Cancer Treatment and Research Communications 16 (2018) 59–63

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

journal homepage: www.elsevier.com/locate/ctarc

Clinical evaluation of the iXip index to reduce prostate re-biopsies

Andrea Benedetto Galosi[a], Lucio Dell'Atti[a,*], Alessandro Bertaccini[b], Massimo Gion[c], Simone Francavilla[d], Stefania Ferretti[d], Umberto Maestroni[d], Andrea Gallotta[e], Chiara Parrozzani[e], Laura Paneghetti[e], Giorgio Fassina[e,*]

[a] Institute of Urology, Polytechnic University of Marche Region, University Hospital "Ospedali Riuniti", Via Conca 71, Torrette, Ancona 60126, Italy
[b] Institute of Urology, S. Orsola – Malpighi Hospital, University of Bologna, Bologna, Italy
[c] Regional Center for Diagnostic, Prognostic and Predictive Biomarkers (CRIBT), ULSS 12, Venice, Italy
[d] Urology Unit, Department of Surgery, Parma University Hospital, Parma, Italy
[e] Xeptagen S.p.A., Via delle Industrie 9, Venice Marghera 30175, Italy

ARTICLE INFO

Keywords:
iXip
PSA-IgM
Re-biopsy
Prostate cancer
Diagnosis

ABSTRACT

Background: Prostate biopsy is the gold standard for prostate cancer (PCa) diagnosis, but it's invasive and associated with adverse events. Novel reliable tumor biomarkers and accurate non-invasive tests are required to avoid biopsies. The immune complex PSA-IgM is a new marker for PCa, and it has been included in an algorithm to generate the diagnostic index iXip, which determines the probability of having PCa. In this study we evaluated the ability of iXip to reduce the number of repeat biopsies in patients with a previous negative biopsy and suspicious for PCa.

Patients and methods: 219 patients referred for prostate rebiopsy were included in the study. Each patient underwent a trans-rectal ultrasound-guided prostate biopsy and prostate volume examination. Blood samples were collected before any prostatic manipulation to determine the serological levels of PSA-IgM and PSA. The iXip index was calculated as previously reported using an online calculator.

Results: iXip values in patients with a positive biopsy were significantly higher than the ones observed in negative patients (p-value = 0.001). Based on iXip values, patients were divided in five risk groups: those with iXip < 0.2 had 0% probability of having PCa. High values of the Gleason score (≥7) were observed mostly in patients with iXip 0.3–0.8.

Conclusion: Our preliminary results show that iXip identifies a sub-group of patients who can safely avoid re-biopsy because they do not have PCa. The index is a promising tool that could reduce the number of unnecessary prostate biopsies and the relative clinical complications and expenses.

Introduction

In Europe, prostate cancer (PCa) is the most common tumor among men (excluding skin cancer) [1]. Prostate specific antigen (also known as PSA or human kallikrein-3) remains the first line and most commonly used serum biomarker for the detection of PCa [2].

Prostate biopsy is the gold standard for PCa diagnosis, however it has diagnostic limitations and its invasive nature increases the risk of adverse events [1,2]. PSA is non-specific marker to support the diagnosis of PCa; therefore, many patients undergo unnecessary prostate biopsies when decisions are made based on this biomarker [3].

Multi parametric magnetic resonance imaging (mpMRI) has been proposed as a reliable method to detect prostate tumors; indeed, when compared to TRUS rebiopsy, this technique has a higher detection rate of clinically significant PCa [1]. However, mpMRI results are subjected to inter-observer variability and heterogeneous definitions, and strategies to include it in regular patients follow up are not defined yet [1].

For these reasons, it is necessary to identify a reliable marker for reducing the number of unnecessary biopsies. In this respect, improving the accuracy of non-invasive tests, possibly based on the assessment of novel tumour markers, is mandatory.

The immune complex formed by PSA and immunoglobulins M

Abbreviations: ASAP, atypical small acinar proliferation; AUC, area under the curve; BPH, benign prostatic hyperplasia; DRE, digital rectal examination; HGPIN, high-grade prostatic intra-epithelial neoplasia; mpMRI, multi parametric magnetic resonance imaging; PCa, prostate cancer; PSA, prostate specific antigen; PV, prostate volume; ROC, receiver operator characteristic; TRUS, trans-rectal ultrasound

* Corresponding authors.
E-mail addresses: Lucio.Dellatti@ospedaliriuniti.marche.it (L. Dell'Atti), fassina@xeptagen.com (G. Fassina).

https://doi.org/10.1016/j.ctarc.2018.07.001
Received 7 February 2018; Accepted 10 July 2018

(IgM), PSA-IgM, has been recently reported as a new biomarker for PCa [4,5]. Compared to PSA, serological levels of PSA-IgM have showed a better accuracy for the diagnosis of PCa [5] and have been included in an algorithm to generate the diagnostic index iXip, which determines the probability of having PCa. The algorithm processes the values of PSA and PSA-IgM, age, and prostate volume (PV) of the patient to provide the probability of that patient of having PCa [6,7]. The index was created to reduce the number of negative biopsies and to assist physicians in making a better-informed decision on whether to recommend the exam for the first time in a man suspected of having PCa. Recent clinical data show that iXip is the only procedure that may reduce unnecessary prostate biopsies without losing any case of cancer (100% sensitivity when iXip cut-off value is 0.2) [6,7].

In this study, we evaluated the ability of iXip to reduce the number of repeat biopsies in patients with a previous negative biopsy and suspicious for PCa.

Patients and methods

Patients selection

This was a prospective multicenter observational study of accuracy in PCa diagnosis approved by the Institutional Review Boards for Human Subjects Research. The study was designed, conducted and reported in accordance with the principles of the Declaration of Helsinki and its appendices, and according to the Standards for the Reporting of Diagnostic Accuracy Studies guidelines [8].

Between April 2012 and October 2016, all consecutive patients referred for prostate rebiopsy, and were screened for possible inclusion in the present study. The inclusion criteria were one of the following: elevated PSA levels (>4.00 ng/mL or >2.5 ng/mL for family history), high PSA kinetic (>0.75 ng/mL/year), suspicious digital rectal examination (DRE), uncertain result of trans-rectal ultrasound (TRUS) exam for cancer. The exclusion criteria were: presence of concomitant tumors, autoimmune diseases, active infections, steroid therapy, and immunosuppressive therapy.

Histological diagnosis [PCa, high intra-epithelial neoplasia (HGPIN), atypical small acinar proliferation (ASAP) or benign prostatic hyperplasia (BPH)] was made according to the U.I.C.C. parameters [9]. Biopsies were guided by TRUS and performed with a standardized sampling scheme with at least 12 cores.

DRE was deemed positive if there was nodularity or induration of the prostate or if the examiner judged the prostate to be suspicious for cancer on the basis of other criteria, including asymmetry [10].

Prostate cancers were graded according to the Gleason Score [11] and patients staged according to the T.N.M. – U.I.C.C. Staging System [9].

Prostate volume (PV) of each patient was assessed by TRUS examination. The volume estimation was an ellipsoidal volume calculation: the prostate is considered ellipsoidal in shape and the volume (mL) is 0.523 × width (cm) × height (cm) × length (cm) [12]. The widths and heights were measured on axial planes, and craniocaudal lengths on sagittal planes at their greatest diameter. An Hitachi Digital EUB-5500 US scanner with a 7 MHz probe was used for all examinations.

Measurement of markers concentration

For all patients, serum samples were collected before any prostatic manipulation to avoid possible transient biomarkers variation. All men gave fully informed consent authorizing blood and diagnostic parameters use for research purposes. Serum PSA-IgM concentration was measured in duplicate using Prostate-IC kit (XG007, Xeptagen SpA, Italy). The analysis with Prostate-IC kit was performed on an open and fully automated ELISA analyzer.

PSA levels were determined using Hybritech Access test on UniCel DxI800 (Beckman Coulter).

The iXip index was calculated as reported by Gallotta et al. [6] by using the online calculator available at http://ixip.xeptagen.com/ (login required): the age, prostate volume, PSA, and PSA-IgM levels of the patient were input in the calculator, and the iXip value (from 0 to 1) was provided immediately.

Statistical analyses

SPSS v.16.0.1 (IBM) was used to perform the statistical analyses and to develop the algorithm. For all statistical comparisons, a p-value < 0.05 was accepted as statistically significant. Tumor marker levels and diagnostic parameter values in positive and negative groups were compared using the Wilcoxon rank-sum test (Mann-Whitney two sample statistic) and differences were shown using the Box-Whisker plot. For each marker, receiver operator characteristic (ROC) curves were constructed and the area under the curve (AUC), a method to evaluate the diagnostic performance, was calculated [13].

Sample size and study power

A study power analysis was performed to determine the ideal sample size [14]. The minimum sample size (n) of two groups (negative and positive population) was calculated with the following formula:

$$n = \frac{(Z_{1-\beta} + Z_{\alpha/2})^2 \cdot (SD_1^2 + SD_2^2)}{D^2}$$

where D is the difference between the means of two populations, SD_1 and SD_2 are the standard deviations of negative and positive populations, and $Z_{\alpha/2}$ and $Z_{1-\beta}$ are the standard normal value for significance criterion (α) and for statistical power (1-β), respectively. The minimum sample size of two groups with D, SD_1 and SD_2 obtained from published data [6], $1-\beta = 80\%$ and $\alpha = 5\%$ was 15 patients. Sample size was confirmed with current dataset.

Results

Study population

Two-hundred nineteen male patients were included in the study; all subjects had clinical suspect of prostate cancer and underwent a TRUS-guided prostate rebiopsy with a standardized sampling scheme. The clinical characteristics of the study population are shown in Table 1.

The negative group included 142 subjects (64.8%) with a diagnosis of BPH, inflammation, ASAP or HGPIN (median age: 66, range 45÷85); the positive group included 77 patients (35.2%) diagnosed with prostate cancer at biopsy (median age: 68, range 46–79). ASAP was observed in, respectively, 19 (13.4%) and 4 (5.2%) patients in the negative and positive group, whereas HGPIN was observed in 51 (35.9%) and 20 (26.0%) patients in the negative and positive group, respectively. The distribution of the pathologic Gleason score was as follows: <7 n = 32 (41.6%), equal to 7 n = 16 (20.8%), and >7 n = 25

Table 1
Clinical characteristics of the study population of patients with negative and positive biopsy for PCa.

	Negative	Positive	Total
Patients (%)	142 (64,8%)	77 (35,2%)	219 (100%)
Age median (range)	66 (45÷85)	68 (46÷79)	67 (45÷85)
ASAP (%)	19 (13.4%)	4 (5.2%)	23 (10.5%)
HGPIN (%)	51 (35.9%)	20 (26.0%)	71 (32.4%)
Pathologic Gleason score (%)			
N/A	–	4 (5.2%)	–
<7	–	32 (41.6%)	–
=7	–	16 (20.8%)	–
>7	–	25 (32.5%)	–