The Future of Prostate Cancer Screening

O Futuro do Rastreio do Cancro da Próstata

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An Almost Perfect Tumour Marker – PSA as a Synonym for Screening

Prostate cancer (PC) is one of the most epidemiologically relevant neoplasms, with an estimated worldwide incidence of 1.8 million/year. In Portugal it is the third cause of cancer death.[1]

The measurement of PSA (prostate specific antigen), a highly sensitive marker, was synonymous of PC screening during the 90s. Aided by digital rectal exam, it would become the propellant that increased the incidence of prostate cancer in the end of the millennium. Equally promising was the development and application of therapeutic techniques with curative intent for localized cancer (10-year survival rate for disease ≤cT2 greater than 90%).[2]

Following the CP incidence curve, we inversely observe a sharp drop in mortality.[3] With the increase in detection, the prevalence of the PC now recognized as clinically insignificant – Gleason 3+3 or Grade Group 1 (GG1) – insidiously increased. The knowledge about the natural history of the disease would evolve, and we currently know that approximately 1 in every 3 prostate cancers detected does not pose a threat to patient survival, and does not even deserve active treatment.[4-6]

During the peak of indiscriminate screening, the indication criteria for prostate biopsy and therapeutic decision algorithms erred on the side of overzealousness, in the absence of a solidly predictive tool for establishing pre-biopsy suspicion and prognosis for diseases with less aggressive histology.

The morbidity associated with biopsies (urinary infection and urosepsis), radical prostatectomy (stress urinary incontinence and erectile dysfunction) and radiotherapy (urinary or intestinal dysfunction) have become the subject of immense concern and consequent critical analysis. Even more concerning was the cumulative evidence that much of this therapeutic endeavor was devoid of impact on overall or specific survival. In this concept lies the genesis of the terms overdiagnosis and overtreatment.[4, 6] Therefore, somewhere at the end of the first decade of 2000, sights converged upstream, on the early screening and diagnosis methodology.

The "Controversy" Surrounding Prostate Cancer Screening

The main fallacy surrounding the controversy over the risks of PC screening is based on the lack of knowledge about the

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heterogeneity of the natural history of the disease, assuming that all cancer must be detected and that all cancer detected is worthy of treatment.

Historically, the massive opportunistic screening was applied indiscriminately in the mid 90s, without full knowledge of the extent of its impact. Despite the drop in mortality due to PC, we should not assume a causal link between both phenomena.

The full expression of this rhetoric occurred in 2012, when the US Preventive Services Task Force (USPSTF) published a recommendation against the measurement of PSA,[7] based on some studies today recognized as biased and unacceptably contaminated.

Time would demonstrate the effects of such a measure, especially in the USA, where screening was abruptly suspended. The incidence rate of metastatic disease and specific mortality reached a record increase during the following 5 years.[8] In 2018, the US Task Force retracted its original recommendation, assuming that there may be some benefit in offering screening to individuals between 55 and 70 years of age.

The relevance of PC Screening has gained new strength in the last 3 years, galvanized by "real world data" and trials such as the European Randomized Study of Screening for Prostate Cancer (ERSPC), which, with 21 years of follow-up, attributes to screening a reduction in 29% of mortality due to PC.[9]

Screening beyond PSA and Digital Rectal Exam – "Screening 2.0"

Beyond oversimplifying screening to a PSA test, in the last 15 years it has been recognized the clinical/diagnostic relevance and prognostic value of quantifying PSA Density (PSAD) and the use of imaging studies - multi-parametric prostate magnetic resonance imaging (multi-parametric prostate magnetic resonance imaging - MRI) - which would change the course of diagnosis and decision-making for PC therapy.

With an already established role for staging, MRI high sensitivity to predict clinically significant disease would consolidate its importance in the assessment of suspected diagnosis.

Incorporating these data into clinical practice through routine and standardized methodology was allowed by updating and optimizing risk calculators and predictive nomograms – Fig. 1.

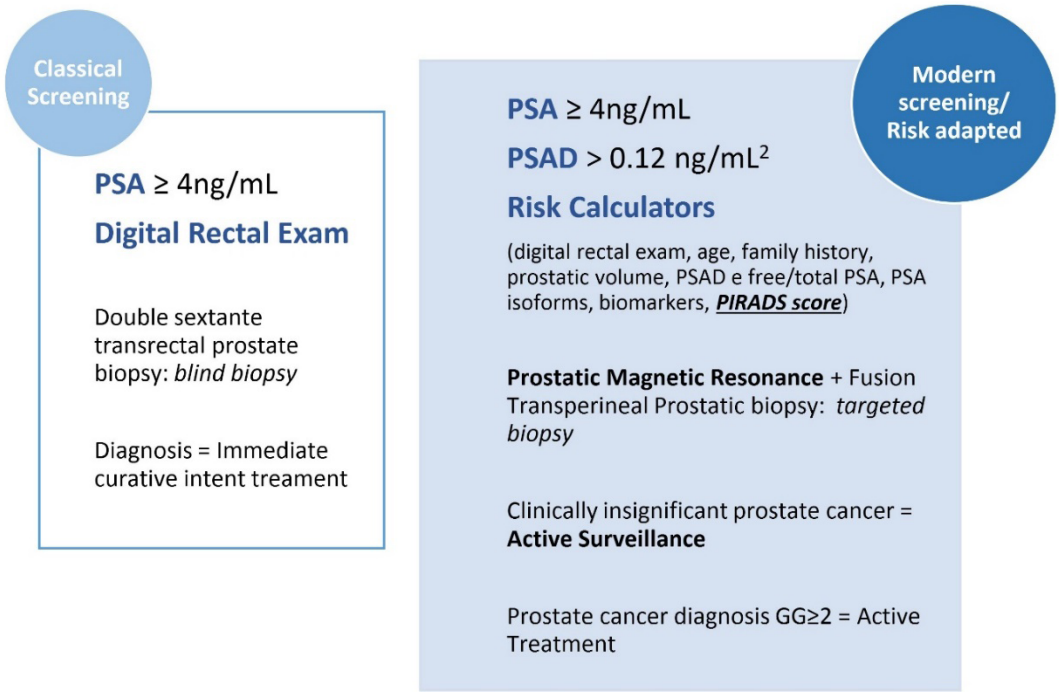

Figure 1. The Shift in Algorithm of Prostate Cancer Screening

Particularly ambitious is the project coordinated by Prof. Hein Van Poppel, supported by European community resources, started in April 2023, which aims to develop within 3 years a risk-adapted screening and early diagnosis algorithm capable of being applied to different realities – in either primary healthcare or hospital setting.[10]

In 2022, the European Commission included PC in the list of oncological pathologies targeted in the "Recommendations for Population Cancer Screening", relaunching the debate around the topic, and challenging political decision-makers to structure a locally applicable screening program in each member state.

In Portugal, widespread population screening for PC remains unregulated. The Clinical Guidance Norms published by the General Directorate of Health only contain a methodological description of opportunistic/optional screening. The Portuguese Urology Association (APU) proposed to fill this gap in 2022, describing an algorithm for applying screening at the Primary Health Care level – Fig. 2.

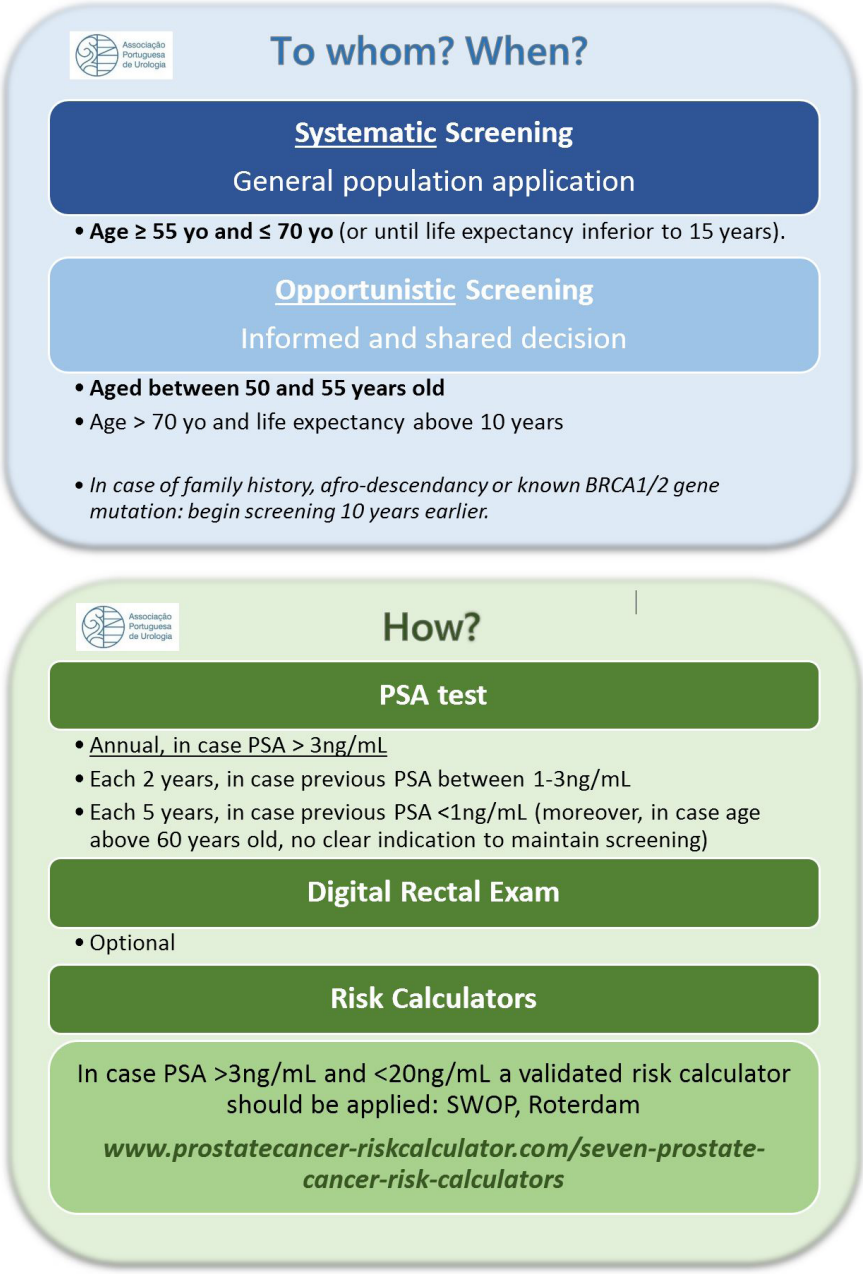

Figure 2. Prostate Cancer Screening Algorithm Proposal (APU – Portuguese Association of Urology - 2022)

The different calculated cut-offs that should motivate referral to Urology Hospital consultation are also the subject of debate.

Prostate Cancer Screening: Future Perspectives – Europe as a Stage

The application of a structured population screening program for PC is not implemented in any member state of the European Union. A reality that the "Europe's Beating Cancer Plan" scientific committee intends to change.

In Europe, mortality from PC reduced approximately three fold in the first decade of the 21st century, and a large proportion of these numbers are now attributed to the widespread screening based on PSA testing.[1,3] It remains imperative to monitor the adverse effects associated with screening – overdiagnosis and overtreatment.[6]

Some fundamental, evidence-based principles should be applied:

- Implement screening according to individual risk stratification (adjust examination scheduling intervals);
- Screen under the condition of admitting delayed treatment (active surveillance) or contemplative (watchful waiting) strategies;
- Do not perform a biopsy without a clear indication (use of risk calculators and predictive nomograms);
- Recognize that screening tends to become irrelevant in advanced ages (>80 years).

Respecting these premises implies modulating the "screening chain" at primary healthcare and hospital settings. On the one hand, providing general practitioners with simple and replicable risk stratification algorithms and predictive calculators. On the other hand, capacitating hospital referral centers with active surveillance clinical protocols and appropriate diagnostic equipment (MRI and trans-perineal prostate biopsy platforms with image fusion).

PSA is a biochemical marker that has saved and continues to save the lives of many men. Once at the expense of probably unnecessary diagnoses and treatments. However, perhaps it is time to recognize that "it is not the messenger's fault", perhaps it is a liability of those who interpret the message and have the burden of deciding according to its meaning. Admitting this weakness and making it into a strength is already within our reach, and is the first step to definitively turn the page on the clinical challenges of PC Screening.

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