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Review

What chance do we have to decrease prostate cancer overdiagnosis and overtreatment? A narrative review

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Summary. In the era of biochemical tests and algorithms, the management of prostate cancer from prevention to treatment is still controversial. The debate is focused on clinically-significant and clinically-insignificant prostate cancer. As it is well known, the diagnostic tools available are not able to distinguish between the two, thus leading to men treated for prostate cancer even if not strictly necessary. Unfortunately, as of today, there is no test available able to predict the clinical aggressiveness of prostate cancer at the time of the diagnosis. However, some indexes, PSA derivatives, immunocomplexes, and diagnostic methods have been proposed. If properly used in the daily clinical practice, these tools may be of support in the decision making process, in the effort to reduce the overdiagnosis and the overtreatment of prostate cancer.For this reason, we believe that a clear knowledge of this tools, indexes and diagnostic methods is of the utmost importance in preventing the morbidities related to unnecessary treatment as weel as preventing the detrimental effect of missing the diagnosis of a clinically significant prostate cancer.This reviews encompasses the most studied tests and diagnostic methods to predict the aggressiveness of prostate cancer, to avoid to miss a diagnosis of clinically significant cancers and to optimize the overall pre-treatment work-up. (www.actabiomedica.it)

Key words: prostate cancer, PSA-IgM, iXip, PCA3, PHI Index, Targeted biopsy

Introduction

The advent of PSA testing more than two decades ago has improved the early detection of prostate cancer, leading to more men being diagnosed and treated.

Interestingly, it is still controversial whether the increased detection and treatment of prostate cancer has led to increased overall survival rates. Data from two long-term screening studies were published in the last few years and reported conflicting results. The Prostate, Lung, Colorectal and Ovarian (PLCO) screening concluded that there is no difference between men who were screened and men who were not (1). On the other hand, the European Randomized Study of Screening for Prostate Cancer found a 20% reduction in the mortality rate in screened men (2).

Actually, many studies have tired to characterize the extent of overdiagnosiss and overtreatment of prostate cancer resulting from prostate cancer screening, with higly variable results. A review of the major studies on overdiagnosis and overtreatment of clinically localized prostate cancer has been published by Loeb S et al (3). According with this review, prostate cancer overdiagnosis ranges from 1.7% to 67%. There are many reasons of such a disparity in the results of the sudies included in this review, all related to the time period of the studies and the features of the undelying populations (e.g. age, comorbities). The definition of overdiagnosis plays a role, also.

However, when a diagnosis of prostate cancer has been made, the major issue is the following decision on treatment, ranging from active surveillance to radi-

cal surgery. The lesson learned from the results of active surveillance protocols shows that not all prostate cancers require active treatment, as not all are life-threatening.

In his editorial on prostate cancer overdiagnosis, Roobol MJ and Schroder F highlight that unfortunetely, as of today, there is no test or combination of test available that can give a yes-or-no answer to the risk of having a life-threatening prostate cancer (4).

Even if there is not a test able to predict if the treatment of a prostate cancer would result in an overtreatment, there are still screening methods, algorythms and diagnostic pathways able to be of help.

Methods of screening for prostate cancer

The European Randomized Study of Screening for Prostate Cancer (ERSPC), with a 30 years follow-up demonstrated that the number needed to treat is decreasing as well as the number needed to screen (6). The results of this study are reported in table 1.

The screening for prostate cancer may be systematic or opportunistic. A comparison of systematic an opportunistic screening suggested overdiagnosis and mortality reduction in the systematic screening group compared to a higher overdiagnosis with a marginal survival benefit in the opportunistic screening regimen (5). Similar results were found in a Cochrane review update (7), indicating that similar to breast and cervical cancer screening, organized screening is more effective than opportunistic in reducing disease-specific mortality.

As Arnsud Godtman R et al report, there are many reasons why opportunistic screening is less effective in achieving the aim of a recuction of mortality, including inappropriate screening density (8) or inappropriate follow-up after a first positive test, screening a people who do not belong to a group of patients who may benefit from screening, due to comorbilities or age.

PSA-IgM and iXiP

It is well known that in healthy persons immunoglobulins are expresseed only on the surface of B-lymphocytes. However, contradictory to this theory, almost all the subclasses of immunoglobulins have been found to be expressed by malignant cells of epithelial origin (9).

In more details, Immunoglobulins M (IgM) are abnormally espressed in liver (10), prostate (11), ovarian (12) and laryngeal (13) cancer. Serological levels of the immunocomplex PSA-IgM is reported to be accurate for the early diagnosis of prostate cancer and have been included in an algorithm to define the iXip, an index able to determine the probability for having prostate cancer (11,14). The output generated by the algorithm is a numerical value ranging from 0 to 100% and directly correlates to the risk of diagnosing a prostate cancer at biopsy.

The algorithm generating the iXip index is based on the value of PSA, the immunocomplex PSA-IgM, prostate volume and patient age. This index was initially created to improve the diagnostic performance of PSA, however it showed to be able to reduce the number of repeat biopsy in patients with a previous negative biopsy and still under suspicion for prostate cancer (11).

The PROXIMA study is a promising ongoing trial. It is a prospective trial whose aim is to demonstrate the ability of iXip to predict the presence of a clinically significant prostate cancer, defined as prostate cancer with a Gleason score > 6.

Prostate Cancer Antigen 3 (PCA3)

The Prostate Cancer Antigen 3 (PCA3) gene, formerly known as DD3, was first identified in 1999 (15). It is non-coding mRNA highly expressed in prostate cancer tissue. In 2003, PC3 mRNA levels showed to be strongly associated with prostate cancer, leading to the development of a urinary assay able to measure this analyte (16).

The PCA3 test is intended for reducing unnecessary biopsies, while maintaining or increasing the detection of prostate cancer.

Kusida Y et al. investigated the expression on PCA3 in lymph node micrometastases. Among the patients with biochemical recurrence, a vast majority showed to be positive to PSA and/or PCA3 if investigated for micrometastases. As lymph node involvement may is known to be an indicator of poor clinical outcome in patients diagnosed with prostate cancer, PCA3 may be supposed to be able to play a role in the identification of clinically significant prostate cancer (17).

However, to our best knowledge, only a few studies addressing PCA3 as a predictor of clinically-significat tumor report data on a long-term period (17,18). In all these study, PCA3 did not achieve the requirements for validation as a marker for intermediate or surrogate outcomes.

Pro-PSA and [-2]pro-PSA

Pro-PSA is a precursor of PSA. One of its isoforms, the [-2]pro-PSA is the more stable form of PSA. It is expressed in the peripheral zone of the prostate and is reported tho have higher levels in the serum of patients diagnosed with prostate cancer (24).

This marker may be considered in patients with high level of PSA in the intent to avoid them to undergo unnecessary biopsies.

In order to improve the performance of PSA and p2PSA to detect prostate cancer and to reduce the number of patients diagnosed with clinically-unsignificant prostate cancer, two other derivatives od p2PSA have been proposed. They are the percentage of p2PSA (%p2PSA) and the Beckman Coulter Prostate Health Index (PHI) (25,26). Compared to the Gleason score, %p2PSA has a sensitivity of 96% and a specificity of 9% for detecting aggressive disease while PHI has a sensitivity of 90% and a specificity of 17% (26).

Multiparametric Magnetic Resonance (mpMR) and targeted biopsy

Targeted biopsy of the prostate following Multiparametric Magnetic Resonance (mpRM) is an alternative to standard transrectal ultrasonography-guided biopsy (TRUS-GB) for prostate cancer detection.

Multiparametric Magnetic Resonance has gained interest in the last few years for its ability in visualising lesions within the prostate, due to its superiority in soft tissue resolution with anatomical zonal delineation that makes it useful in distinguishing indolent from aggressive disease (19). The PROMIS and PRECISION studies confirmed the superiority of mpRM and MR-targeted biopsy to TRUSGB. Also, these studies report the superiority of targeted biopsy in diagnosing clinically-significant prostate cancers (20-21).

The more recent study of van der Leest M et al confirms the "no immediate biopsy approach" after non-suspicious mpMR scans. The MR-pathway compared with the TRUSGB pathway results in an identical detection rate of clinically-significant prostate cancer, with significantly fewer non clinically-significant prostate cancer cases (22).

Conclusion

Despite high prevalence of disease, most prostate tumors are indolent and are unlikely to progress to clinical significance. In addition, every kind of prostate cancer treatment, as well as active surveillance, may lead to comorbidity and complications.

Another crucial point in prostate cancer diagnosis is the prostate biopsy: although it is generally well tolerated, prostate biopsy is an invasive diagnostic tool and is reported to carry side effects and complications.

This study focuses on the methods to reduce overdiagnosis and overtreatment of prostate cancer and may shed more light on the tests and diagnostic tools available.

As a consequence, the proper usage of tests, tools and algorithms able to detect clinically significant prostate tumors may be of help when candidating a patient to treatment, thus achieving the goal of reducing the impact of surgery, radiotherapy, chemoteraphy and other strategy of treatment.

In other words, keeping into account the additional information carried by these tests could give the opportunity to make a more informed, scientific decision with regard to choosing optimal candidates to a specific therapeutic strategy.

Even if an algorithm or an index able to integrate the information given by all these tests and tools has not been reported so far, it is likely that in the next future a comprehensive index for prediction of clinically-significance or aggressiveness of prostate cancer will be available, as already proposed for candidating patients to specific prostate cancer treatments, such as High-Intensity Focused Ultrasound (23) or other therapeutic strategies.

Conflict 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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