Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

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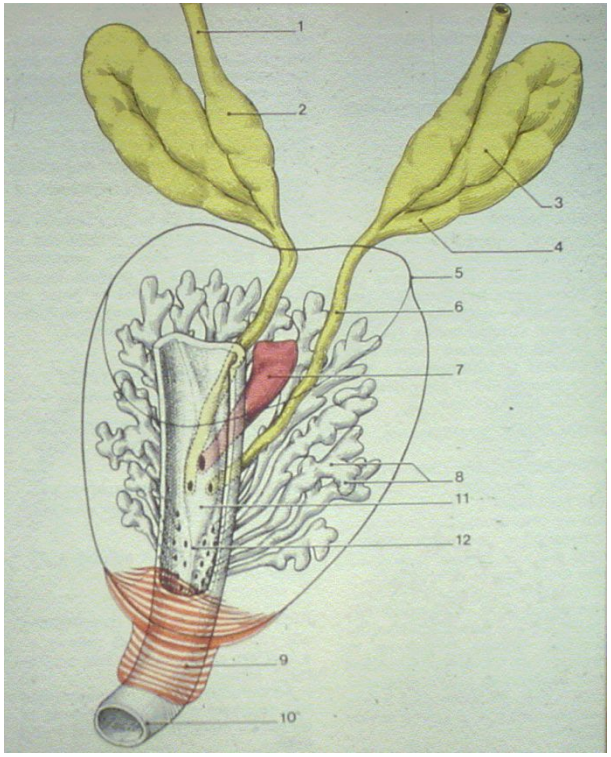
PSA élevé: que faire?

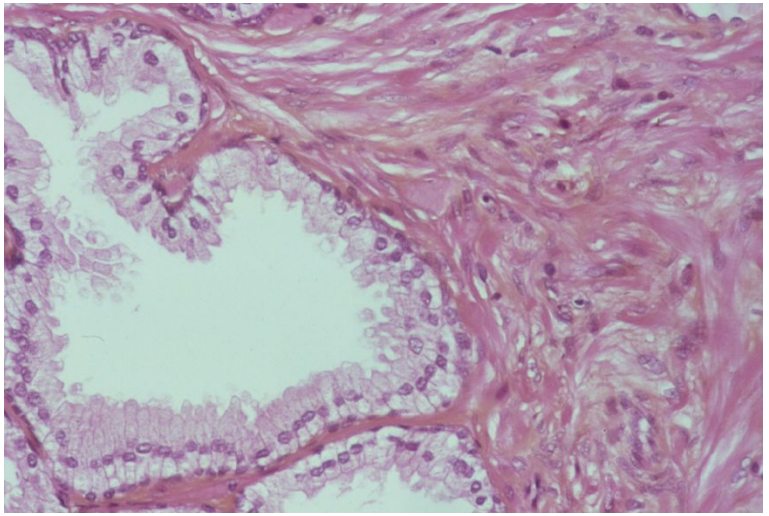
François Desgrandchamps

Hôpital Saint-Louis, Paris

PSA: Antigène spécifique de la Prostate

- Produit par les cellules ductales et glandulaires de la prostate
- Protéase chymotrypsine-like régulée par les androgène
- Sert à la liquéfaction du sperme après l'éjaculation





Hori S. BJUInt 2013 – Stamey TA. NEJM 1987 – Pallas M Actas Urol Esp 1995

PSA: Antigène spécifique de la Prostate

- Spécifique d'organe (mais pas de maladie)
- Concentration un million de fois plus faible dans le sérum que dans le liquide prostatique
- Fluctuations normales du PSA sérique (jusqu'à 30% !)
- Variation sans corrélation entre les méthodes de dosage de différents laboratoires
- Non modifié
  - Ni par le toucher rectal
  - Ni par l'éjaculation
  - Ni par le vélo
- S'élève en cas de prostatite, d'hypertrophie bénigne de la prostate, de cancer de la prostate, de biopsie de prostate
- Demi-vie de 2 à 3 jours

Hori S. BJUInt 2013 – Stamey TA. NEJM 1987 – Pallas M Actas Urol Esp 1995

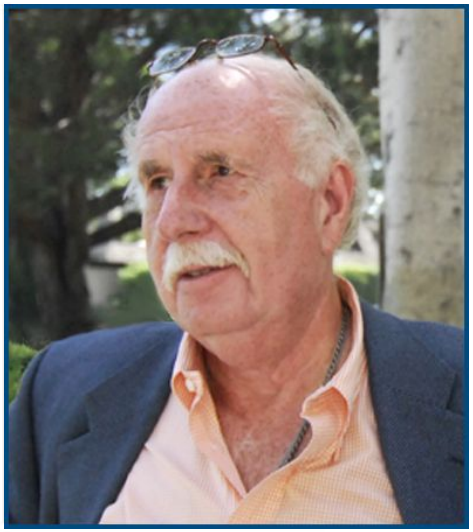
The New York Times

OP-ED CONTRIBUTOR

The Great Prostate Mistake

By RICHARD J. ABLIN
Published: March 9, 2010

Tucson



André da Loba

EACH year some 30 million American men undergo testing for prostate-specific antigen, an enzyme made by the prostate. Approved by the Food and Drug Administration in 1994, the P.S.A. test is the most commonly used tool for detecting prostate cancer.

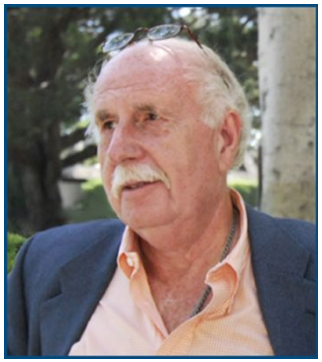
The test's popularity has led to a hugely expensive public health disaster. It's an issue I am painfully familiar with — I discovered P.S.A. in 1970. As Congress searches for ways to cut costs in our health care system, a significant savings could come from changing the way the antigen is used to screen for prostate cancer.

Americans spend an enormous amount testing for prostate cancer. The annual bill for P.S.A. screening is at least $3 billion, with much of it paid for by Medicare and the Veterans Administration.

Related

Times Topics: Prostate Gland

The New York Times

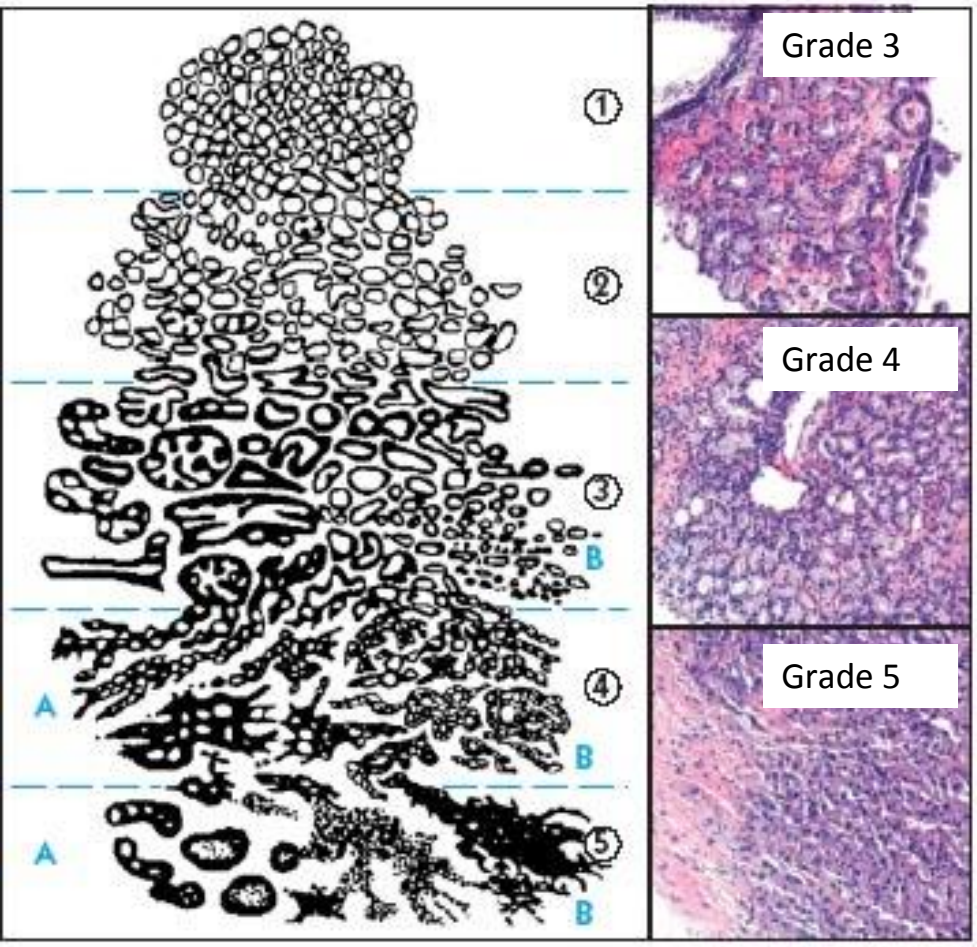


Prostate cancer may get a lot of press, but consider the numbers: American men have a 16 percent lifetime chance of receiving a diagnosis of prostate cancer, but only a 3 percent chance of dying from it. That's because the majority of prostate cancers grow slowly. In other words, men lucky enough to reach old age are much more likely to die with prostate cancer than to die of it.

Even then, the test is hardly more effective than a coin toss. As I've been trying to make clear for many years now, P.S.A. testing can't detect prostate cancer and, more important, it can't distinguish between the two types of prostate cancer — the one that will kill you and the one that won't.

Instead, the test simply reveals how much of the prostate antigen a man has in his blood. Infections, over-the-counter drugs like ibuprofen, and benign swelling of the prostate can all elevate a man's P.S.A. levels, but none of these factors signals cancer. Men with low readings might still harbor dangerous cancers, while those with high readings might be completely healthy.

Le score de Gleason



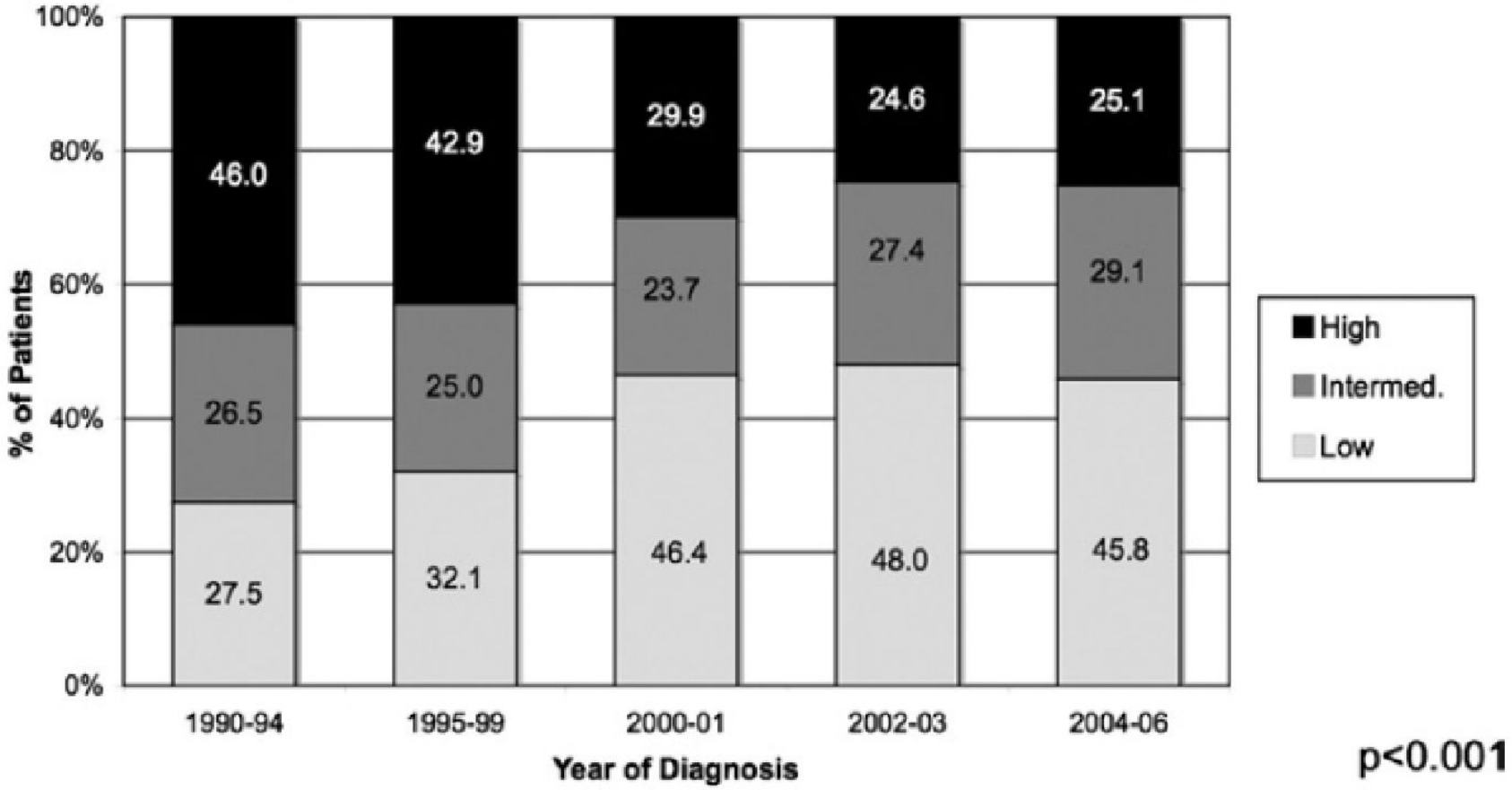
- Sur les biopsies, le score de Gleason s'établit en additionnant le grade le plus représenté et le grade le plus péjoratif ; pas de score 4 ou moins sur les biopsies ; en cas de grade 2 ou 3 très minoritaire (<5%), on en tient pas compte dans le score.
- Le score de Gleason sur les prostatectomies s' établit en additionnant les 2 grades les plus représentés. En cas de haut grade (4 ou 5) minoritaire par rapport aux 2 autres, le mentionner en tant que grade tertiaire, mais ne pas l'inclure dans le calcul du score; en cas de grade 2 ou 3 très minoritaire (<5%), on en tient pas compte dans le score.

Reco AFU 2013

Trends in risk group assignments for localized prostate cancer (1990-2006)

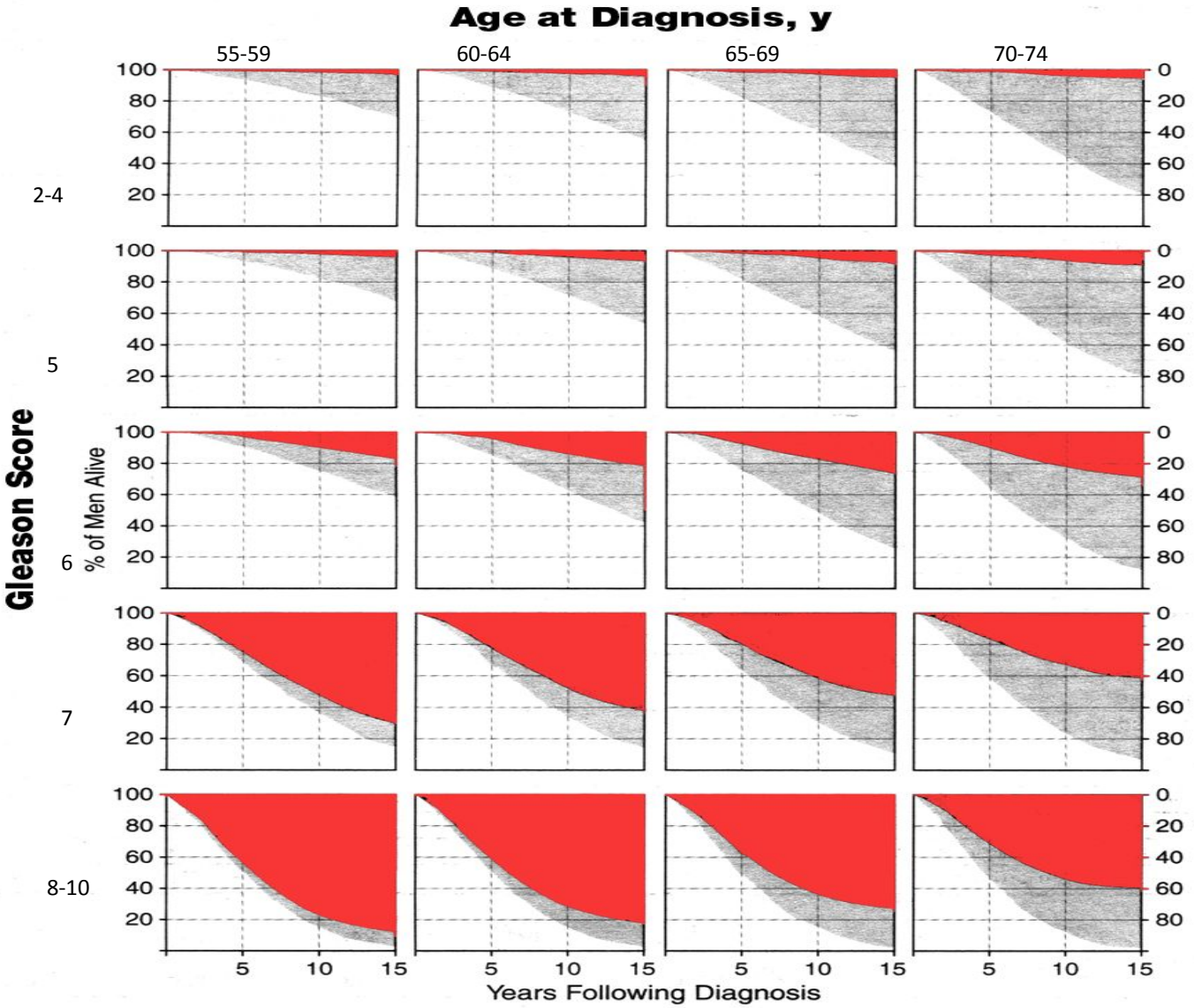
(10385 men from CaPSURE registry) Cooperberg MR. J Urol 2007

Trend toward more low and less high risk disease at diagnosis is significant



- Low risk : PSA 10 ng/ml or less, Gleason 6 or less and stage 2a or less
- Intermediate risk : PSA 10.1 to 20 ng/ml, Gleason 7 and/or stage T2b
- High risk : PSA> 20 ng/ml, Gleason 8 or greater and/or stage T2c-3a

Survie du cancer de la prostate non traité



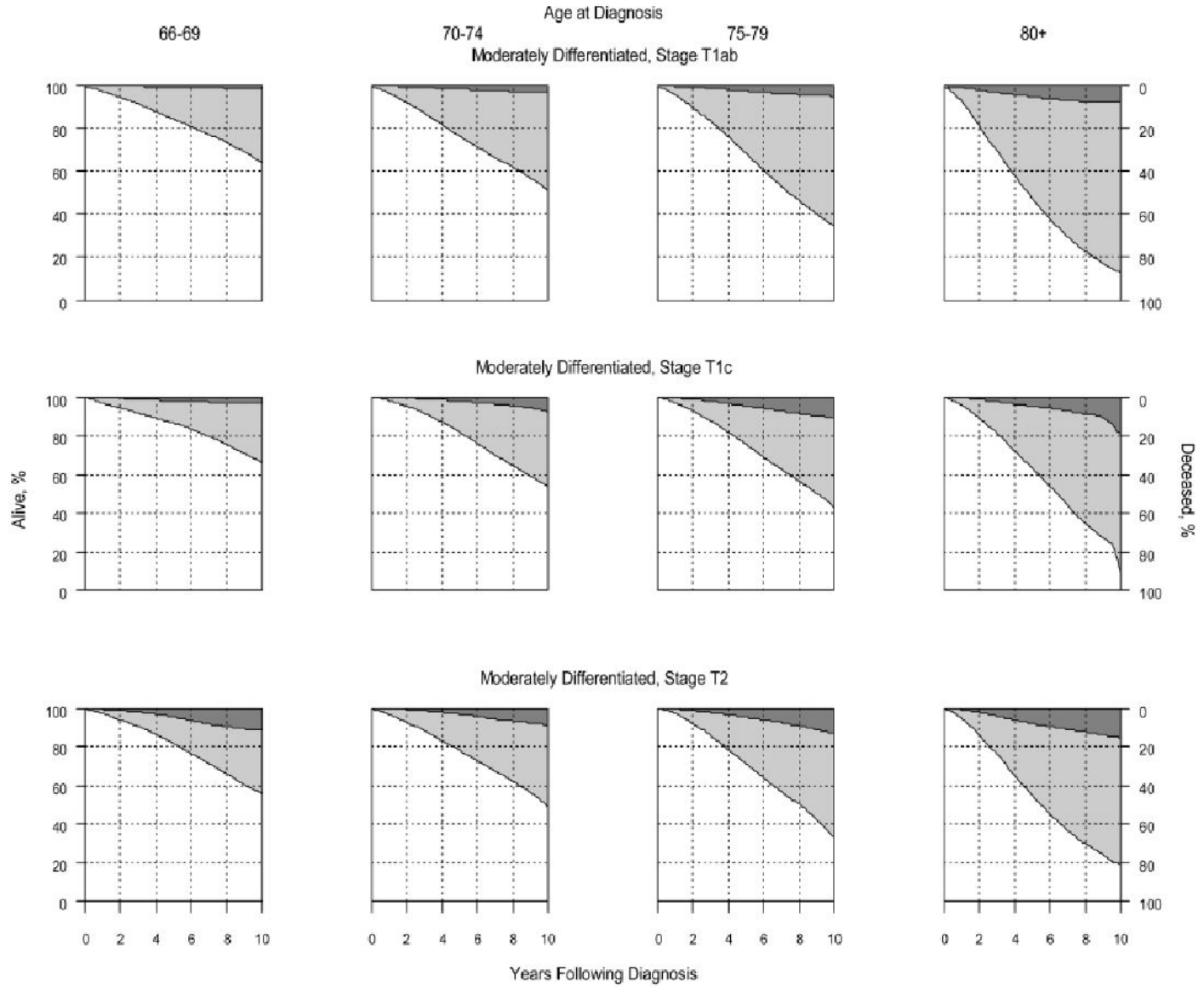
ALBERTSEN: JAMA 280:975, 1998

767 patients, retrospectif,
non traité ou TRT Hal, suivis 10 à 20 ans

Mortalité spécifique

Mortalité non liée au cancer

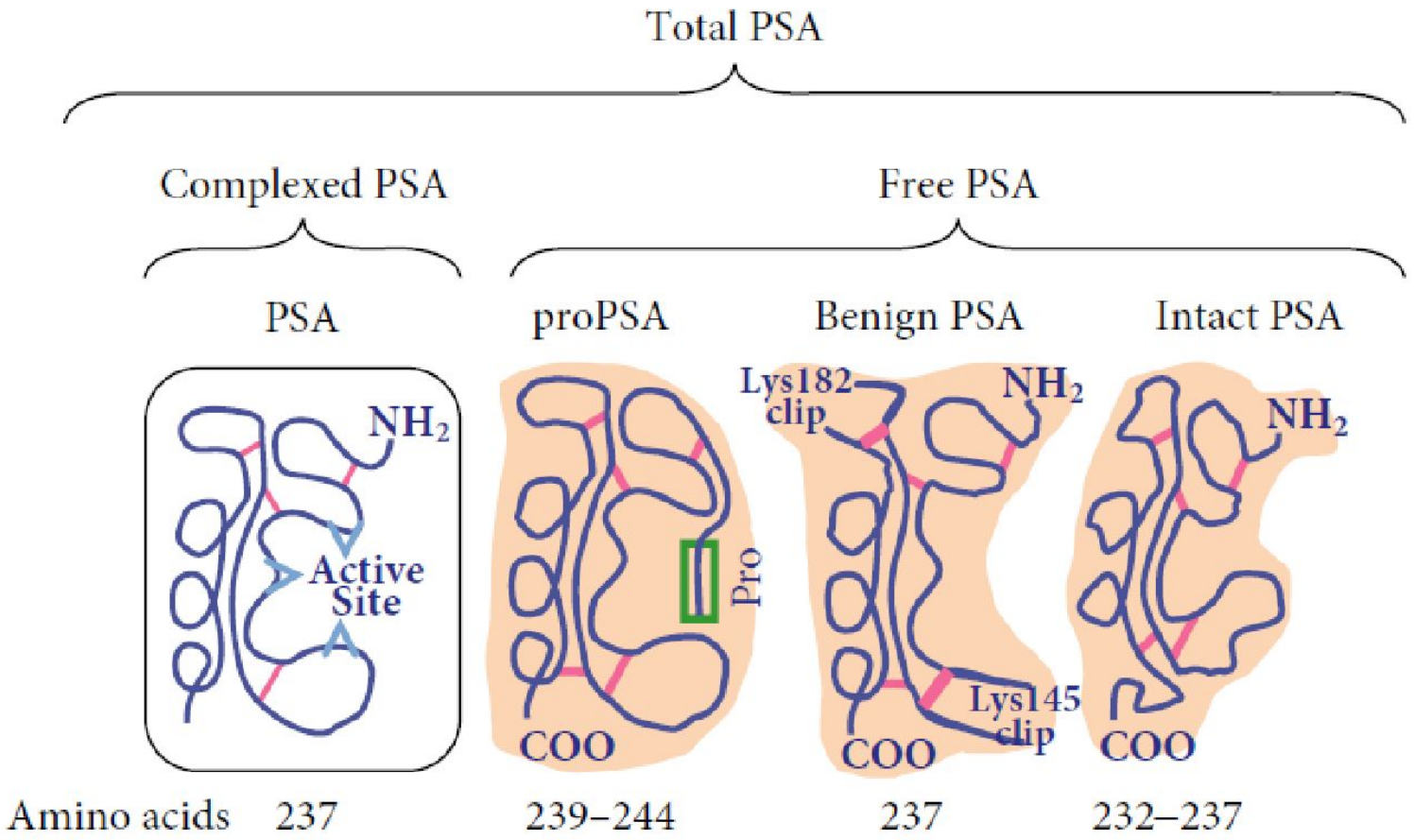
14 516 hommes traités de façon conservative. SEER registry



Moderately-Differentiated (Gleason 5-7) Cancer

Lu-Yao GL. JAMA 2009

Différentes formes de PSA circulent dans le sang



- Le BPSA est exprimé préférentiellement dans la zone de transition et le Pro PSA dans la zone périphérique. Dans le sérum 90% du tPSA est lié à différents inhibiteurs de protéases : cPSA

Hori S. BJUInt 2013

Le taux de PSA s'élève avec l'âge et le volume de la prostate

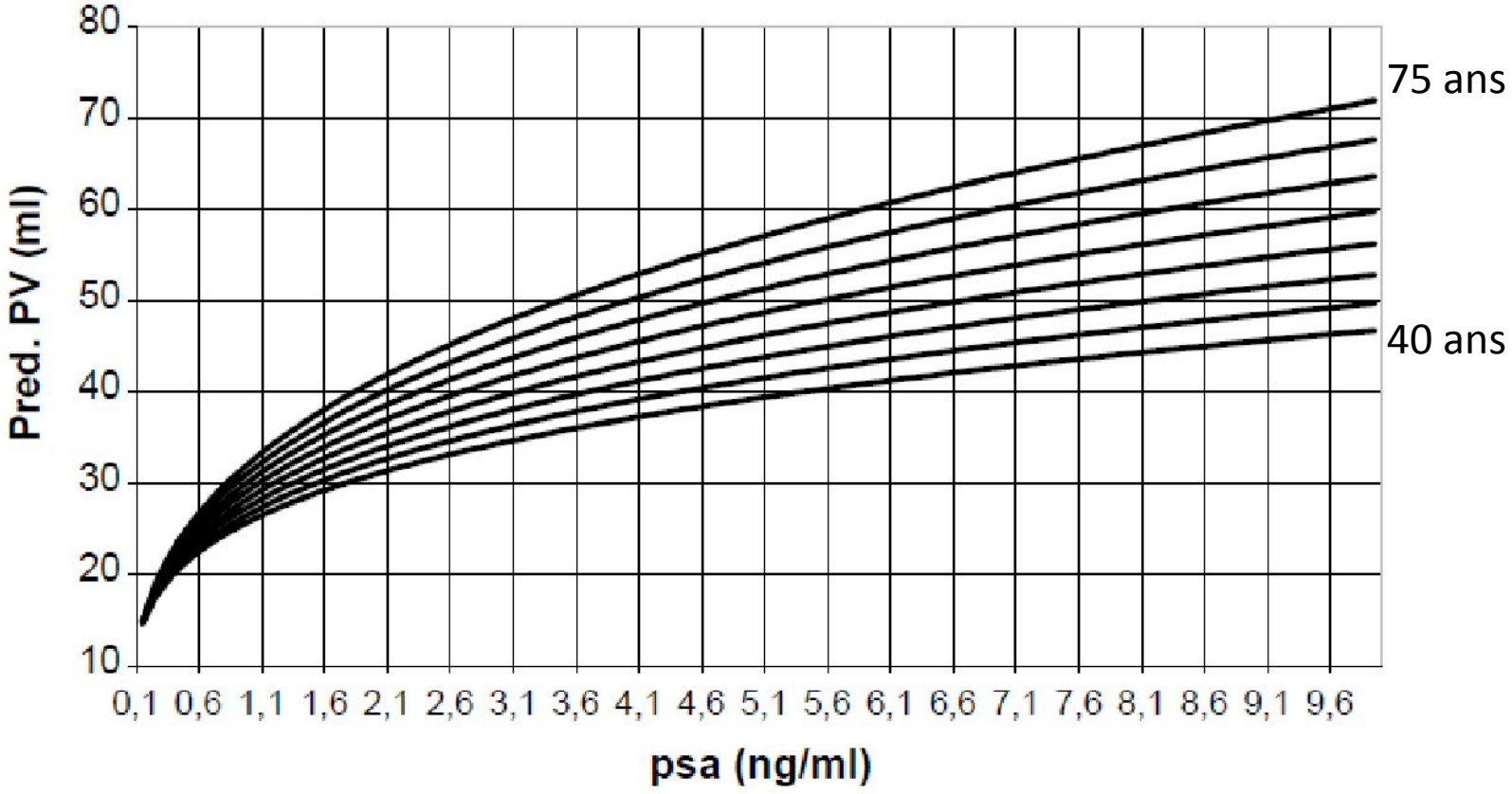
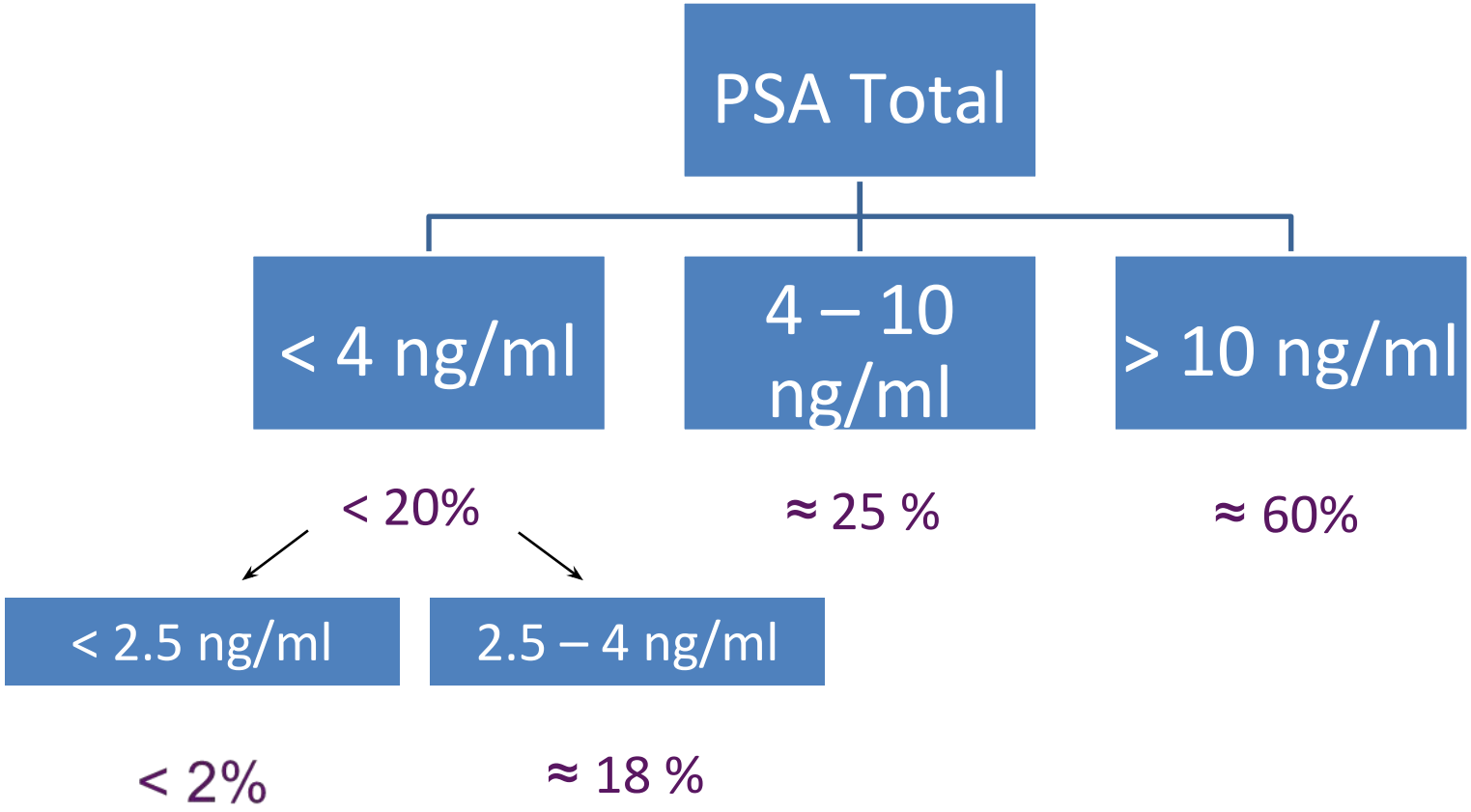


Fig. 1. Nomogram of estimated PV as a function of serum PSA value at 5 years interval, beginning at 40+ years (the lowest curve) and ending at the 75+ years line (the highest curve).

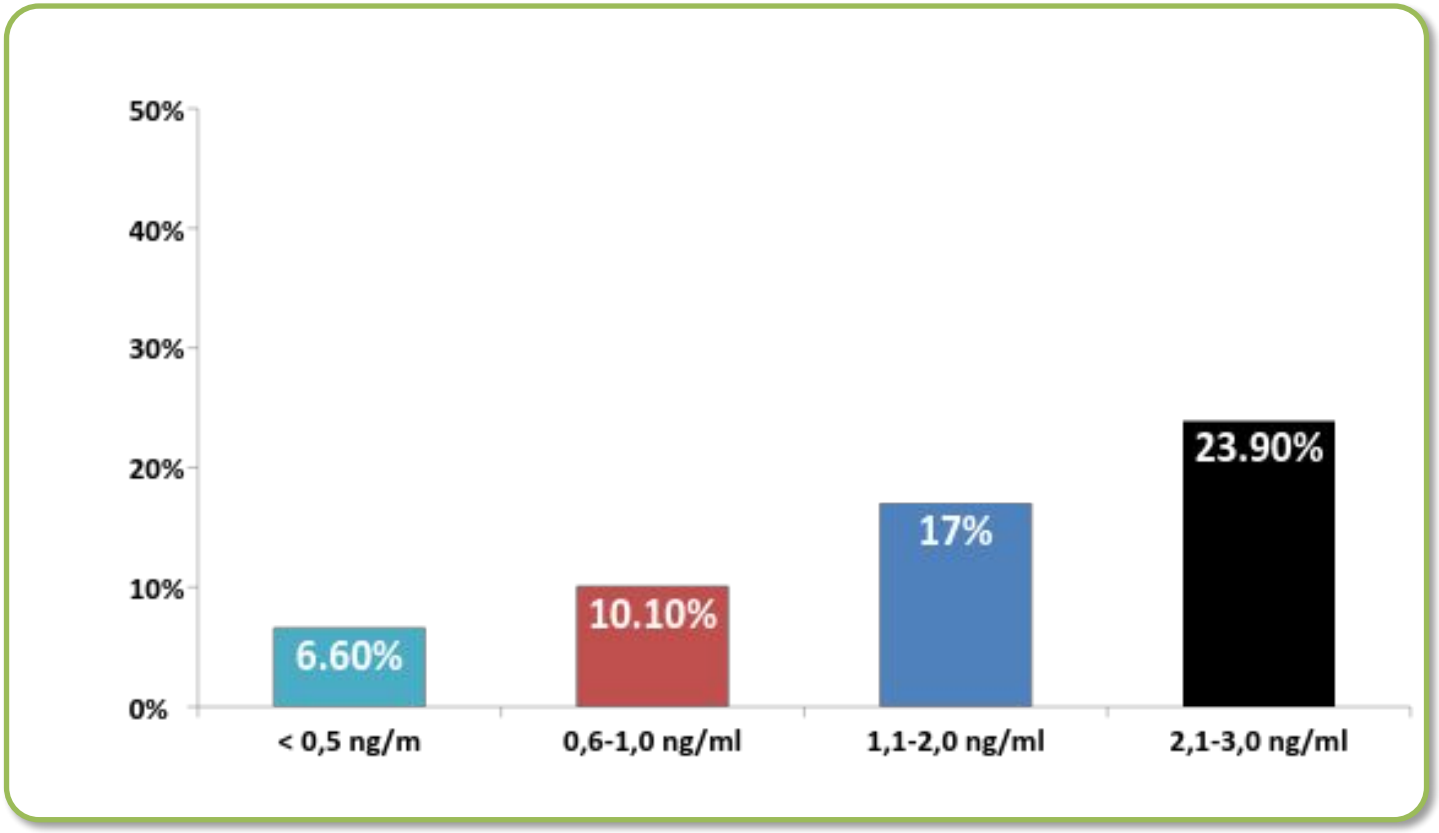
Mochtar CA. Eur Urol 2003

Probabilité de cancer de la prostate en fonction du taux de PSA total



Gretzer M. Cambell-Walsh 9th ed p2899

Risque de cancer de la prostate sur des biopsies systématiques chez des patients ayant un taux de PSA < 3,0 ng/ml



Prostate Cancer Prevention Trial: Thomson IM. NEJM 2004

Recommandations de l'Association française d'urologie

L'AFU recommande de :

– proposer une détection individualisée précoce du cancer de la prostate après information objective des hommes à partir de 50 ans sur les enjeux de la démarche ;
– ne pas sous-traiter l'homme porteur d'un cancer de la prostate agressif, donc diagnostiquer à temps pour traiter à temps ;
– éviter le « surdiagnostic » et le « surtraitement » des formes d'évolution plus lente.

Cette démarche repose sur :

– l'information du patient pour obtenir une décision éclairée ;
– la recherche de facteurs de risque ;
– l'examen clinique (toucher rectal) ;
– le dosage du PSA, à proposer plus précocement en cas de facteurs de risque ;
– la biopsie prostatique (si nécessaire).

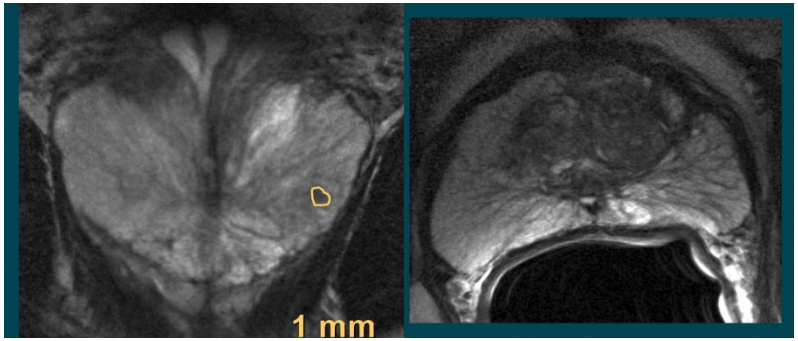
PSA élevé: que faire?

- 1er dosage de sa vie ou dosage inhabituellement élevé sans signe évocateur de prostatite:
  - Toucher rectal
    - Anormal: IRM et biopsies (à discuter en fonction de l'âge si >75 ans, et de l'état général)
    - Normal : PSA de contrôle à 3 semaines
- Elévation du PSA confirmée:
  - Homme jeune sans symptôme urinaire: IRM fonctionnelle et biopsies ciblées éventuelles
  - Homme symptomatique avec hypertrophie de la prostate:
    - IRM fonctionnelle et biopsies ciblées éventuelles
    - ou test Dutasteride et biopsies si élévation secondaire du PSA
  - Homme âgé asymptomatique : scintigraphie osseuse et biopsie si lésion secondaire
  - Homme âgé symptomatique (douleurs, hématurie) : biopsie

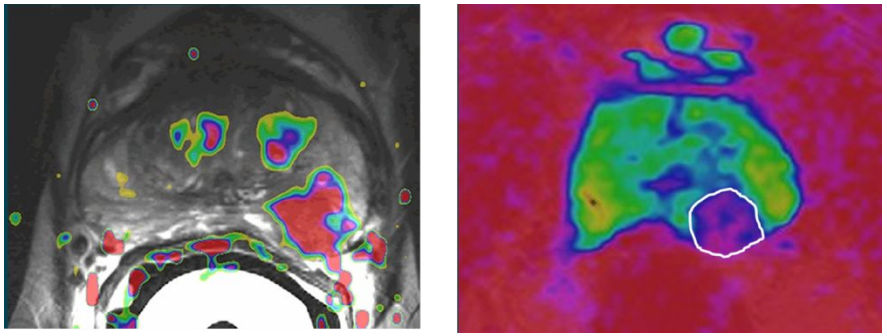
- Patient de 55 ans, 1er PSA de sa vie : 9.30 ng/ml, élévation confirmée à 8.75 ng/ml 4 semaines plus tard
- TR: discrète induration limitée lobe gauche

- Que faites vous?

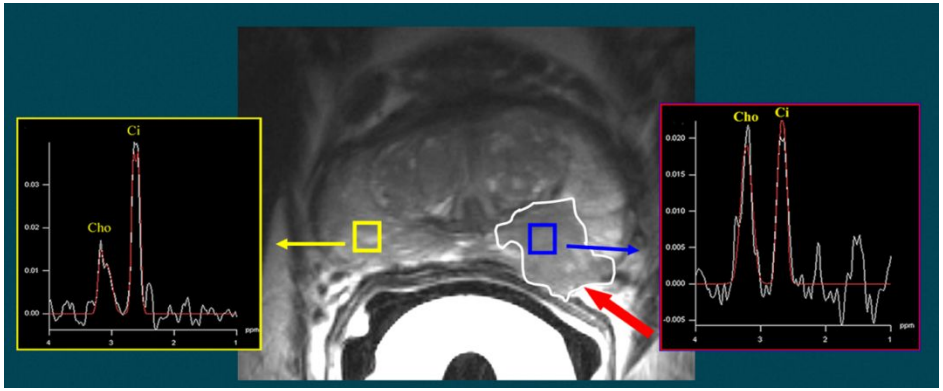
IRM fonctionnelle prostatique



T2



Perfusion : angiogénèse / diffusion: cellularité

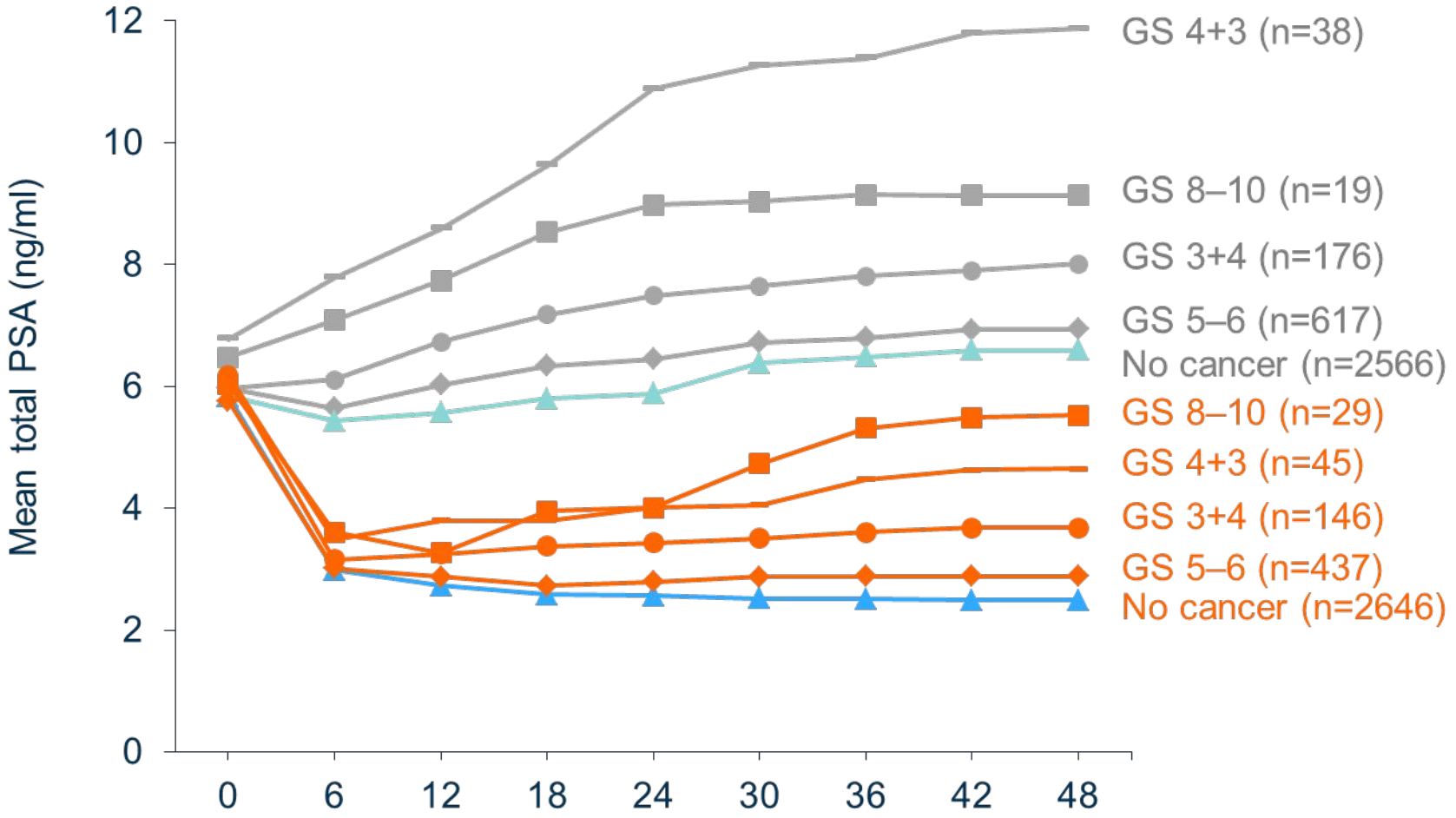


Ratio Choline/Citrate élevé

- Patient de 72 ans, pollakiurie et dysurie malgré un traitement par alfuzosine
- PSA : 7,28 ng/ml vs 7.O2 il y a 6 mois
- TR: HBP 80 g, non suspecte
- ECT: Prostate périphérique homogène 85g, vessie RAS, résidu 170 ml

- Que faites vous?

Modifications du taux de PSA induites par les 5ARI : étude Reduce



Marberger M. BJU int 2012

- Patient de 85 ans bon état général, sans symptôme urinaire ni osseux
- PSA prescrit par son cardiologue: 72 ng/ml vs 12 ng/ml en 2010
- TR induration suspecte prenant tout le lobe droit dans une prostate de 50 g

- Que faites vous?

Faut-il utiliser les autres tests du PSA?

- Rapport PSA libre/PSA total
- Densité du PSA (ng/ml ^{2})
- Vélocité et temps de doublement du PSA
- proPSA et BPSA
- Prostate Health Index (phi) = (proPSA/FPSA)x$\sqrt{TPSA}$

→ Non si l'IRM est bien interprétée

Rapport PSA libre/PSA total pour un taux de PSA total entre 4 et 10 ng/ml

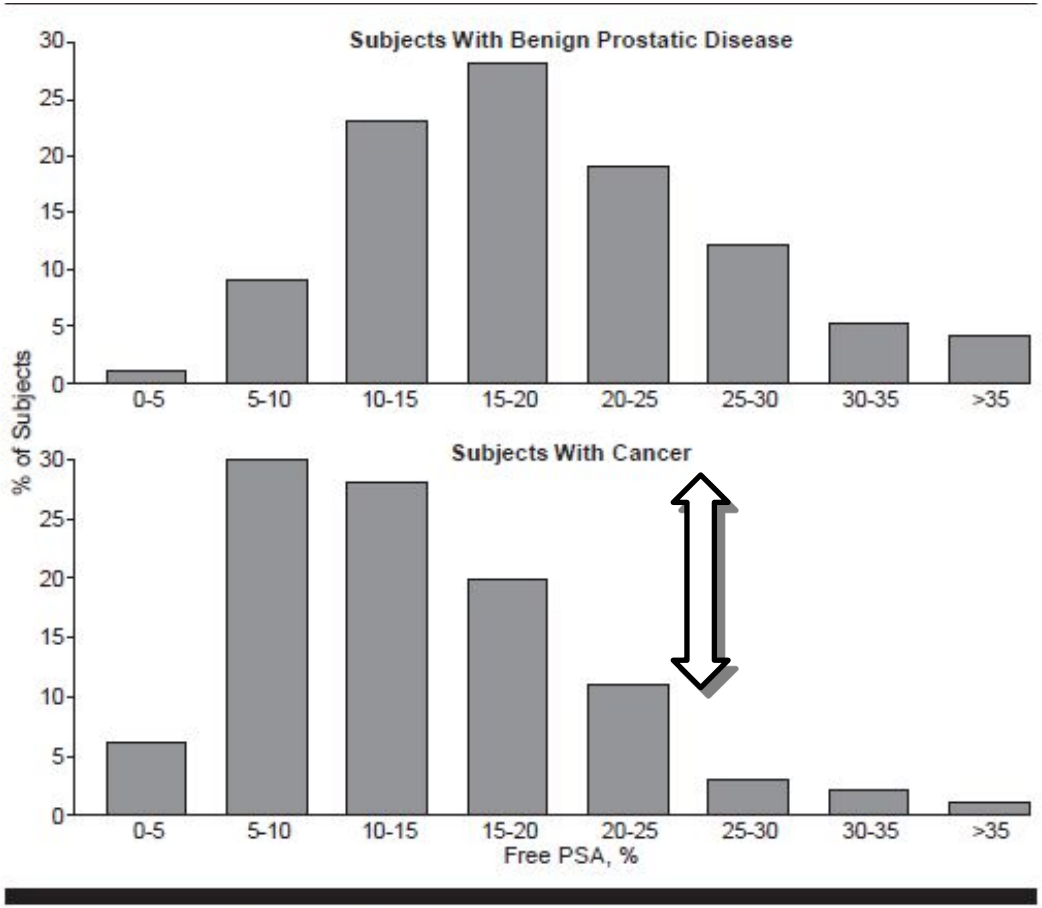
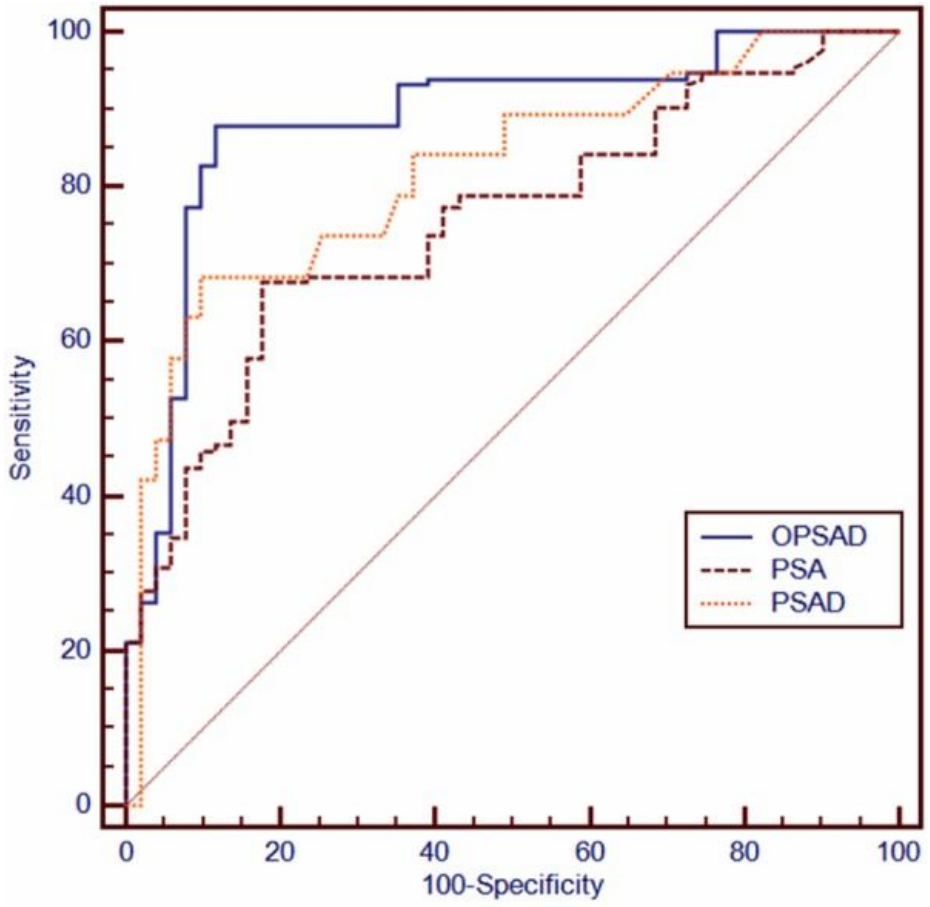


Figure 1.—Distribution of percentage of free prostate-specific antigen (PSA) by diagnosis.

- Un rapport inférieur à 25% est lié à un risque plus élevé de cancer avec un odd ratio de 3.2

Catalona WJ. JAMA 1998

Densité du PSA = PSA/volume de la prostate (ng/ml^2)



- Dans cette étude un cut-off de 0.69 ng/ml^2 pour la zone périphérique donne une sensibilité de 94.7% et une spécificité de 88.2%...

Zhang HM. Int J Clin Exp Pathol 2014

Vélocité et temps de doublement du PSA

	High risk	Other	*p* value
(a)			
PSAV (ng/ml per year)			
Median	2.1	0.07	
Mean (SD)	10.2 (26.9)	0.15 (0.62)	<0.0001
PSA DT (years)			
Median	3.1	9.7	
Mean (SD)	5.7 (13.3)	−7.9 (330.6)	0.303

- Pas d'intérêt du temps de doublement
- Le PSA peut « normalement » s'élever de 0,6 ng/ml/an

Loeb S. Eur Urol 2008

Méta-analyse : Vélocité et temps de doublement peu d'avantage par rapport au PSA seul !

Table 5. Description of Articles Comparing Accuracy of PSA and PSA Dynamic

First Author	No. of Patients	End Point and Cohort	Results	Comment
Eggener[6]	995	Biopsy result in men with initial negative biopsy	Negative predictive value of PSA velocity slightly higher (91% *v* 88%) than PSA	PSA and PSA velocity used as binary predictors would different cut points have given different results?
Djavan[17]	559	Biopsy result	AUC greater for PSA than PSA velocity	Unclear whether AUC for PSA and PSA velocity were calculated on the same patients
Djavan[18]	273	Biopsy result	AUC greater for PSA than PSA velocity	Unclear whether AUC for PSA and PSA velocity were calculated on the same patients
Sun[19]	12,078	Cancer diagnosis in men undergoing PSA screening	AUC greater for PSA than PSA velocity	Verification bias: men not undergoing biopsy assumed to be cancer free
Moul[20]	11,861	Cancer diagnosis in men undergoing PSA screening	AUC greater for PSA than PSA velocity	Verification bias: men not undergoing biopsy assumed to be cancer free
Ciatto[21]	87	Biopsy result in men with initial negative biopsy	AUC higher for PSA velocity than PSA (0.74 *v* 0.67)	Only 13 cases; CIs around AUC likely to be wide
Lynn[22]	158	Biopsy result	AUC greater for PSA than PSA velocity	Short interval between PSA measurements
Ukimura[23]	110	Biopsy result in men with initial negative biopsy	AUC greater for PSA velocity than PSA (values not given)	Specificity of PSA and PSA velocity similar at high sensitivity
Carter[5]	980	Long-term prediction of prostate cancer death from archived blood samples	AUC for PSA velocity slightly greater than for PSA (0.75 *v* 0.74) when PSA values restricted	Only 20 cases; CIs around AUC likely to be wide
Berger[24]	4,800	Cancer diagnosis in men undergoing PSA screening	AUC much greater for PSA velocity than PSA (0.87 *v* 0.65)	Verification bias: men not undergoing biopsy assumed to be cancer free; unclear whether AUC for PSA and PSA velocity were calculated on the same patients
Whittemore[25]	320	Long-term prediction of prostate cancer death from archived blood samples	AUC greater for PSA than change in PSA	All samples within 7 years of diagnosis
Barak[26]	147	Biopsy result	PSA velocity had slightly lower sensitivity but much higher specificity than PSA	PSA and PSA velocity used as binary predictors would different cut points have given different results?
Loeb[16]	6,844	Cancer diagnosis in men undergoing PSA screening	AUC slightly greater for a model that included both PSA velocity and PSA compared with a model that included PSA alone (0.83 *v* 0.81)	Verification bias: men not undergoing biopsy assumed to be cancer free
Thompson[15]	5,519	Biopsy in men participating in the Prostate Cancer Prevention Trial	PSA dynamics did not improve prediction	High-quality data from a randomized trial

Vickers AJ. J Clin Oncol 2009

proPSA : « promising results » …

Table 3 Summary of studies evaluating the role of [-2]proPSA in prostate cancer.

Reference	Year	PSA range, ng/mL	Number of patients	Methods	Main findings
Sokoll et al. [33]	2008	0.48–33.18	123	Retrospective, multicentre analysis of sera obtained from men prospectively enrolled in the EDRN study who underwent TRUS-guided biopsy	%[-2]proPSA was the best predictor of prostate cancer detection compared with %fPSA.
Stephan et al. [35]	2009	0.26–28.4	586	Retrospective, ANN analysis of sera obtained from men undergoing TRUS-guided biopsy	Incorporation of %[-2]proPSA into an ANN and logistic regression model enhanced the diagnostic accuracy to differentiate between malignant and non-malignant prostatic diseases.
Sokoll et al. [34]	2010	0.29–310.6	566	Retrospective, multicentre analysis of sera obtained from men prospectively enrolled in the EDRN study who underwent TRUS-guided biopsy	%[-2]proPSA performed significantly better than %fPSA in PSA level range of 2 to 4 ng/mL. %[-2]proPSA was also noted to increase with increasing Gleason score and in aggressive cancers.
Rhodes et al. [36]	2012	<8.8	443	Retrospective analysis of sera obtained from men enrolled in a population based study (OCS)	Men subsequently diagnosed with prostate cancer had more than twice the rate of increase in [-2]proPSA levels compared with those men without prostate cancer.
Rhodes et al. [37]	2012	0.5–1.8*	748	Retrospective analysis of sera obtained from men enrolled in two population based studies (OCS and FMHS)	Baseline [-2]proPSA levels were slightly higher in Black men compared with White men (median 6.3 vs 5.6 pg/mL). Men with higher baseline [-2]proPSA were at an almost eight-fold increased risk of developing subsequent prostate cancer.

Hori S. BJU Int 2013

proPSA/BPSA…

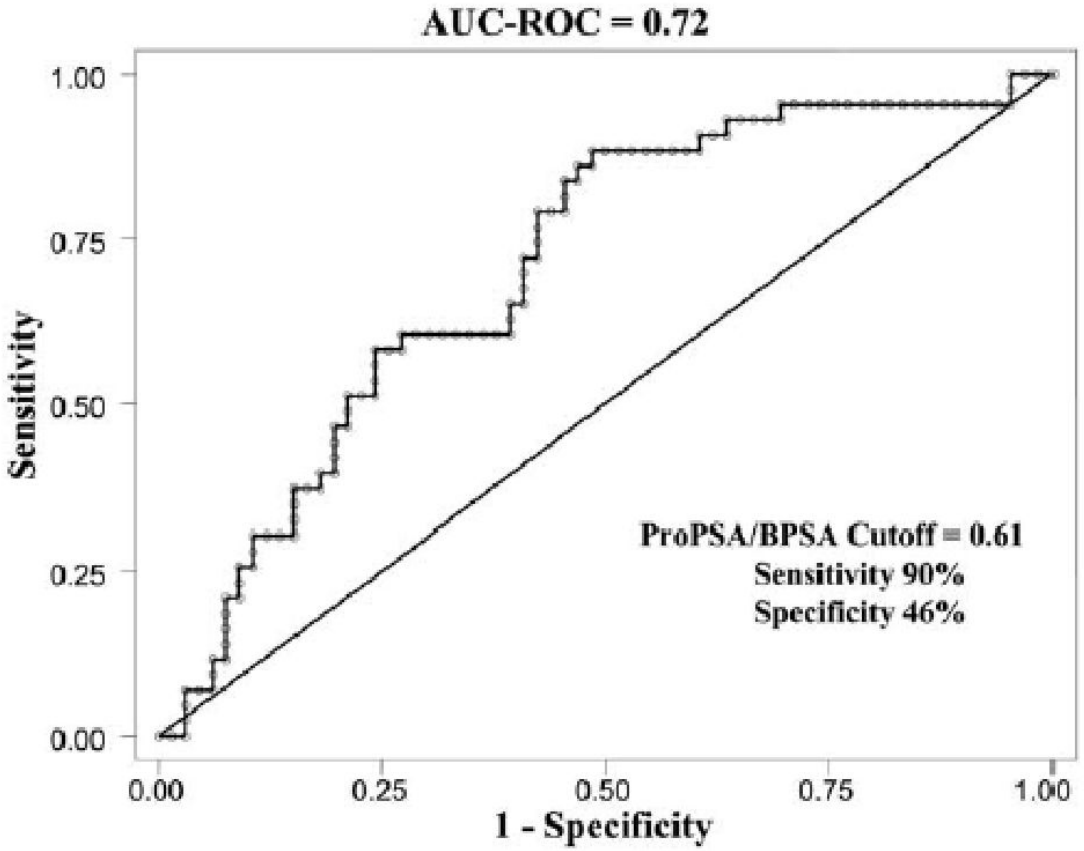
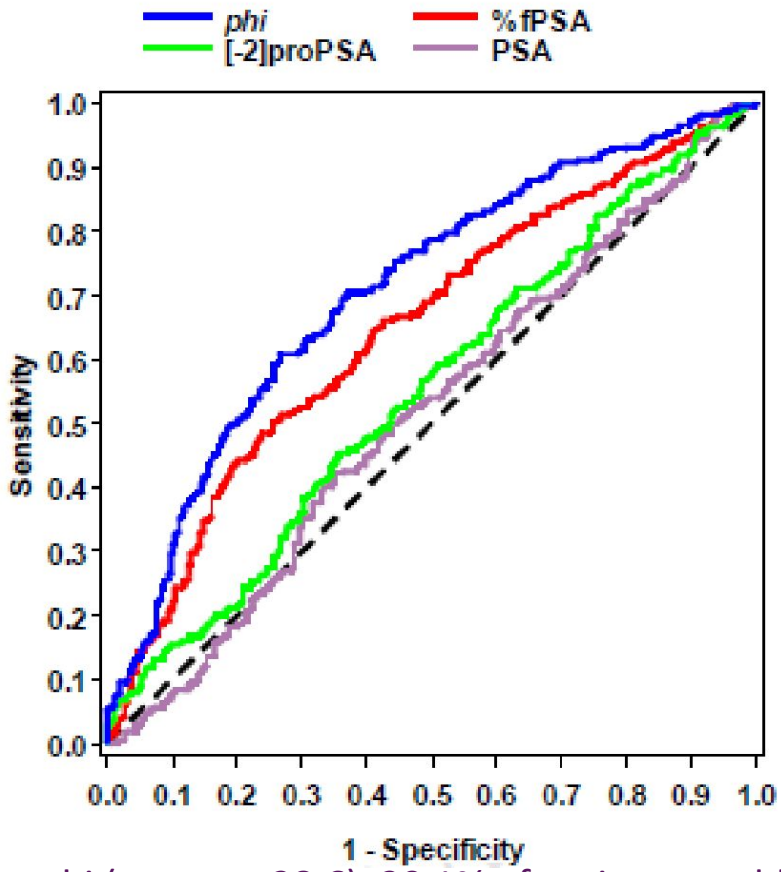


FIGURE 1. *ROC curve for ability of proPSA/BPSA to detect prostate cancer in 161 men with percent free PSA less than 15%.*

Khan MA. Urology 2004

Prostate Health Index (phi) (proPSA/FPSA)x$\sqrt{TPSA}$

- "FDA approval as an aid to early prostate cancer detection for men with PSA levels from 4 to 10 ng/ml."



At the 90% sensitivity cutpoint for phi (a score <28.6), 30.1% of patients could have been spared an unnecessary biopsy for benign disease or "insignificant" prostate cancer compared to 21.7% using %fPSA.

Loeb S. J Urol 2014

Faut-il utiliser les autres tests du PSA?

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→ Non si l'IRM est bien interprétée

Un taux de PSA initial peut prédire le risque de cancer à long terme

- Seuil à 0.7 ng/ml ? (Loeb S. Urology 2006)
  - 1178 hommes entre 40 et 50 ans
  - 14.6 fois plus de cancer pour PSA entre 0.7 et 2.5 vs <0.7 ng/ml

- Seuil à 0.5 ng/ml ? (Lilja H. J Clin Oncol 2007)
  - 21277 hommes de moins de 53 ans
  - Suivi médian de 18 ans
  - 462 cancers diagnostiqués