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Utility and Diagnostic Performance of the Free PSA / Total PSA Ratio: Results of a North African Population

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Original Research Article

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Abstract: Prostate cancer became a major public health problem on the threshold of the third millennium. The trilogy rectal touch, PSA-iso forms and biopsy is the pillar of the diagnostic approach and a pragmatic reflection. This is a retrospective study including the analysis of the medical records of 1053 patients admitted between 2000 and 2015. The inclusion criterion is a rate of PSA-T between 4 and 10 ng / ml which corresponds to 783 patients (74.3%) constituting two groups, one of 253 (prostate cancer), the other of 530 (adenomas = control group). The aim of our study is to evaluate the interest of the PSAL / T ratio in the North African population. The median age of patients was 63 years, 70.3% were symptomatic. The median PSA-T is 6.9ng / ml with a PSAL / T ratio ranging from 7% to 32% with an average of 19%. The mean prostatic volume is 57 cm3. 32, 3% with prostate cancer. The sensitivity and specificity of the PSA L / T ratio according to the cut-offs were studied at the time of diagnosis of prostate cancer and the value of 17% was retained with the best compromise between specificity (68%) and sensitivity (57%). A PSAL / T ratio <15% is the best detection rate for prostate cancer (52%). The contribution of the PSA-L / PSA-T report is indisputable since the first contact with the patient in consultation; the results in the Maghreb are comparable to those found in the literature. This iso PSA form reduces many unnecessary biopsies when it is greater than 25%.
Key words: Prostate cancer, free PSA / total PSA ratio, North African population.

INTRODUCTION

Since the advent of PSA and the trivialization of its prescription, the analytical and descriptive epidemiology of prostate cancer has been disrupted: a 26% reduction in mortality, an increase in localized forms early 21 to 83% between the early 1990s and 2012 [1, 2].

The rectal examination trilogy, PSA and biopsy is the mainstay of the diagnostic approach and a pragmatic reflection endless, especially for PSA between 4 and 10 ng / ml, (3.4) for this range (4-10ng / ml): the positive biopsy rate for cancer is 20.5 to 31.2%, by race and ethnicity; it is easy to denote that 70 to 80% of biopsies will be negative and may be abusive.(5.6) It therefore becomes lawful and logical to develop further isoforms of PSA (PSA-f / PSA-T report), PSA density, PSA Velocity, PSA Dt) to select citizens in whom the risk of cancer is imminent and spare, with an improper biopsy gesture; others in whom the probability of cancer is derisory.

The purpose of our statistical and analytical work is to evaluate the diagnostic and prognostic contribution of the PSA - f / PSA - T ratio; in the light of the literature data. Indeed the question arose if the interpretation of the results of this report is equally valid for the African population (in this case the Maghreb population).

MATERIALS AND METHODS

This is a retrospective study including patients admitted to our institution for the treatment of benign hypertrophy or prostate cancer, between 2000 and 2015 for duration of 15 years. The analysis of the medical files of 1053 cases was carried out at the level of the urology department of the Mohammed V military training hospital in Rabat (Morocco). This analysis focused on the clinical (digital rectal examination) and para-clinical profiles (PSA-T, PSA-f, PSA-f/PSA-T ratio, abdominopelvic ultrasound and, finally, anatomopathological biopsies and operative parts).

For ethical reasons and to avoid unnecessary inconvenience for patients, only those whose PSA-T is greater than or equal to 4 ng / mL with or without abnormality during digital rectal examination (RE) or ultrasound, have benefited from a prostatic biopsy puncture. In this study, the patients selected were those with a PSA level of between 4 and 10 ng / ml, which

corresponds to 783 patients (74.3% of the cases), it was necessary to exclude incomplete files (lack of the PSA Let's report PSA-f / PSA-T, anatomopathological findings ...).

Finally, 783 files were selected for analysis and only patients with prostate histology from 12 echo-guided biopsy cores, trans-urethral resection of the prostate or adenomectomy were retained. All of these patients constitute two groups, one of 253 with adenocarcinoma of the prostate, the other of 530 with benign prostatic hypertrophy (control group).

The purpose of our study was to evaluate, in the Maghreb population, the interest of the assay of PSA-T, PSA-f and PSA-f / PSA-T ratio in the diagnosis of prostate cancer.

Dosage techniques: PSA is a protease produced by normal prostate epithelial cells. It is specific for prostate tissue and not for prostate cancer. The sera were stored serologically at -70 ° C. Assays were performed with PSA-RIACT® kits for total PSA and PSA-f RIACT® for free PSA from CIS-BIO International. These immunoradiometric techniques use two monoclonal antibodies with equimolar recognition of free PSA and alpha-1-antichymotrypsin-related PSA. The limit of detection of total PSA is 0.03 ng / ml with a normal lower than 4 ng / ml. The limit of detection of free PSA is 0.02 ng / ml.

STATISTICAL REMINDERS

Sensitivity is the frequency with which the test is positive in sick subjects (Sensitivity = true positives / patients).

Specificity is the frequency with which the test is negative in healthy subjects (with benign prostatic hypertrophy (BPH) or other non-prostatic disease). (Specificity = true negatives / healthy subjects)

RESULTS

In our population, the age of the patients varies between 49 and 77 years with a median of 63 years, and 70.3% of our patients were symptomatic. Table 1 summarizes the clinical characteristics of the patients included in our study.

The concentration of total PSA is between 4.1 and 10 ng / ml with a median of 6.9 ng / ml. The free PSA ratio on PSAt varies between 7% and 32% with an average of 19%. The prostatic volume varies between 27cm3 and 86cm3 with an average of 57cm3.

After PB, 253 patients had prostate adenocarcinoma 32.3%, 126 with a Gleason score of 6 (3 + 3) or 49.8%, 73 patient with a Gleason score 7 (3 + 4) or 28.8 %, 49 patients with Gleason score 7 (4 + 3) or 19.3% and 5 patients with Gleason score 8 or 2%.

253 radical prostatectomies were performed.

Graph 1: Distribution of prostate cancer by Gleason score.

Table 2: Accuracy of the PSA-f / PSA-T ratio according to cut-offs at the time of prostate cancer diagnosis

Graph 2: Prostate cancer rate as a function of the PSA-f / PSA-t ratio

Table 3: Pathological findings in the prostate cancer group

Table-1: The clinical characteristics of the patients included in the study

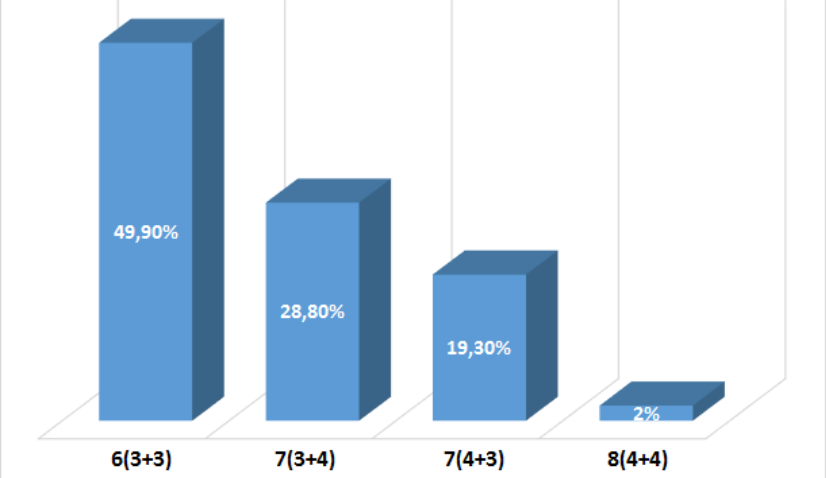
	Prostate Cancer (n=253)	BPH (control group n=530)
Age (years) Average + / - DS	49-77 63+ /- 7, 8	56-77 66,5+ /- 10
Rectal examination	83,2% Not Suspect 17 ,8% Suspect	90,4% S 9,6% S
Age group (years) <50 50_60 60_70 70_77	2 cas (0,2%) 391 cas (50,3%) 216cas (27,5%) 172cas (21,9%)	
Symptomatology(%) Obstructive syndrome irritative Syndrome Mixed syndrome	45,6% 34,1% 20,3%	

Table-2: Accuracy of the PSA-L / PSA-T ratio according to cut-offs at the time of prostate cancer diagnosis

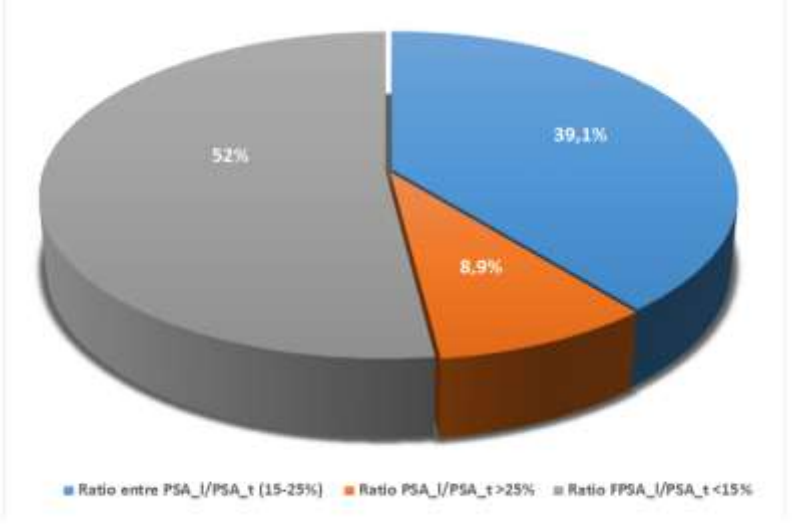
CUT-OFF valuePSA-L(%)	Specificity(%)	Sensibility(%)
14	32	7
17	68	57
20	71	42
23	82	27
26	86	12

Table-3: Pathological findings in the prostate cancer group

PSA-f /PSA-t ratio	PT3a	Gleason Score >7
<15%	62%	69%
15_25%	27%	23
>25	11%	8%



Graph-1: Distribution of prostate cancer by Gleason score



Graph-2: Prostate cancer rates by free PSA / PSA-t ratio

DISCUSSION

The early diagnosis of cancer at a curable stage is an important issue for the patient's prognosis of healing. The markers of a cancerous tissue, when they exist, represent the first signs detected during tumor growth; unfortunately, these markers lack specificity and / or sensitivity.

For early detection of prostate cancer, PSA is a first-line examination with digital rectal examination.

In France, mass screening is not recommended [7], but in recent years, PSA testing has tended to be part of an individual screening approach for early detection of prostate cancer at a localized stage of the disease being still operable.

PSA is a marker with good clinical performance, nevertheless if it is specific for organ and not specific for cancer, because benign pathologies (benign prostatic hypertrophy [BPH], prostatitis) and malignant of prostate are responsible for elevating the PSA.

Recently, the dosage of circulating forms of PSA can bring a gain in specificity with PSA-f or complexed PSA (PSAC) or pro-PSA.

A more global approach combining clinical data (age, digital rectal examination, prostate ultrasound size calculated in grams) and biological results (PSAT, PSA-f ratio / PSA-T), allows to calculate a risk of cancer rather than to consider each element individually in absolute value compared to a reference threshold.

The value of 4 ng / mL of total PSA is conventionally used; however, it has been proposed to adjust this threshold according to age (lowered threshold for men under 50 and increased for men over 70). A high PSA assay results in an indication of biopsies. The choice of biopsy prescription threshold for diagnosing cancer remains problematic and controversial for learned societies (UAE, AUA, AFU). The usual value of 4 ng / mL is still the unanimous threshold for most prostate biopsy recommendations. The free PSA assay and the PSA-f / T% ratio (or PSA complexed to calculate PSA-f) are optional: f / T ratio lower in the presence of cancer than BPH. A ratio greater than 25% would unnecessary avoid biopsies. Many authors, showed the existence of confined prostate cancer for low PSA values included between 2 and 4 mg / L.(08-09)

The PSA level is correlated with the probability of a presence of prostate cancer: 09 to 13% for the 2 to 4 ng / mL and 23 to 28% for the 4 to 10 ng / mL. If the decision threshold is lowered from 4 to 2 ng/mL, the number of biopsies induced would be multiplied by three. Yet, the majority of biopsies made because of a high PSA are remains negative and need to be repeated. It seems appropriate to improve the specificity of PSA for the detection of prostate cancer so as not to generate requests for unnecessary and abusive biopsies. The use of the proportion of free PSA allows a better discrimination between BPH and cancer in the gray zone of 2 to 10 ng / mL of total PSA, because the ratio f / T is higher (or the ratio complexed / total C / T is lower) for benign prostatic hypertrophy, while the f / T ratio is lower (or the C / T ratio is higher) for cancer [10].

The associated use of PSA f/T ratio versus PSA-T for a series of 4560 patients followed at Cochin hospital including 1950 HBP, 1380 prostate cancers, 910 healthy volunteers, 130 prostatitis and 190 other urogenital cancers (kidney, bladder, penis, testis) allows to distinguish on the diagram zones favoring sensitivity (PSAT threshold at 4 ng /mL and f / T ratio at 25%) or specificity (PSA T threshold at 6 ng /mL and f-ratio at 10%) for the detection of prostate cancer, this being comparable to the results of our study (see Table 2).

The use of nomograms such as the Partin et al tables has been widely advocated to assess the likelihood of latent or confined prostate cancer [11].

An algorithm for prostate cancer risk calculation based on the principle of artificial neural networks associating clinical data (age, rectal examination, ultrasound volume of the prostate) and biological (total PSA, free PSA ratio / total PSA in percentage) has been developed and validated by several multicentric studies[12].

Given Front to a high result of total PSA in a first screening assay, it is possible to implement a kinetic study at short notice, or to use a prostate cancer risk calculation algorithm that combines clinical data in addition to the conventional free PSA ratio determination on total PSA, allowing for early detection of more reliable prostate cancer while avoiding to generate anxiousness for the patient and unnecessary biopsy prescriptions.

Many studies have shown that the PSA-f / T ratio is lower in subjects with prostate cancer. Catalona et al published a major study on the role of this PSA f /T report.(13) This study, conducted in seven institutions, evaluated male subjects who were free from cancer and had a total PSA between 4 and 10 ng/ ml. A ratio of less than 25% has a sensitivity of 95% with a 20% improvement in specificity over PSA-T. Djavan et al. presented an exhaustive review of the results concerning different limit values of the PSA f / T report. They demonstrated that this report is the main predictive factor of cancer on the first biopsy and successive biopsies when the volume of the prostate is less than 40 cm3[14,15].

The same authors have determined that PSA-f /T limit values of 10 to 20% detect 33 to 46% of prostate cancers in subjects with PSA-T between 4 and 10 ng / ml.

In an identical group of subjects with PSA-T between 2.1 and 4.0 ng / ml, Scadina *et al*. have shown that a PSA-f / T ratio between 0.1 and 0.15 can be used to diagnose all large tumors, not limited to the prostate, in the advanced phase, and 30% of apparently insignificant tumors [16].

There is, however, a problem with the PSA-f / T ratio because of the limited stability of PSA-f in vitro, particularly in serum. This requires a very precise manipulation of the sample, with serum / plasma separation of the blood cells during the few hours following the sampling; otherwise, the specimen should be frozen (if possible at -70 ° C for long-term preservation) for optimal analysis [17].

The probability of finding a prostate cancer is 17% and 32% when PSA-T is respectively 4 and 10 ng/ml. However, in this range the probability of prostate cancer is only 2% to 5% when the PSA f / T ratio is 35% while the probability is 39% 60% when it is 7%. This is true in our study, so at a certain value of PSA-T, changes in the PSA f / T ratio can cause more than 6 times the difference in the risk of prostate cancer. Moreover, when PSA-T is 3 ng / ml, that is to say "normal", the probability of prostate cancer is greater than 17% when the PSA f / T ratio is less than 10%[18].

The strengths that emerge from our statistical study and in light of the literature are:

- The results of a North African population are comparable to those found in the literature.
- The decision to perform a prostate biopsy or to eliminate this aggressive attitude depends on a pragmatic reflection; inspired by the statistical data of the guidelines, according to the probability of existence or not of a cancer.
- The statistical risk is difficult to convert in almost certainty in a Lambda citizen.
- The rate of free and / or total PSA is influenced by a myriad of factors: ethnicity, race; age, the subclinical histological events that are experienced by the prostate over the decades (endogenesis and phylogeny of the male and the gland), density; the kinetics and velocity of this marker.
- All the factors studied in our retrospective work must be compiled and arranged with the promising factors, in a near future, to limit the number of fake positives and fake negatives induced by PSA and its isoforms. These future prospects are: the PCA3; the TMPR gene SS2; the MRI spectro, and the PIRADS score.

The limits of the study:

- This is about a retrospective study.
- A study spread over a critical period in terms of urological and oncological recommendations with a lot of changes with the advent of newer diagnostic markers and better prognostics such as the Pro PSA, the index PHI, PCA3 ... all these markers have more specificity, sensitivity, positive and negative predictive values, and better area under the ROC curve compared to free PSA.

CONCLUSION

The contribution of the PSA-f / PSA-T ratio is certainly unavoidable since the first contact with the patient in consultation, to be able to speak a rational language (statistical and understandable).

The results of a North African population are comparable to those found in the literature.

This PSA isoform reduces a lot of unnecessary biopsy; when it is greater than 25%; on the other hand it authorizes us to persevere on the patients whose report is inferior 15% in spite of a first series of negative biopsy, it authorizes us to repeat this puncture -biopsy after 3 to 6 months of waiting.

PSA-f / PSA-T ratio; PSA density; PSA velocity, PCA3 and fusion genes, aims to optimize the early detection of a cancer potentially 100% curable and prevent abusive biopsies in citizens all of whom biochemical indices above are rather at reassuring rates.

The ultimate goal is to take advantage of biomolecular, biophysical and surgical advances to further improve the prognosis of this disease.

REFERENCES

1. Roy, C. (2005). Cancer de la prostate: forme commune Feuillets de Radiologie, 2005, 45, n 5, 323-344© Masson.
2. Cheng, L., Sebo, T. J., Slezak, J., Pisansky, T. M., Bergstralh, E. J., Neumann, R. M., ... & Bostwick, D. G. (1998). Predictors of survival for prostate carcinoma patients treated with salvage radical prostatectomy after radiation therapy. *Cancer*, *83*(10), 2164-2171.
3. Celhay, O., De La Taille, A., Salomon, L., Doré, B., Abbou, C. C., & Irani, J. (2007). PSA "en dents de scie" et PSA "en escalier": quelles implications pronostiques?. *Progrès en Urologie*, *17*(5), 943-946.
4. McNeal, J. E. (1968). Regional morphology and pathology of the prostate. *American journal of clinical pathology*, *49*(3), 347-357.
5. Hermabessière, J., & Taillandier, J. (1993). Physiologie de la prostate. Encycl Med Chir.
6. Lemaitre, L., Delebarre, A., Villers, A., & Puech, P. (2007). echographie et imagerie par résonance magnétique de la prostate normale. *Radiodiagnostic–Urologie Gynécologie*, 34-420.
7. Graham, A. J., Gelfand, G., McFadden, S. D., & Grondin, S. C. (2004). Levels of evidence and grades of recommendations in general thoracic surgery. *Canadian journal of surgery*, *47*(6), 461.
8. Catalona, W. J., Smith, D. S., & Ornstein, D. K. (1997). Prostate cancer detection in men with

serum PSA concentrations of 2.6 to 4.0 ng/mL and benign prostate examination: enhancement of specificity with free PSA measurements. *Jama*, *277*(18), 1452-1455.

9. Catalona, W. J., Ramos, C. G., Carvalhal, G. F., & Yan, Y. (2000). Lowering PSA cutoffs to enhance detection of curable prostate cancer.
10. Catalona, W. J., Smith, D. S., Wolfert, R. L., Wang, T. J., Rittenhouse, H. G., & Ratliff, T. L. (1995). Increased specificity of PSA screening through measurement of percent free PSA in serum. *J Urol*, *153*(Suppl 4), 312A.
11. Partin, A. W., Kattan, M. W., Subong, E. N., Walsh, P. C., Wojno, K. J., Oesterling, J. E., ... & Pearson, J. D. (1997). Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer: a multi-institutional update. *Jama*, *277*(18), 1445-1451.
12. Stephan, C., Xu, C., Cammann, H., Graefen, M., Haese, A., Huland, H., ... & Wildhagen, M. F. (2007). Assay-specific artificial neural networks for five different PSA assays and populations with PSA 2–10 ng/ml in 4,480 men. *World journal of urology*, *25*(1), 95-103.
13. Catalona, W. J., Partin, A. W., Finlay, J. A., Chan, D. W., Rittenhouse, H. G., Wolfert, R. L., & Woodrum, D. L. (1999). 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*, *54*(2), 220-224.
14. Djavan, B., Zlotta, A., Kratzik, C., Remzi, M., Seitz, C., Schulman, C. C., & Marberger, M. (1999). PSA, PSA density, PSA density of transition zone, free/total PSA ratio, and PSA velocity for early detection of prostate cancer in men with serum PSA 2.5 to 4.0 ng/mL. *Urology*, *54*(3), 517-522.
15. Catalona, W. J., Partin, A. W., Slawin, K. M., Brawer, M. K., Flanigan, R. C., Patel, A., ... & Subong, E. N. (1998). Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. *Jama*, *279*(19), 1542-1547.
16. Piironen, T., Pettersson, K., Suonpää, M., Stenman, U. H., Oesterling, J. E., Lövgren, T., & Lilja, H. (1996). In vitro stability of free prostate-specific antigen (PSA) and prostate-specific antigen (PSA) complexed to α1-antichymotrypsin in blood samples. *Urology*, *48*(6), 81-87.
17. Stamey, T. A., Yang, N., Hay, A. R., McNeal, J. E., Freiha, F. S., & Redwine, E. (1987). Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *New England Journal of Medicine*, *317*(15), 909-916.
18. Finne, P., Auvinen, A., Aro, J., Juusela, H., Määttänen, L., Rannikko, S., ... & Stenman, U. H. (2002). Estimation of prostate cancer risk on the basis of total and free prostate-specific antigen, prostate volume and digital rectal examination. *European urology*, *41*(6), 619-627.