INTERMITTENT ANDROGEN DEPRIVATION IN ADVANCED PROSTATE CANCER: A REPORT OF ONE CASE.

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INTRODUCTION

Optimal androgen deprivation therapy (ADT) in advanced PC has many controversial issues including those of intermittent therapy vs continuous therapy.

We review one case of metastatic PC managed by intermittent androgen deprivation (IAD) to assess the efficacy, inclusion criteria, and ADT-resuming criteria.

PATIENT AND METHODS

We review one case of metastatic prostate cancer managed by intermittent androgen deprivation at the Department of Urology B, Binh Dan hospital

We consulted the current literature concerning IAD in terms of :

- Inclusion criteria
- PSA levels for retreatment
- The outcome of the newest clinical trials
- The considerations in the latest versions of the Guidelines.

RESULTS

Phan Van D. Male YOB 1935 (73 years old)

Date of admission: 11/30/ 2008

Chief complaint: Urinary retention

Physical examination: DRE induration in both lobes of prostate with signs of infiltration of left seminal vessicle.

Laboratory findings:

NGFL: WBC=9630 ; RBC: 4.67 M/uL; Hct=44,6%, Hb=14,9 g/dL

Serum creatinin =102 umol/L

Serum PSA = 45.65 ng/mL

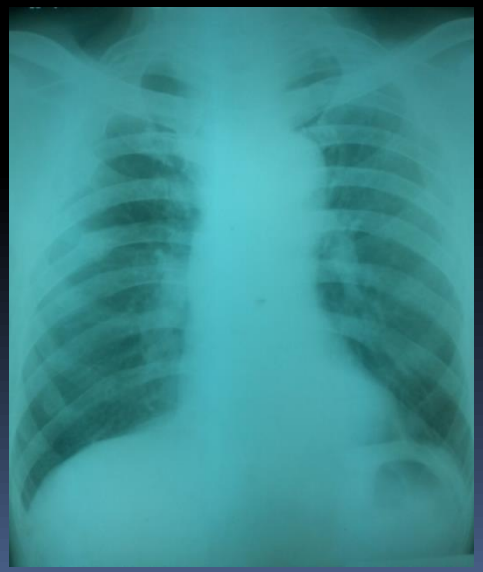
RESULTS

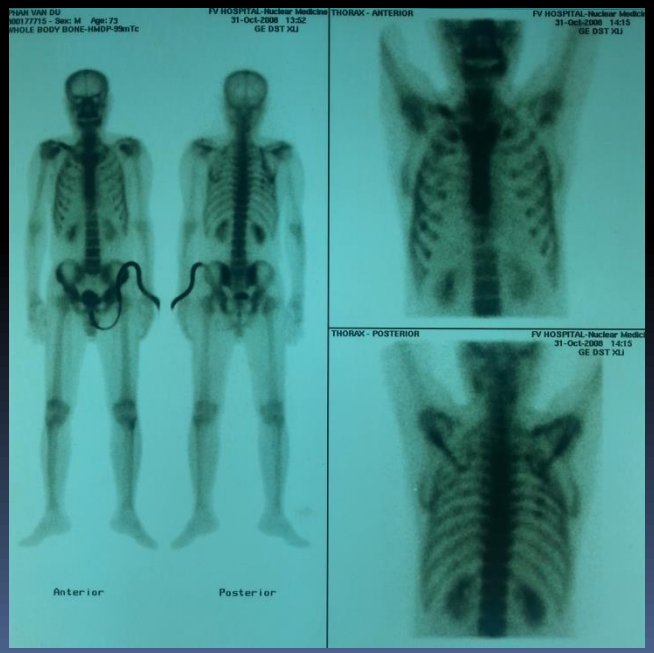
Chest X ray: normal lung, old lesions of rib cage

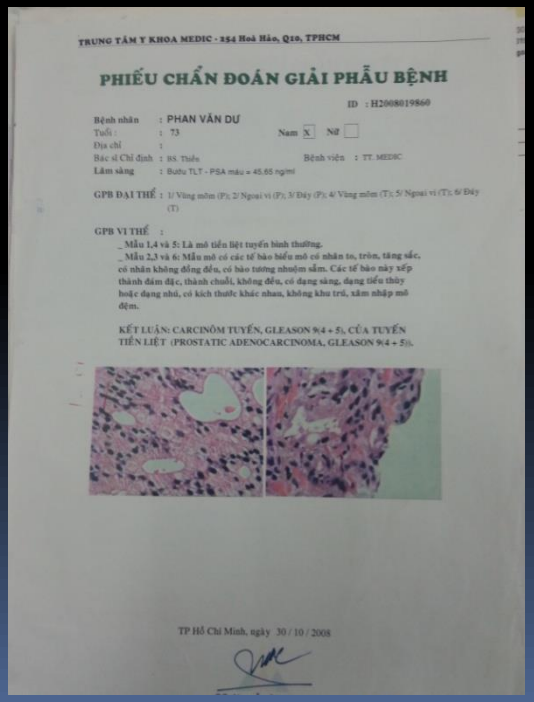
Bone scan (10/31/2008): secondary lesions in right clavicle , right scapula, right rib cage

Sextant prostate biopsy (10/30/2008): adenocarcinoma of prostate, Gleason score= 4+5

Clinical diagnosis: PC , cT3b Nx M1







RESULTS

Management

- TURP , on 11/03/2008

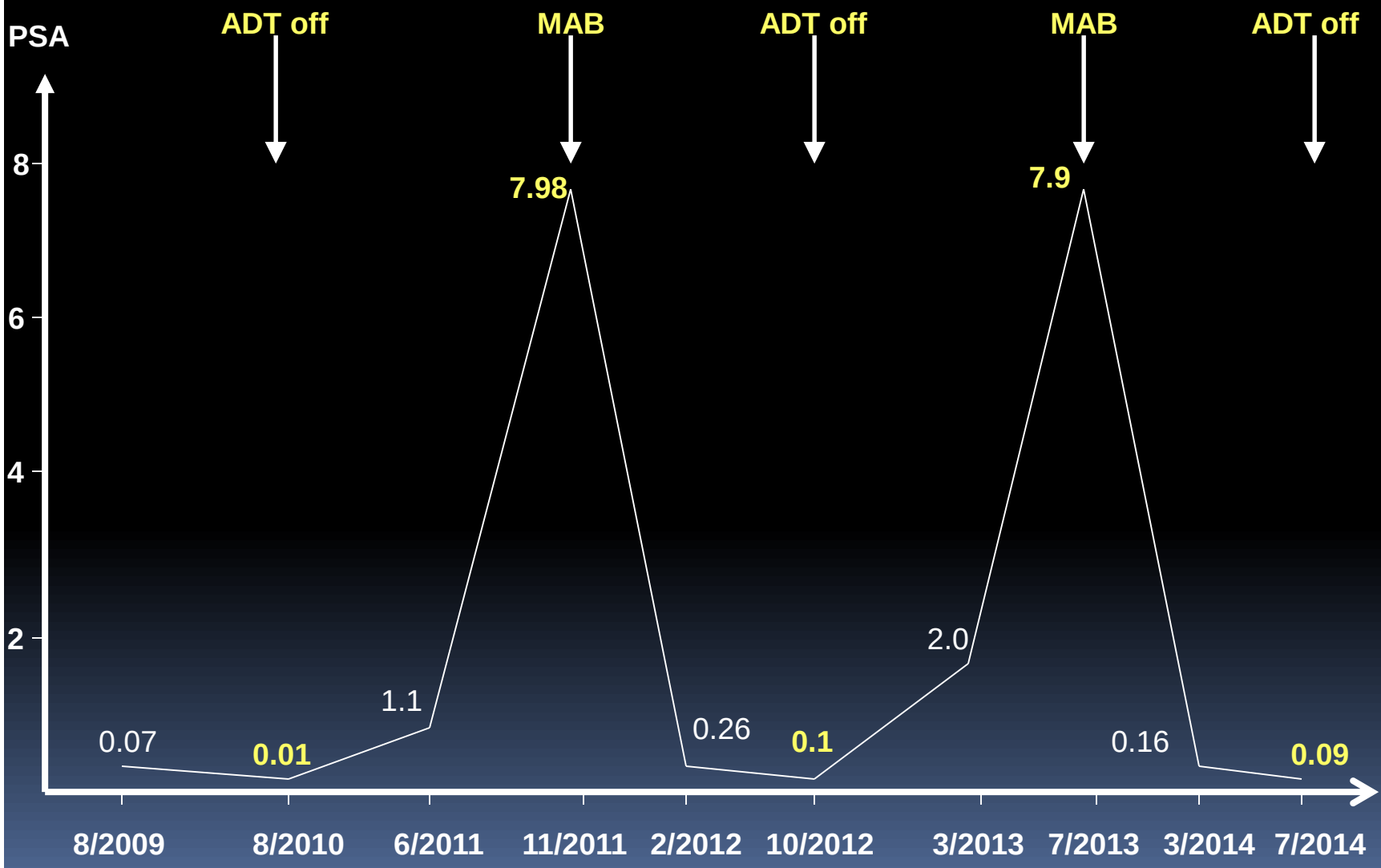
  Anatomopathology: adenocarcinoma of prostate

  Gleason score = 5+3

- ADT : MAB : goserelin acetate (Zoladex® 3.6 mg, SC) + bicalutamide (Casodex® 50mg, PO.), intermittenty

RESULTS

MAB, INTERMITTENTLY



DISCUSSION

Current risk groups classifications

	Nguy cơ rất thấp	Nguy cơ thấp	Nguy cơ trung bình	Nguy cơ cao	Tiến triển tại chỗ
D' Amico 2008		PSA < 10 ng/mL and GS < 7 and cT1-2a	PSA 10-20 ng/mL hay GS < 7, hay cT2b	PSA > 20 ng/mL, hay GS > 7, hay cT2c-3a	
NCCN 2014	cT1c, GS < 7, PSA < 10 ng/mL, PSAD < 0.15, < 3 mẫu sinh thiết (+)	PSA < 10 ng/mL, GS < 7, cT1-2a	PSA 10-20 ng/mL, hay GS 7, hay cT2b-2c	PSA > 20 ng/mL, hay GS > 7, hay cT3a	cT3b-4 hay N1 hay M1
EAU 2014		PSA < 10 ng/mL, GS < 7, cT1c	PSA 10-20 ng/mL, hay GS 7, hay cT2b-	PSA > 20 ng/mL, GS 8-10 hay ≥ cT3a	

DISCUSSION

Risk groups : NCCN guidelines 2.2014

- Very low: T1c and Gleason score ≤ 6 and PSA<10 and < 3 biopsy cores (+) and PSA density <0.15ng/mL/g
- Low: T1-T2a and Gleason score ≤ 6 and PSA < 10ng/ml
- Intermediate: T2b -T2c or Gleason score=7 or PSA 10-20 ng/ml
- High: T3a or Gleason score 8-10 or PSA > 20ng/ml
- Very high: T3b -T4 or N1 or M1

This patient: very high risk with bone metastasis

Therapy: ADT

NCCN Guidelines Version 2.2014
Prostate Cancer

NCCN Guidelines Index
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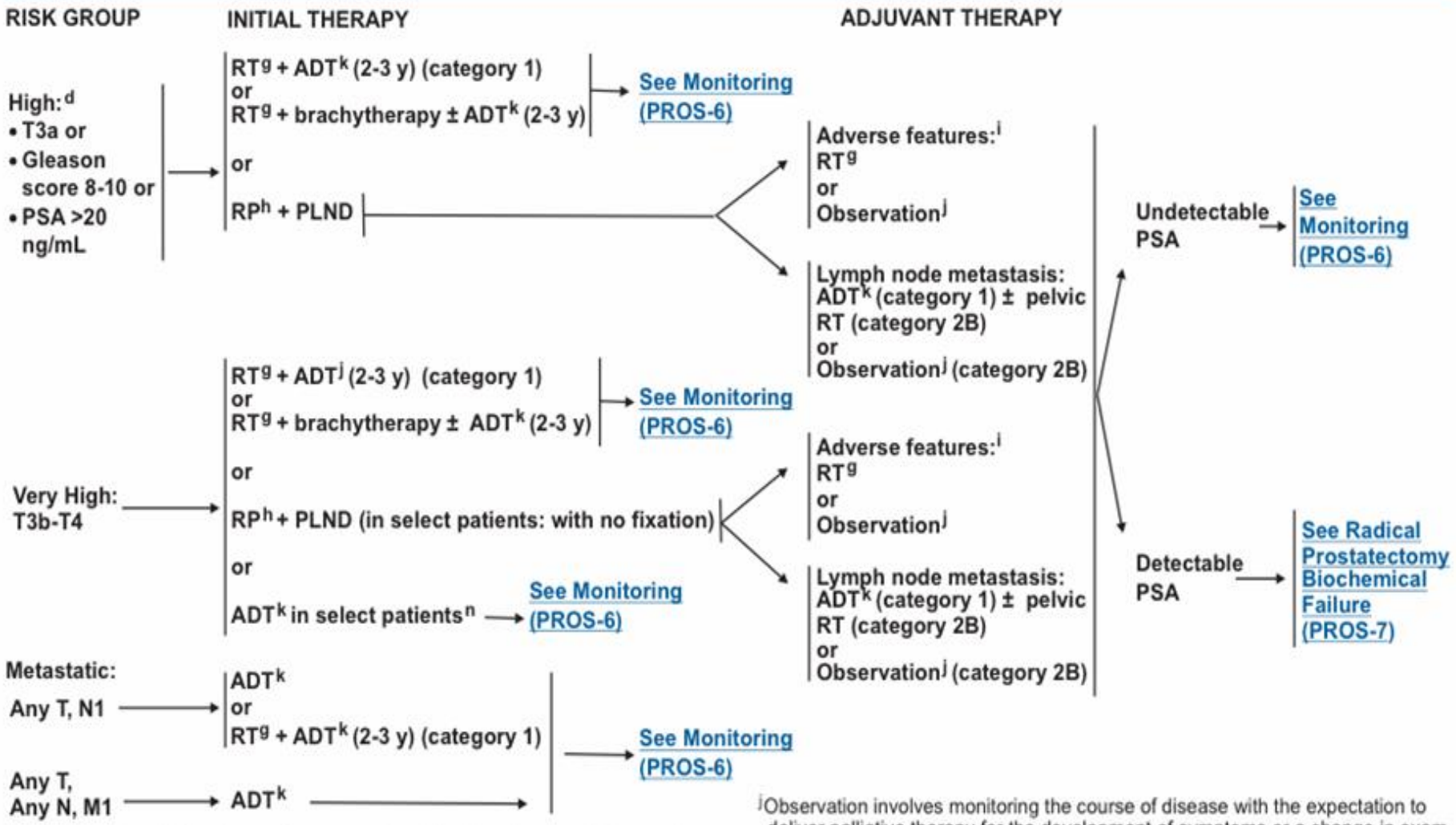


[d] Patients with multiple adverse factors may be shifted into the next highest risk group.

[g] See Principles of Radiation Therapy (PROS-D).

[h] See Principles of Surgery (PROS-E).

[i] Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.

[j] Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).

[k] See Principles of Androgen Deprivation Therapy (PROS-F).

[n] Primary therapy with ADT should be considered only for patients who are not candidates for definitive therapy.

DISCUSSION

Why intermittent ADT (IAD) in advanced PC ?

- MAB (Maximal Androgen Blockade) : deprives both testicular and adrenal androgen , with some side effects after 3-6 months
- When continuous ADT (CAD) : after 24 months: rise of PSA and development of castration resistant phenomenon- CRPC.
- Administration of IAD could prolong time to castration resistance in experiments

DISCUSSION

The comparative studies between IAD vs CAD: 3/11 important phase III studies: Crook , Calais da Silva, and Hussain

	Population	No. of pts	Study Coordinator
NCIC/PR7/SWOG	PSA relapse after RT	1386	Crook
EC 507	PSA relapse after RP	244	Tunn
ICELAND	PSA relapse/locally advanced	700	Schulman
Yamanaka	Advanced PCa	188	Yamanaka
De Leval	T3-4,M+	68	De Leval, Boca
SEUG	Advanced PCa	626	Da Silva
AP 17/95	Advanced PCa and M +	325	Miller
SWOG 9346	M+ PCa (PSA > 5 ng/mL)	1512	Hussain
EC 210	M+ PCa (PSA > 20 ng/mL)	387	Mottet
Erasmus	M+	366	De Rijke
FinnProstate VII	M+,N+	554	Salonen

DISCUSSION

The studies comparing IAD vs CAD with regard to OS and PFS

Study	Disease	Progression	OS
Miller	Metastatic	=	=
Tunn	Recurrent RP	=	NR
Mottet	Metastatic	=	=
Calais da Silva (SEUG 9401)	Mixed	=	=
Crook/Klotz (SWOG JPR.7)	Recurrent M0	+	=
Hussain (SWOG 9346)	Metastatic	NR	Inferior

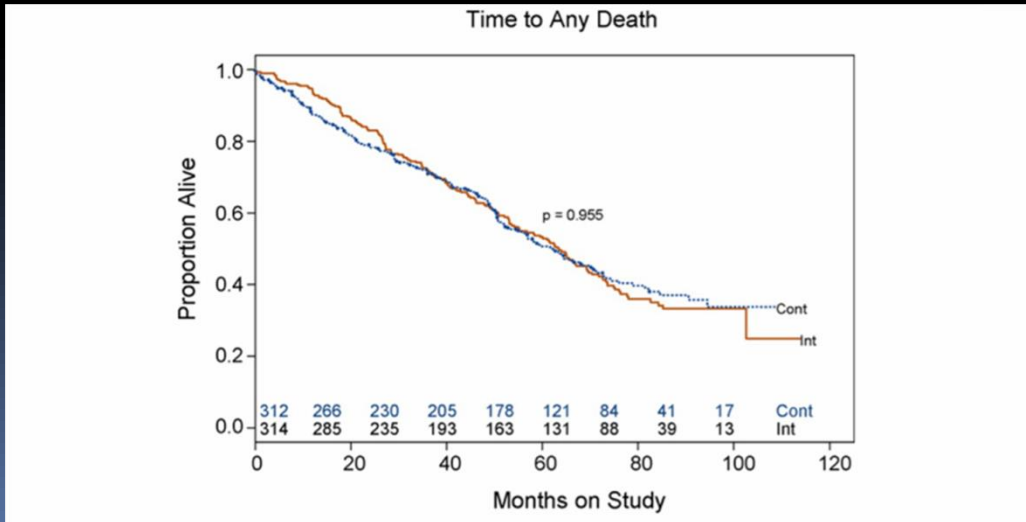
Key studies

Tunn U. et al.. *BJU Int* 2007;99 (Suppl 1):19-22

DISCUSSION

The SEUG 9401 (South European Urooncology Group) : Locally advanced / Metastatic PC

- 626 patients with T3-4 Mo-1. Initially treated with MAB. The patients with subsequent PSA < 4 ng/mL or a decrease of PSA > 80% of baseline were randomized to 2 groups: IAD or CAD . In the IAD: the subgroup PSA < 4 ng/mL resumes MAB when PSA > 10 in symptomatic patients or PSA > 20 in non-symptomatic patients ; the subgroup with >80% decrease of PSA resumes MAB when PSA rises > 20% of nadir
- Results: no OS difference between 2 groups

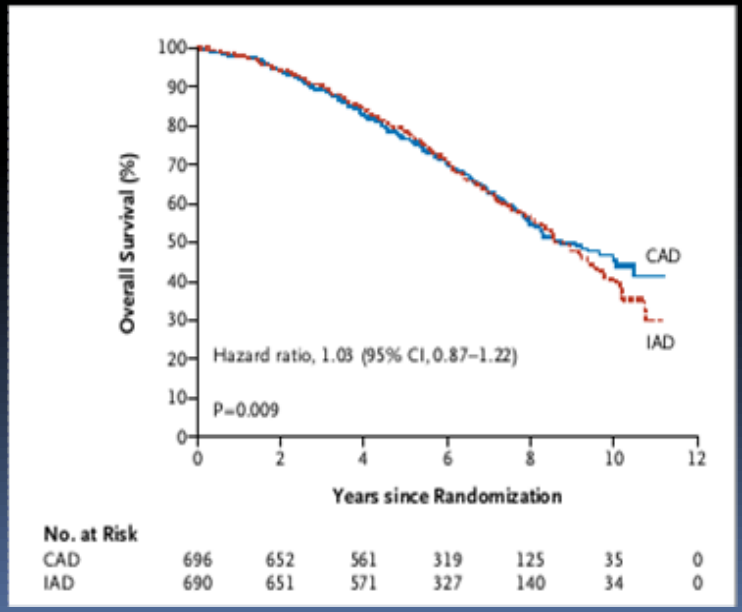


Calais da Silva F, et al, *Eur Urol* 2009; 55-1269-77

DISCUSSION

The SWOG JPR.7 : Biochenical recurrence

- Crook randomized 1386 Patients with PSA > 3 ng/mL after RT to IAD or CAD group
- After 6.9 years:: no OS difference between 2 groups (8.8 vs 9.1 years; HR=1.02, 95% CI, 0.86-1.21)
- More patients died of PC in IAD group but more patients died of other causes in CAD group . In IAD group: fatigue, LUTS, hot flush, libido, erectile function improved



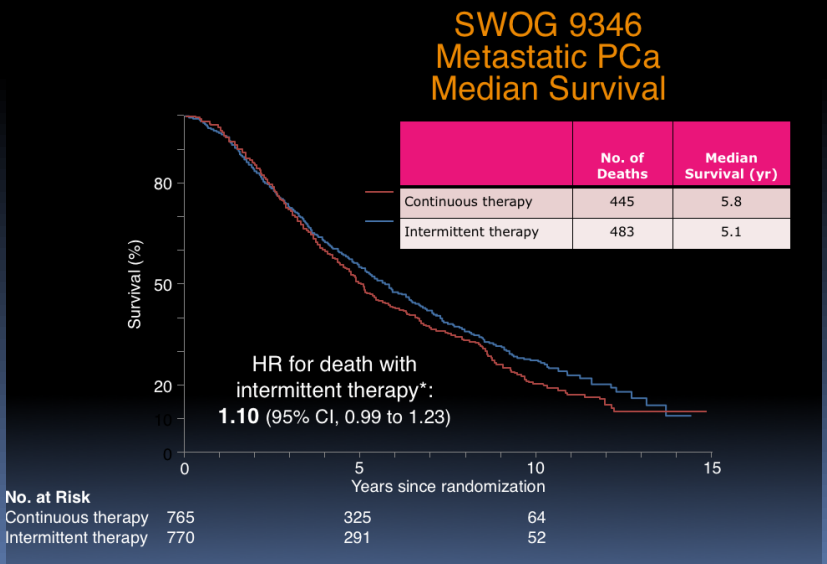
Crook, J.M. et al. NEJ, 367:895-903, Sept 2012

DISCUSSION

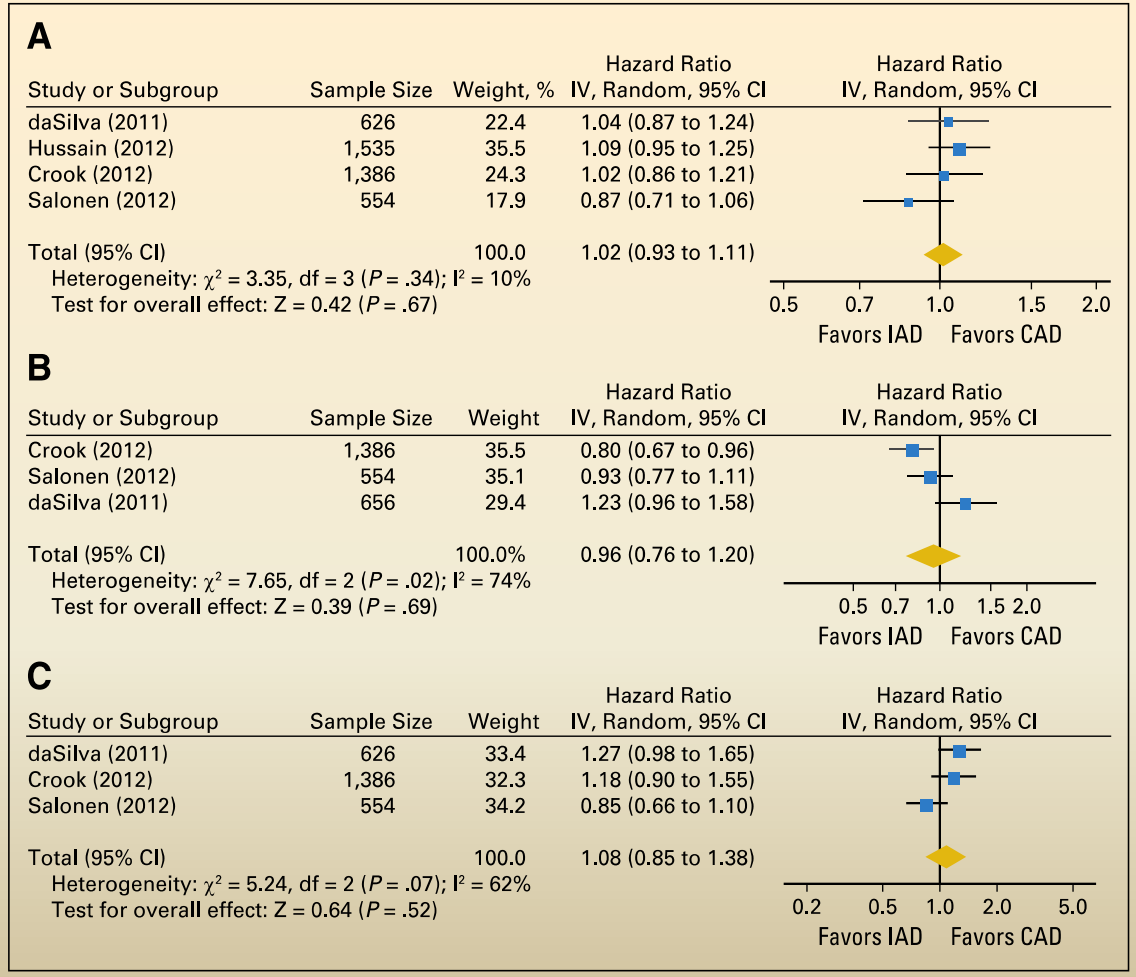
The SWOG 9346 : Metastatic PC

- Hussain compared IAD vs CAD. After 7 months of ADT, 1535 patients with PSA ≤ 4 ng/mL were randomized to IAD or CAD group . After 9.8 years: OS: 5.1 years vs 5.8 years, HR=1.10, 95% CI, 0.99-1.23
- Conclusion: inconclusive of OS, higher mortality of 20% in IAD group not excluded. In IAD group: better erectile function and mental health after 3 months but not clear anymore thereafter.

Adapted from Hussain M, *et al. N Engl J Med* 2013;368(14):1314-25.



Pooled estimate of HR for (A) OS, (B) TTP, (C) PCaSS: IAD vs. CAD



Niraula, et al. JCO 31.2013

DISCUSSION

IAD- Who can be treated ?

Mottet et al, 2011: patients responding to ADT **with a decline of PSA to normal values** : patients previously untreated: PSA < 4 ng/mL, PSA relapse after RT or Surgery: PSA < 0,5 ng/mL

When to restart ADT ?

The Retreatment PSA triggers:

CaP patients	PSA [ng/ml]
Without previous treatment	M_0: 6–10
	M_+: 10
PSA relapse	After RP > 3 ng/ml After RT > 8–10 ng/ml

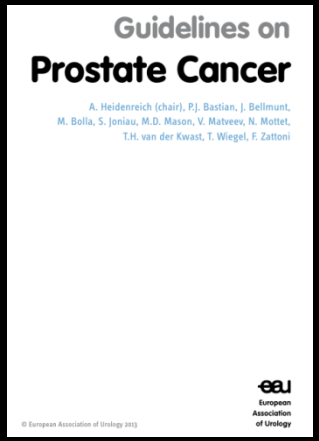
Mottet et al. *Eur Urol* 2011; 59: 572-583

DISCUSSION

Remarks on this patients

- Diagnosis:: PC, cT3b Nx M1, very high risk, with bone metastasis
- From Nov 2008 to July 2014: in *nearly 6 years*, patients received 3 cycles (MAB-ADT off) without the development of castration resistance status. *Time to progression to CRPC seems to be prolonged* significantly in this patient
- This patient was not treated previously, but he was at ADT-off at very low PSA (0.1ng/mL). This makes the ADT-on period nearly 1 year (recommendation : 6-9 months). The retreatment PSA trigger in this patient was 8 ng.mL (recommendation: 10 ng/mL)

DISCUSSION



The EAU Guidelines 2013-2014

- IAD has not been shown to prolong hormone –sensitiv e status or an increase in OS
- Although the QoL benefit is less than expected or absen t, except in few studies, IAD is better tolerated and sometimes benefits sexual function
- Other longtem benefits, which are not clearly proven, include bone protection and/or protective effects against metabolic syndrome.
- Testosteron recovery is seen in most studies, leading to an intermittent castration .

CONCLUSION

- IAD had *similar outcomes* as those of CAD, with advantages of better patient tolerance and quality of life.
- This clinical case is an evidence for *recommendation of IAD* if the patient meets some criteria.
- This kind of therapy is now *introduced into the latest versions of EAU Guidelines and NCCN guidelines*, with some reservation.

Thank

You