ARTICLE ORIGINAL

PSA, digital rectal examination and the indication of prostate biopsy

PSA, toucher rectal et indication de la biopsie prostatique

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Abstract

Background: Despite it is an invasive procedure with a limited detection efficiency, prostate biopsies remain the "gold standard" for prostate cancer diagnosis. Digital rectal examination (DRE) and prostate specific antigen (PSA) may be helpful to better indicate the biopsy.
Objective: We studied the contribution of Digital rectal examination, prostate specific antigen and their combination with the indication of the biopsy.

Patients and methods: Our retrospective study included 122 patients aged between 52 and 95 years who underwent between 2010 and 2012, prostate biopsy because they presented clinical signs of prostate disease, a suspect Digital rectal examination (DRE+) and/or a total prostate specific antigen (tPSA)≥4 ng/ml.
Outcome measurements and statistical analysis: Every patient underwent a transrectal ultrasound-guided 12-core prostate biopsy. Total prostate specific antigen was analyzed by microparticle enzyme immunoassay technique.

Results: Only 69 of the 122 biopsies (56.55%) were positive. Digital rectal examination is more effective in predicting positive biopsy results with fewer false negatives than that of total prostate specific antigen. The combination between Digital rectal examination and total prostate specific antigen improves the biopsy efficiency but does not reduce false negatives. Prostate biopsies were negative in four cases with (DRE-) and Total prostate specific antigen<4 ng/ml.

Conclusion: Digital rectal examination and prostate specific antigen could, in some cases, limit the indication for prostate biopsy.

Key words: biopsy; digital rectal examination; prostate cancer; prostate specific antigen

Résumé

But : La biopsie prostatique qui est une procédure invasive, demeure le « gold standard » pour poser le diagnostic d'un cancer de la prostate. Le toucher rectal (TR) et l'antigène spécifique de la prostate (PSA) peuvent être utiles pour mieux indiquer la biopsie. Nous avons étudié l'apport du toucher rectal, de l'antigène spécifique de la prostate et de leur combinaison sur l'indication de la biopsie.

Patients et méthodes : Notre étude rétrospective compte 122 patients âgés de 52 à 95 ans ayant bénéficié d'une biopsie prostatique pour leur présentation de signes cliniques évocateurs d'une pathologie prostatique, d'un toucher rectal suspect (TR+) et/ou d'un antigène spécifique de la prostate total (PSAT) ≥ 4 ng/ml. Analyse statistique : Chaque patient avait subi une biopsie prostatique écho-guidée transrectale à 12 prélèvements. L'antigène spécifique de la prostate total a été dosé par technique immunoenzymatique microparticulaire.

Résultats: uniquement 69 biopsies sur les 122 (56.55%) se sont avérées positives. le toucher rectal est plus efficace dans la prédiction des résultats positifs de la biopsie avec un taux de faux négatifs moindre que celui des valeurs seuil 4 et 10 ng/ml de l'antigène spécifique de la prostate total. La combinaison entre toucher rectal et l'antigène spécifique de la prostate total améliore l'efficacité de la biopsie mais ne diminue pas les faux négatifs. Les biopsies étaient négatives et s'avéraient inutiles chez quatre patients ayant TR(-) et l'antigène spécifique de la prostate total < 4 ng/ml.

Conclusion : Ainsi le toucher rectal et le dosage de l'antigène spécifique de la prostate pourraient dans certaines situations limiter l'indication de biopsie prostatique.

Mots clés : *Biopsie ; Toucher rectal ; Cancer de la prostate; Antigène spécifique de la prostate*

INTRODUCTION

Prostate cancer is the fourth most common cancer in both sexes combined and the second most common cancer among men. An estimated 1.1 million men worldwide were diagnosed with prostate cancer in 2012, accounting for 15% of the cancers diagnosed in men, with almost 70% of the cases (759,000) occurring in more developed regions [1]. The diagnosis is based on a triad of digital rectal examination (DRE), biological analysis of the prostate specific antigen (PSA) and the anatomopathological examination of prostate biopsies which remains the "gold standard" for diagnosis of prostate cancer and also for its stratification [2].

Because it is the easiest to practice without any side effects, DRE is the first test to be used in the typical cases of prostate cancer. The DRE detected an irregular painless nodule with hard consistency which can distort the prostatic lobe (3).

However, DRE has some limitations since it depends on the practitioner's skill and on the fact that only the posterior and lateral portions of the prostate could be palpated [3].

Many blood and tissue diagnostic biomarkers of prostate cancer have been reported as: kallikrein 2 [4], insulin growth factor binding protein 3[5], prostate cancer antigen 3[6]. However, the PSA remains the most widely used tumor marker in the diagnosis of cancer prostate and PSA and DRE remain the main tests mentioned in the main international recommendations for prostate cancer screening.

The limits of sensitivity and specificity of these two tests are that they are not reliable enough for mass screening or even less to make the diagnosis of prostate cancer [7]. However, they can be useful to streamline the indication of prostate biopsy, which despite its technological evolution, remains invasive.

We conducted a retrospective study involving a group of patients who all underwent a prostate biopsy because of a strong suspicion of prostate cancer. Our object is to study the contribution of the PSA, the DRE and their contribution with the prostate biopsy indication

MATERIAL AND METHODS

Patients

In our retrospective study (from January till May 2012), we consulted the register of anatomopathological examinations from which we selected 122 cases of prostate biopsies. All patients had been referred by the urology department of Sahloul university hospital (Sousse, Tunisia) for presenting pronounced prostatic disease clinical signs (dysuria with pollakiuria especially at night), and for having an abnormal DRE or a total PSA (tPSA) superior or equal to 4 ng/ml. Four of the 122 selected patients underwent a prostate biopsy despite normal DRE and tPSA <4 ng / ml.

We considered only the results of tPSA analyzed before any medical or surgical intervention on the prostate problem.

DRE

DRE was practiced by an urologist. It was considered abnormal (DRE+) when faced with a firm or a hard consistency of the prostate or the presence of the stony nodules. In contrast, DRE was considered normal (DRE -).

PSA analysis

Serum PSA analysis was performed in the clinical biochemistry laboratory of Sahloul University Hospital (Sousse, Tunisia). tPSA was analyzed by microparticle enzyme immunoassay technique (MEIA) on the Axsym autoanalyzer (Abbott).

Prostate biopsy

Every patient underwent 12 biopsies after a 48-hour intake of antibiotic prophylaxis. Biopsies were performed by a transrectal ultrasound probe system with a detachable needle holder and with needles using an automatic "Biopsy Gun" (18G). Sagittal plane was chosen to track the path of the needle.

Statistic analysis

Positive and negative predictive values, sensitivities and specificities were determined for the 4 and 10 tPSA thresholds, for the DRE as well as for their combination. The chi-squared test and the odds ratio were performed by the SPSS (v16.0) software. The significance level was set at 0.05.

RESULTS

Population's characteristics

The characteristics of our population are summarized in Table 1.

The patient's ages range from 52 to 95 years old with a mean of 72.36 ± 8.04. Subjects with prostate cancer are older (73.6 ± 7.74 vs 70.75 ± 8.21 years old, p = 0.053) and exhibit a significantly higher tPSA [25.21 (0.58 - 3057) vs 12.08 (0.40 to 114) ng/ml, p <10-3]

Distribution of the prostate pathologies depending on age

We noted a significant difference in the distribution of prostate diseases on the basis of age
(p = 0.016) with a predominance of prostate adenoma

Table 1 : Population characteristics

Characteristics	Size of the study population (n=122)
Age	
52 – 59 years	5,73%
60 – 69 years	29,50%
70 – 79 years	46,72%
80 – 89 years	15,57%
90 – 95 years	2,45%
Anatomopathological results	
Prostate cancer	69 (56,56%)
Prostate adenoma	45 (36,88%)
Prostatitis	1 (0,82%)
Prostatitis + Prostate adenoma	3 (2,46%)
Non specific prostate chronic inflammation	3 (2,46%)
Absence of prostate pathologies	1 (0,82%)

among subjects aged between 50 and 59 years old (71.42%) while in elderly patients older than 60 years, the prostate cancer predominates to reach a frequency of 79% among subjects aged between 80 and 89 years old.

Role of DRE and PSA in assessing the efficiency of prostate biopsy

We considered prostate biopsy as positive when it shows a prostate cancer and negative when it shows a normal prostate or a prostate pathology other than prostate cancer. The results are summarized in Table No2.

We noted that in four patients who had (DRE-) and a tPSA less than 4 ng / mL, the biopsy was negative whereas for 11 patients who had (DRE-) and a tPSA less than 10 ng / ml, three individuals had a positive biopsy.

Diagnostic performance of PSA and DRE in the detection of prostate cancer

Table No3 summarizes the performance of DRE and of the two threshold values 4 and

10 ng/ml of the tPSA considered separately or in combination with the DRE.

For DRE and the two tPSA thresholds values of 4 and 10 ng/ml, considered separately, DRE is the most specific for the detection of the prostate cancer (61.11 vs 12.96 vs 37.04%) and has the highest positive and negative predictive values. However it is less sensitive than tPSA threshold value of 4 ng / ml (88.24 vs95.59 %). We noted that the combination of DRE with tPSA improves specificity but decreases sensitivity.

DISCUSSION

Although the imaging systems such as the magnetic resonance imaging (MRI) and more particularly the shear wave elastography appear to be promising in the diagnosis of prostate cancer [8, 9], they are not commonly used. This is not the case of the DRE and the PSA we were interested in, so we studied their contribution in streamlining the indication of prostate biopsy which remains the "gold standard" in prostate cancer diagnosis. Among the 122 biopsies of our study, only 69 (56.55%) were positive diagnosing a prostate cancer and 53 were negative (43.44%) diagnosing a normal prostate or the presence of prostate diseases other than prostate cancer

Table 2 : Results of the prostate biopsies in function of the DRE and the tPSA levels

	Results of the prostate biopsies		Chi square, p	Odds ratio, limits
	Biopsy (+) N (%)	**Biopsy (-) N (%)**		
(DRE +) (N=81)	60 (74.07)	21(25.92)	30.10 , p<10-3	10,15 (4,16 – 24,76)
- tPSA (ng/ml)				
≥4 ng/ml (N=112)	66 (58.9)	46(41.1)	3.127, p=0,077	3,34 (0,82 – 13,62)
≥ 10 ng/ml (N=92)	59 (64.13)	33(35.86)	8.733, p=0,003	3,57 (1,49 – 8,57)
-DRE and tPSA (ng/ml)	57 (76)	18(24)	29.952, p<10-3	9,23 (3,97 – 21,45)
(DRE+) +t PSA≥4 ng/ml (N=75)	53 (85.83)	9(14.52)	42.933, p<10-3	16,19 (6,52 – 40,20)
(DRE+) +tPSA≥10 ng/ml (N=62)				

DRE : digital rectal examination, tPSA : total prostate specific antigen

Table 3 : Performance of the DRE and the tPSA in prostate cancer diagnosis

	Sensitivity (%)	Specificity (%)	Negative predictive value (%)	Positive predictive value (%)	False positive cases (%)	False negative cases (%)
(DRE +) (N=81)	86.96	60.38	78.05	74.07	25.93	21.95
tPSA ≥4 ng/ml (N=112)	95.65	13.21	70	58.93	41.07	30
tPSA ≥ 10 ng/ml (N=92)	85.51	37.74	66.67	64.13	35.87	33.33
(DRE +) + tPSA≥4 ng/ml (N=75)	82.61	66.04	74.47	76	24	25.53
(DRE +) + tPSA≥10 ng/ml (N=62)	76.81	83.02	73.33	85.48	14.52	26.67

DRE: digital rectal examination, tPSA : total prostate specific antigen

(prostatic adenoma, prostatitis, non specific chronic inflammation) which may reflect the improper indication of this invasive procedure.
Chang et al had reported 44% of positive biopsies in 273 patients suspected of having prostate cancer and presenting abnormal DRE and/or a tPSA higher or equal to 4 ng/ml [10].
We noted that 74.07% of patients with (DRE +) had a positive biopsy so they were 10.15 times more likely to have prostate cancer ((4.16 - 24.76), p <10-3).

We noted that positive biopsies were about 58.55% of 111 patients with tPSA ≥4 ng/ml and about 64.13% of the 92 patients with the tPSA ≥10ng/ml. Thus DRE is more effective in predicting positive results for prostate biopsy with a false negative rate less than that threshold values 4 and 10 ng / mL of tPSA (21.95% vs 30% vs 33.33%).
These findings are consistent with the measure of performance of DRE and tPSA in the diagnosis of prostate cancer which revealed a better specificity of DRE than both tPSA threshold values 4 and 10 ng / ml (61.11 vs 12.96 vs 37.04), and a better negative (80.49 vs 70 vs 66.67) and positive (74.07 vs 58.04 vs 63.04) predictive values than tPSA. However, we noted that the threshold value of 4 ng / ml of tPSA, had better sensitivity for prostate cancer diagnosis than the threshold value of 10 ng / ml and than the DRE (95.59 vs 85.29 vs 88.24).

DRE is an important tool in the diagnosis of prostate cancer (3) in spite of some limitations due to the fact that some prostate cancers cause only very small changes in the prostate gland that cannot be detected by DRE. DRE palpates the posterior aspect of the prostate gland adjacent to the rectum while the anteriorly located part as well as median lobe of the prostate cannot be palpated during a DRE; so normal DRE does not completely exclude a prostate cancer (3). The literature reports variable DRE sensitivities between 45% and 82% and variable PPV ranges between 24 and 67% (10,11,12). We think that such variability in DRE performance is mainly due to the variability in knowledge and skills of the practitioner since DRE remains a subjective examination that requires training (3).
PSA is a specific organ tumor marker and could be elevated at any prostatic pathology. Its circulating level is influenced by the mass of the prostatic tissue and is elevated if membrane permeability of prostate cells is altered [11].

Hoffman et al reported that the threshold value of 4 ng/ml of the tPSA, gave a sensitivity of 86% and a specificity of 33%. The positive predictive value was about 41% and the negative predictive value about 81%.
The consideration of the threshold value of 10 ng/ml reduces the sensitivity to 38% and increases the specificity to 84%.
Moreover, the performance of tPSA in prostate cancer diagnosis depends on age. There is a gradual increase in sensitivity and a gradual decrease in specificity of tPSA depending on age [12].
The combination of the DRE and the tPSA improves the efficiency of the prostate biopsy indication. However, it does not decrease the false negative cases. Among the 75 patients with (DRE +) and tPSA≥4 ng / ml, 57 (76%) had positive biopsy, so they were 9.23 times more likely to have prostate cancer ([3.97 to 21.45], p <10-3). Among the 62 patients with (DRE +) and tPSA≥10 ng / ml, 53 (85.83%) had a positive biopsy so they were 16.19 times more likely to have prostate cancer ([6.52 to 40.20], p <10-3).

Improvements in the indication of the prostate biopsy efficiency could be explained by the improved specificity and positive predictive value that provides the combination of the DRE and the tPSA compared to the DRE and the tPSA considered separately. However, sensitivity has not been improved which may explain the rather high persistence of false negative results on biopsy.
In some cases, an indication of prostate biopsy is unnecessary. Indeed four of our patients having normal DRE and a tPSA less than 4 ng / ml, had a negative biopsy.
Therefore, the indication for prostate biopsy would be reviewed to avoid, as much as possible, an invasive procedure which is not well tolerated by the patient.
However, a study with a larger population size is needed to confirm such results since Catalona WJ et al reported in a cohort study of 368 men with all normal DRE and a tPSA less than 4 ng/ml, 54 cases (14.67%) of prostate cancers confirmed by biopsy [13].

CONCLUSION

We found that the combination of DRE with tPSA improves the efficiency of prostate biopsy. We also noted that biopsies were negative in patients with normal DRE and a tPSA less than 4 ng/ml. In such cases we only suggest the tPSA as a follow up test.
Thus DRE and PSA could in certain cases limit the indication of prostate biopsy.

RÉFÉRENCES BIBLIOGRAPHIQUES

1. Prostate Cancer. Estimated Incidence, Mortality and Prevalence Worldwide in 2012. http://globocan.iarc.fr/old/FactSheets/cancers/prostate-new.asp ;(accessed on 02/04/2018).
2. Nafie S, Mellon JK, Dormer JP, Khan MA. The role of transperineal template prostate biopsies in prostate cancer diagnosis in biopsy naïve men with PSA less than 20 ng ml-1. Prostate Cancer Prostatic Dis. 2014; 17:170-73.
3. Ojewola RW, Jeje EA, Tijani KH, Ogunjimi MA, Anunobi CC. Clinico-pathological Correlation of Digital Rectal Examination Findings Amongst Nigerian Men with Prostatic Diseases: A Prospective Study of 236 Cases. Niger J Surg 2013; 19: 26–31.
4. Partin AW, Catalonac WJ, Finlayd JA, Darte C, Tindall DJ, Young CYet al. Use of human glandular kallikrein 2 for the detection of prostate cancer: preliminary analysis. Urology 1999; 54: 839–45.
5. Prager AJ, Peng CR, Lita E, McNally D, Kaushal A, Sproull M et al. Urinary aHGF, IGFBP3 and OPN as diagnostic and prognostic biomarkers for prostate cancer. Biomark Med 2013; 7:831-41.
6. Hessels D, Schalken JA. The use of PCA3 in the diagnosis of prostate cancer. Nat Rev Urol. 2009; 6: 255.
7. Mistry K, Cable G. Meta-Analysis of Prostate-Specific Antigen and Digital Rectal Examination as Screening Tests for Prostate Carcinoma. J Am Board Fam Pract 2003;16:95–101
8. Correas J, Khairoune A, Audenet F, Timsit M, Mejean A, Helenon O. IRM multiparamétrique et élastographie ultra sonore par ondes de cisaillement dans le diagnostic du cancer de prostate : performances relatives. Prog Urol 2014 ;(24) : 814-15.
9. Di Campli E, Delli Pizzi A, Seccia B, Cianci R, d'Annibale M, Colasante A et al. Diagnostic accuracy of biparametric vs multiparametric MRI in clinically significant prostate cancer: Comparison between readers with different experience. Eur J Radiol. 2018: (101): 17-23
10. Chang JJ, Shinohara K, Bhargava V, Presti JC Jr. Prospective evaluation of lateral biopsies of the peripheral zone for prostate cancer detection. J Urol 1998; 160: 2111-14.
11. Oesterling JE. Prostate specific antigen: a critical assessment of the most useful tumor marker for adenocar cinoma of the prostate. J Urol. 1991; 145: 907-23.
12. Hoffman RM, Gilliland FD, Adams-Cameron M, Hunt WC, Key CR. Prostate-specific antigen testing accuracy in community practice. BMC Fam Pract. 2002; 3:19-26. .
13. Catalona WJ, Partin AW, Finlay JA, Chan DW, Rittenhouse HG, Wolfert RL et al. Use of percentage of free prostate-specific antigen to identify men at high risk of prostate cancer when PSA levels are 2.51 to 4 ng/mL and digital rectal examination is not suspicious for prostate cancer: an alternative model. Urology. 1999; 54: 220–24.