Sequence						
ENZA-ABI	Ref [1.0]			Ref [1.0]		
ABI-ENZA	0.56	0.41 - 0.76	<0.001	0.56	0.35 - 0.90	0.017
Institution						
Kyoto University	Ref [1.0]			Ref [1.0]		
Johns Hopkins	0.54	0.40 - 0.74	<0.001	0.68	0.37-1.23	0.200
Gleason						
<8	Ref [1.0]			Ref [1.0]		
8-10	1.74	1.30 - 2.34	0.002	1.88	1.15-3.09	0.012
ECOG PS						
0-1	Ref [1.0]			Ref [1.0]		
>1	1.62	0.91 - 2.86	0.099	1.04	0.50-2.17	0.923
Baseline PSA Level						
Continuous variable	1.00	1.00 - 1.00	0.443	1.00	1.00 - 1.00	0.447
Time to first ABI/ENZA						
Continuous variable	1.00	0.99- 1.00	0.780	0.99	0.98 - 1.00	0.045
Visceral Disease						
No	Ref [1.0]			Ref [1.0]		
Yes	1.07	0.52 - 2.18	0.859	1.80	0.76-4.23	0.178
No of prior antiandrogen						
0-1	Ref [1.0]			Ref [1.0]		
≥2	1.16	0.86-1.57	0.334	0.92	0.54-1.57	0.761

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Results – OS

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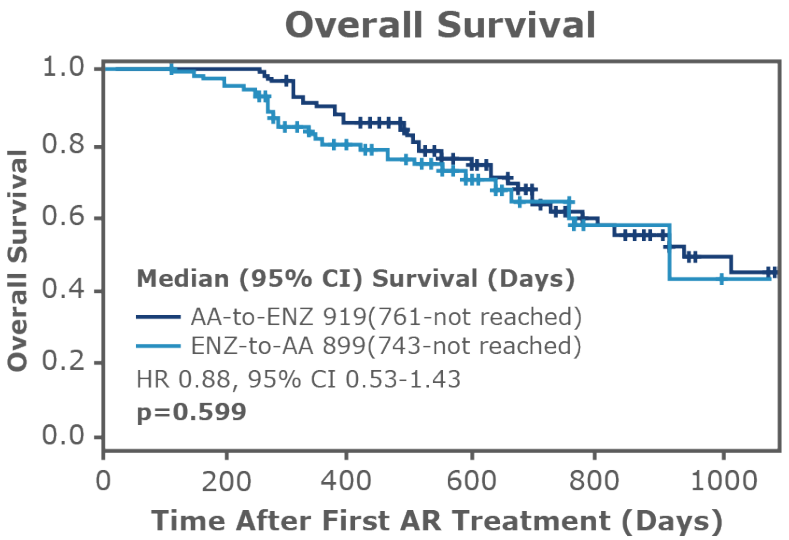
- **The treatment sequence was not correlated with OS in univariate (HR 0.88, 95% CI 0.53–1.44, P = 0.599) and multivariable analysis (HR 0.81, 95% CI 0.49–1.35, P = 0.427)**



Cox Model for OS

	Univariate			Multivariate		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Treatment sequence						
ENZA-ABI	Ref [1.0]			Ref [1.0]		
ABI-ENZA	0.88	0.53–1.44	0.599	0.81	0.49–1.35	0.427
Institution						
Kyoto University	Ref [1.0]					
Johns Hopkins	1.07	0.64–1.78	0.796			
Gleason						
<8	Ref [1.0]					
8–10	1.34	0.77–2.31	0.301			
ECOG PS						
0–1	Ref [1.0]					
>1	1.73	0.74–4.02	0.207			
Baseline PSA Level						
Continuous variable	1.00	1.00–1.02	<0.001	1.00	1.00–1.01	<0.001
Visceral disease						
No	Ref [1.0]					
Yes	0.80	0.25–2.54	0.702			
No. prior anti-androgens						
0–1	Ref [1.0]					
≥2	0.65	0.40–1.06	0.084			

Sekvence ARTA opět neovlivnila OS u CHT naivních pacientů

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Některé poznatky I.

- Účinnost obou taxanů srovnatelná, toxicita se však liší (periferní neuropatie, alopecie, edémy z retence tekutin u doce vs. neutropenie, průjmy a hematurie u caba)
- Preklinicky nižší účinnost doce a enza na buněčných liniích rezistentních na AA
- Po selhání docetaxelu a při rezistenci na AA a enzalutamid caba, ne rechallenge doce[1]
- Pokud ARTA indikována v prechemo indikaci, je sekvence ARTA-docetaxel lepší, než ARTA – ARTA[2]

1. Nuhn et al. Update on Systemic Prostate Cancer Therapies: Management of Metastatic Castration-resistant Prostate Cancer in the Era of Precision Oncology. j.eur- uro.2018.03
2. Matsubara et al. Clin Genitourin Cancer. 2017 Dec;15(6):e1073-e1080

Některé poznatky II.

- Enza po aspoň 2 letech AA lepší, než AA po enza[1]
- Trojsekvence lepší než dvousekvence
- Při ARTA/ARTA riziko zkřížené rezistence
- Po doce ARTA/ARTA, ARTA/cabazitaxel či cabazitaxel/ARTA bylo dosaženo 12měsíčního celkového přežití v 28,5%, 61,3% a 76,4%[2]

1. de Bono JS et al. Antitumour activity and safety of enzalutamide in patients with metastatic castration resistant prostate cancer previously treated with abiraterone acetate plus prednisone for 24 weeks in Europe. Eur Urol 2018;74:37– 45.
2. Crit Rev Oncol Hematol. 2015 Dec;96(3):498-506

Závěrečná sekvence

- Kombinatoricky není neomezený počet postupů
- Místo pro CHT u viscerálního a masivnějšího postižení
- Není-li vhodný doce, je velmi omezená možnost CHT (caba v 1. linii? FIRSTANA, PROSELICA negat., jiné režimy nejsou k disp.)
- ARTA po ARTA – nepříliš vhodné přes odlišný mechanismus účinku
- Preference ARTA z hlediska kvality života, compliance pac. se symptomy
- Splice varianta genu pro androgenní receptor AR-V7 – rezistence k ARTA, ale možná reverze na negativitu po CHT doce[1]

1. Nakazawa M, et al. Serial blood-based analysis of ARV7 in men with advanced prostate cancer. Ann Oncol 2015; 26:1859–65.

Blízká budoucnost sekvencí v novém ?

- Výhledově olaparib (PARPi) u hlavně BRCA2 a ATM mutací (RR 88% vs. 6%, OS 13,8 vs. 7,5 měs.), studovány též veliparib, rucaparib, niraparib a talazoparib[1]
- řada studií s dalšími zástupci cílenými na AR – inhibitory CYP17A1 orteronelem a seviterolenem či antagonisty AR apalutamidem a darolutamidem
- Dráha PI3K-Akt hraje specifickou roli u PTEN deficientního mCRCP a je spojena s horší účinností abirateronu, tudíž zkoušen cabozantinib nebo XPO-1 inhibitor selinexor[2]
- výsledky studií s ipilimumabem, nivolumabem, atezolizumabem, pembrolizumabem i avelumabem ?

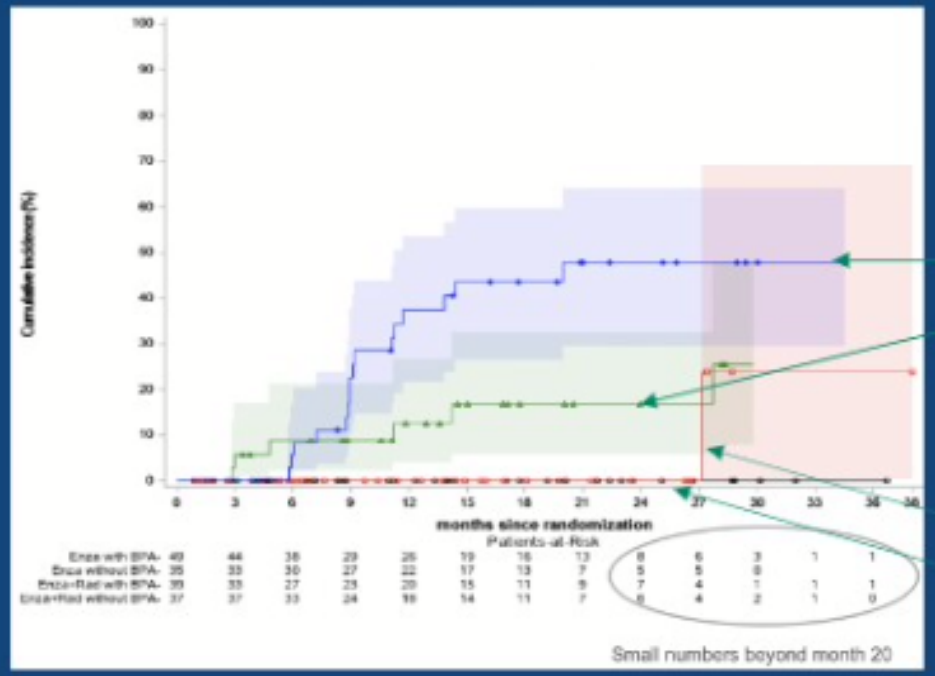
1. D Lorente, et al. Optimal Treatment Sequence for Metastatic Castration-resistant Prostate Cancer. Eur Urol Focus 2 (2 0 1 6) 4 8 8 – 4 9 8
2. P Nuhn, et al. Update on Systemic Prostate Cancer Therapies: Management of Metastatic Castration-resistant Prostate Cancer in the Era of Precision Oncology. https://doi.org/10.1016/j.eur- uro.2018.03.

Metody vakcinace – zatím neuspokojivé

- Autologní vakcinace: sipuleucel-T (delší OS byl zaznamenán v nemocných s méně agresivními rysy choroby již v úvodu
- Allogenní vakcinace: GVAX (Studie fáze III VITAL-2, randomizace GVAX vs GVAX + docetaxel + prednison (n=408), symptomatický pacient mCRPC, ale zvýšená úmrtnost u pacientů zařazených do intervenční skupiny)[2]
- DNA vakcíny (např. pTVG-HP, plasmid, který kóduje PAP protein, u biochemického relapsu CaP prodloužení doby do zdvojení PSA)[3]
- Vakcíny na bázi virových vektorů (PROSTVAC-VF: u pacientů s nemetastatickým CaP, zpomaluje dobu PSA –DT z 5,3 na 7,7 měsíce)[4]
- Checkpoint inhibitory (Ipi, Nivo, Atezo)

1. Kantoff et al.2010, 2. Small et al 2009, 3. Becker et al. 2009, McNeel et al.2009, 4. DiPaola et al., 2015

April 2017, PEACE trial amended to require addition of BPA in both arms



No BPA:
Enza + r223
Enza

With BPA:
Enza + r223
Enza

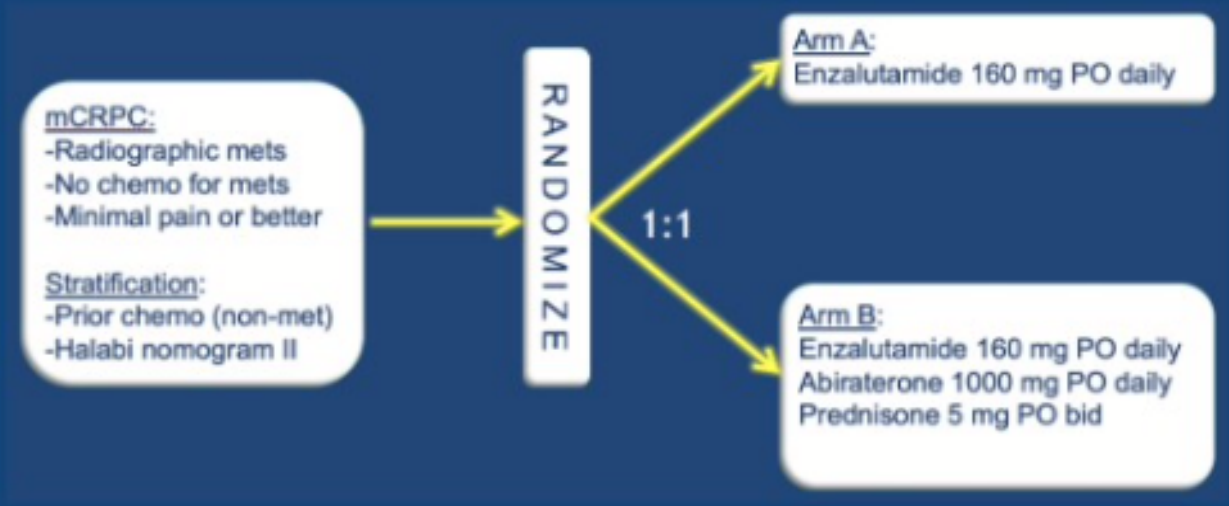
- Patients without BPA had more fractures over time in both arms
- Addition of BPA eliminated fracture risk to date

- European Society for Medical Oncology[1]
  - Zoledronic acid or denosumab should be started as soon as possible in all patients with bone metastases secondary to solid tumors, regardless of the presence or absence of symptoms
  - Continuous treatment is recommended for patients with progression of underlying bone metastases, a recent skeletal-related event, or elevated bone resorption markers
- NCCN[2,3], AUA[4], CUA[5] similar guidelines
- Message: BPA underutilized but clearly impact fracture risk

1. Coleman et al Ann Oncol 2014,
2. and 3. National Comprehensive Cancer Center Network, Prostate Cancer v1.2004 and v 1.2011.
4. Cookson et al J Urol 2015 5. Saad et al Can Urol Assoc 2015

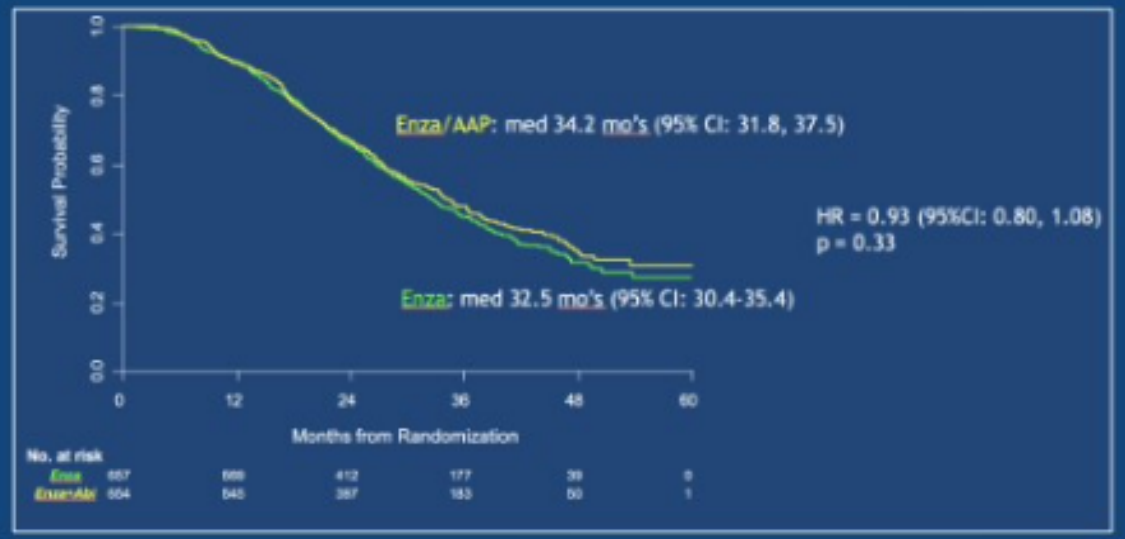
Abstract 2008: Alliance Phase 3 trial of enzalutamide versus enzalutamide and abiraterone for mCRPC

- Rationale
  - Enzalutamide and abiraterone both extend OS when used in the front line setting mCRPC
  - Different MOA
  - Different resistance mechanisms



Results

No improvement in OS



No differences in PSA decline