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Review

PSA-IgM and iXip in the diagnosis and management of prostate cancer: clinical relevance and future potential. A review.

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Abstract. The Prostate Specific Antigen (PSA) is the first filter in the diagnosis of prostate cancer. Unfortunately, it is organ-specific but not cancer-specific. In addition, some prostate cancers are not clinically-significant and their diagnosis and treatment may lead to overdiagnosis and overtreatment. For these reasons, other markers have been proposed in the last years, such as PCA3 and PHI, but none of these are currently used in the clinical practice on large scale. In the last decade, PSA-IgM and the algorithm iXip have emerged for the diagnosis of prostate cancer and showed to perform well in decreasing the detection of clinically-insignificant prostate cancer and in reducing the number of unnecessary prostate biopsies. This review focuses on data reported in the literature on PSA-IgM and iXip as well as on the future perspectives of their usage in the clinical practice on large scale. (www.actabiomedica.it)

Key words: prostate cancer, PSA-IgM, iXip, active surveillance, immunocomplex

Introduction

It is well known that Prostate Specific Antigen (PSA) is not cancer specific. Although many efforts have been done so far in the field of molecular biology of prostate cancer, there is still a lack of a cancer specific marker.

The Prostate Cancer Antigen 3 (PCA3) is a non-coding mRNA highly expressed in prostate cancer tissue, but it did not show the requirements for validation as a marker for clinically-significant prostate cancer (1,2).

Similarly, the p2PSA and the Beckman Coulter Prostate Health Index (PHI) do not perform well as markers of prostate cancer on large scale. Compared to Gleason score, p2PSA has a sensitivity of 96% and a specificity of 9% for aggressive disease, while PHI has a sensitivity of 90% and a specificity of 17% (3-5).

In addition, one of the much discussed topics in the field of the diagnosis and clinical management of prostate cancer, is how to differentiate clinically-significant and clinically-insignificant prostate cancer. On one side, many indexes are available for predicting limph-node involvement at the time of the diagnosis and for predicting the risk of disease recurrence after definitive therapy as well as after focal therapies (6-8).

However, on the other side, no indexes able to predict the aggressiveness of prostate cancer on the bases of clinical variables have been proposed.

The immunncomplex PSA-IgM and the algorithm iXip, on which this review focuses, may be promising in reducing unnecessary prostate biopsies and potentially selecting those patients who are at risk of clinically-significant prostate cancer.

The rationale of focusing on PSA complexed with Immunoglobulin M (PSA-IgM) in prostate cancer

The research in the field of biomarkers has led to more insight in the existence of immunocomplexes as an emerging typology of markers whose performance

in early stage diagnosis may be comparable with or higher than that of corresponding free biomarkers.

Although immunoglobulins are expressed on the surface of B-lymphocytes in healthy persons, it has been reported that almost all the subclasses of immunoglobulins are expressed by malignant cells of epithelial origin (9).

The immune context characterization is a milestone in many tumors and is a filed of study in urologic tumors, also. Pulmonary metastases from renal cell carcinoma are only a cutting-edge example of the advantages of knowing more about the immune context of tumoral masses. As it is well known, it may lead to accurately predict the effectiveness of immunotherapy (10).

Conversely, the studies on immune-surveillance show that the immune system is able to recognize the precursors of cancer and clear cancer cells before they become clinically evident (11,12).

Even if immunotolerance is often induced towards cancer cell antigens, the presence of tumor cell antigens complexed with immunoglobulin has been demonstrated by many Authors in the last years (11).

In the majority of cases, these complexes are made up of the cancer cell antigen complexed with an IgG. This is what happens, for example, in the case of carcinoembryonic antigen (CEA) (13).

However, not only IgG, but also IgM immunocomplexes, play a role in the tumor-host interaction. Beneduce et al, for example, proposed the Squamous Cell Carcinoma antigen-IgM (SCCA-IgM) complexes as a novel biomarker for hepatocellular carcinoma and poined out their increase in cirrhotic patients who developed hepatocellular carcinoma (14).

Similarly, marker-IgM immunocomplexes have been found in several other neoplastic diseases, such as colorectal and prostate cancer (15).

The clinical relevance of PSA-IgM

Even if many steps forward have been done in the last years, the management of prostate cancer is still controversial.

While in other urologic tumors, the diagnostic process is based on imaging, the case of prostate cancer is still different, as diagnosis is based on histology.

More importantly, we have no diagnostic tool able to distinguish between clinically significant and clinically-insignificant prostate cancer.

Indeed, prostate biopsy is the only way to detect prostate cancer. Although this technique underwent many refinements, thanks to multiparametric MRI and with the concurrent advent of fusion biopsy (16-18), the diagnosis cannot be provided by imaging alone an prostate biopsy remains crucial.

Despite its good tolerability, prostate biopsy still carries the risk of complications ad adverse events, such as infection, urinary retention and hematuria (19).

The use of the immunocomplex PSA-IgM has the potential to reduce the number of repeat biopsy, thus avoiding unnecessary biopsies (20). The predictive index iXip (21), combining PSA-IgM, total PSA, patient's age and prostate volume, has been implemented to reduce the proportion of unnecessary biopsies and to identify the patients with clinically-significant prostate cancer (22).

The performance of PSA-IgM and the iXip algorithm in the prediction of prostate cancer

In 2007, in a series of 50 patients, Beneduce L et al demonstrated the presence of the immonocomplex PSA-IgM in the sera of patients diagnosed with prostate cancer. Particularly, this study compares with prostate cancer and patients with benign prostatic hyperplasia, showing that PSA-IgM levels was significantly elevated in 40% and 12% of patients with prostate cancer and benign prostatic hyperplasia respectively, compared to PSA, which was high in 22% and 29% (15).

This study represents the first evidence of PSA-IgM in patients with a diagnosis of prostate cancer and suggests evidence of PSA-IgM as a marker potentially able to differentiate prostate cancer from benign prostate hyperplasia.

Gallotta A et al in 2013, in order to increase the diagnostic performance of PSA-IgM, proposed a multivariable model including serum biomarkers, like traditional PSA, and diagnostic parameters, such as patient's ages and prostate volume (21).

This study, that was carried out on 160 patients with clinical suspect of prostate cancer undergoing

a trans-rectal ultrasound guided prostate cancer, led to the iXip algorithm, that represents the predictive probability for prostate cancer.

This algorithm increases the diagnostic performance of PSA-IgM and is intended as a second level diagnostic tool in patients who are suspected of prostate cancer or who have already undergone a first prostate bioptic mapping.

However, the accuracy of iXip in predicting prostate cancer at initial biopsy was investigated in a multicenter study carried out by Gallotta A et al in 2017. This study not only validates the diagnostic accuracy of iXip for the detection of prostate cancer but also evaluates the association of iXip with the aggressiveness of prostate cancer at prostate bioptic mapping (20).

This study confirms the correlation between iXip values and prostate cancer aggressiveness, defined as cancer with a Gleason score ≥ 7 on biopsy. The Authors maintain that if we accept to miss the diagnosis of prostate cancer in patients with clinically insignificant prostate cancer, we are able to increase the number of avoidable biopsies to 21,6%.

In this framework, the introduction of iXip in the clinical practice would lead to the reduction of unnecessary prostate biopsies. This means the the iXip may have the utility to contribute to the identification of the patients with clinically significant prostate cancer, thus leading to a decrease of overdiagnosis and potentially overtreatment.

These results are corroborated by Galosi AB et al in 2018, who demonstrated that iXip is able to identify the subgroup of patients that could avoid repeat prostate biopsy as they at minimal risk of being diagnosed with clinically-insignificant prostate cancer, thus avoiding not only overdiagnosis and overtreatment but also potential side effects and complications (23).

Even if there is common agreement about the effectiveness of iXip, some Authors reported that this algorithm is too weak compared to traditional PSA. Particularly, Lombardo L et al in a recent study on 160 patients stated that iXip is no more precise than a flip coin. Although the data reported by these Authors are not in line with the literature, it is the first study including multiparametric MRI in the evaluation of the predictive accuracy of iXip. Data reported in this study suggest a lack of correlation between PIRADS score and iXip (24).

As argued by Antonelli A et al, the PROXIMA study will contribute to better investigate the role of PSA-IgM and iXip algorithm in the diagnosis and the management of prostate cancer (25).

iXip during follow-up and active surveillance

Interestingly, in a study carried out on a small number of patients on active surveillance, Milanese G et al reported that iXip values were significantly higher in upstaged cases. More specifically, in this study iXip performed well as a tool able to predict Gleason score upgrading in low-risk prostate cancer (26). If this results were confirmed by perspective controlled trials, multiparametric MRI and iXip would play a role in active surveillance and would be of help in determining the timing for surgery or other definitive treatment.

Traditionally, MRI does not have a main role in the first approach to urological tumors. However, the refinements in the technique have led to reconsider it as an usefull imaging tool. This has become evident in almost all urologic cancers, including adrenal masses. Recently, this concept was highlighted by d'Amuri FV et al. (27).

Particularly, in prostate cancer surveillance, multiparametric MRI plays a role for a better targeting of the lesion as well as for predicting an increase in cancer aggressiveness, when a higher PI-RADS score is found.

Unfortunately, besides PSA value, imaging alone is still not enough to confirm surveillance or to recommend local treatment. For this reason, the availability of a further index would be largely useful to balance the decision to proceed to an immediate prostate mapping or to counsel the patient for a wait-and-see attitude.

In this view, iXip would be a good candidate to move the balance needle, as it is easy to obtain and cost-effective.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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