SPECIAL ARTICLE

The role of prostate-specific antigen in light of new scientific evidence

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Abstract

Objective: Review the scientific evidence acquired in recent years on prostate-specific antigen (PSA).

Acquisition of evidence: Analysis of the available evidence on the current role of PSA, according to a panel of experts who recorded their experience on the subject.

Summary of the evidence: Currently, PSA cannot be considered solely an indicator of the presence or absence of prostate cancer. Rather, the determination of PSA assists the urologist in indicating the most appropriate treatment for a patient with benign prostatic hypertrophic (BPH), as well as in suspecting a prostatic tumor when the PSA reading increases >0.3 ng/ml, in patients treated with 5-alpha-reductase inhibitor, over the reading achieved at six months of having initiated this treatment. Moreover, PSA is a key factor in the follow-up of patients with prostate adenocarcinoma who undergo surgery, radiation therapy or minimally invasive techniques. PSA helps to define biochemical recurrence, suggests the existence of a local or distal recurrence and proposes or rules out adjuvant therapies.

Conclusions: New data on the current role of PSA in the management of patients treated for BPH and/or prostate cancer should be taken into account.

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PALABRAS CLAVE
Antigeno prostático específico; Hipertrofa prostática benigna;

Papel del antígeno prostático específico ante las nuevas evidencias científicas

Resumen

Objetivo: Revisar las evidencias científicas que se han producido en los últimos años con respecto al antígeno prostático específico (PSA).

Adquisición de evidencia: Análisis de la evidencia disponible acerca del papel actual del PSA, según la consideración de un panel de expertos que recoge su experiencia en el tema analizado.


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Introduction

Although it is well known that the discovery of prostate-specific antigen (PSA) revolutionized the specialty of urology within the context of diagnosing more prostate cancers, and particularly at earlier stages, our increased knowledge of the antigen enables us to improve the diagnosis of benign prostatic hypertrophy (BPH), to better predict its future behavior and to stratify these patients in order to give them the most effective treatment possible.

The latest scientific evidence has also helped us to discriminate those patients treated with 5-alpha-reductase inhibitors with an increased risk of having developed prostate cancer. In addition, new evidence has clarified the use of PSA in the screening or early diagnosis of prostate cancer, as well as in its monitoring after using different treatments with curative intent.

That is why, nowadays we cannot consider PSA as an antigen which is only important when evaluating the risk of developing prostate cancer, or when assessing its evolution after treatment with curative or palliative intent, but also when dealing with benign prostatic enlargement.

Prostate-specific antigen as a progression criterion of benign prostatic hypertrophy

For over a decade, there have been data in the literature which show the direct relationship between PSA levels and the risk of both prostate enlargement and acute urinary retention (AUR). We are referring to the PLESS and PROSCAR studies. These same studies also reported the relationship between PSA levels and prostate volume.

The Olmsted County study, carried out 2 years earlier, showed that the severity of lower urinary tract symptoms, urinary flow, prostate volume, and the age of patients were the most important factors influencing the evolution of this disease. This same study also evaluated the expected annual increase in PSA depending on its baseline level and analyzing per tertiles: 0.2–1.3 ng/ml; 1.4–3.2 ng/ml and 3.3–9.9 ng/ml, with an increase of 0.7 ng/ml, 2.1 ng/ml and 3.3 ng/ml per year respectively, which also helps

Síntesis de evidencia: Actualmente no puede considerarse el PSA únicamente un elemento orientativo en cuanto a la presencia o no de cáncer de próstata, sino que esta determinación ayuda al urólogo a indicar cuál es el tratamiento más conveniente ante un paciente con hiperplasia prostática benigna (HPB), así como a sospechar la existencia de un tumor prostático cuando la cifra de PSA se eleva >0.3 ng/ml en pacientes bajo tratamiento con inhibidor de 5-alpha-reductasa sobre la cifra alcanzada a los 6 meses de haber iniciado dicho tratamiento. Por otro lado el PSA resulta clave para el seguimiento de pacientes tratados por adenocarcinoma prostático con cirugía, radioterapia o técnicas mínimamente invasivas, para definir recidiva bioquímica, sospechar la existencia de recidiva local o a distancia, así como plantear o descartar tratamientos adyuvantes.

Conclusiones: Nuevos datos acerca del papel actual del PSA en el manejo de pacientes tratados por HPB y/o cáncer de próstata deben tenerse en cuenta.

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Prostate-specific antigen and therapeutic management of benign prostatic hypertrophy

The 2 studies that provide more information about stratifying patients and, consequently, indicate more accurately the most effective therapy are the MTOPS and the CombAT studies.

The first study concluded that combination therapy, as well as treatment with finasteride, reduced the risk of BPH progression, though this study was limited by the fact that the average prostate volume of the men enrolled was about 30 cm³.

The CombAT study, and above all the 4-year results from analyzing 4844 men with prostate volume greater than 30 cm³, showed that using combination therapy or dutasteride in men with PSA levels >1.5 ng/ml and prostate volume >40 cm³ reduces the risk of surgical treatment when compared to patients who only took tamsulosin, between 43 and 77%. Nevertheless, this improvement is not achieved when it comes to patients with a lower prostate volume.

That is why, we have data with scientific evidence levels 1b to discriminate between different medicines (alpha blockers, 5-alpha-reductase inhibitors, and combination therapy) depending on prostate volume, the severity of the symptoms and PSA levels, knowing beforehand which treatment could be more effective in each case. Clinical guidelines and a large number of scientific associations, including the Spanish Association of Urology, have already added these criteria, and they have even been subject to a Delphi method that tries to reach a consensus on scientific evidence and usual practice in the management of BPH by Spanish urologists.
Prostate-specific antigen in patients treated with 5-alpha-reductase inhibitors

Lessons learned from the REDUCE study\textsuperscript{12} show that the kinetics of PSA change when the patient is treated with dutasteride and, in that regard, a new basal PSA level should be established after 6 months of therapy. This figure may decrease after those 6 months if we are clearly faced with a patient with BPH. On the contrary, when we detect a confirmed increase, even if we find PSA ranges within normal considered parameters, from the nadir achieved, above 0.3 ng/ml the suspicion of either prostate cancer or non-compliance with treatment should be considered, and we should act accordingly depending on the man’s life expectancy.

Prostate-specific antigen in prostate cancer screening

PSA testing was approved by the Food and Drug Administration in 1994 for prostate cancer screening after the study carried out by Catalona et al.,\textsuperscript{13} which showed its effectiveness together with a digital rectal examination. The probability of detecting prostate cancer in men with PSA <4 ng/ml and a suspicious digital rectal examination was estimated to be 20%, 30% in men with a normal digital rectal examination, and more than 50% when the PSA was >10 ng/ml.

Widespread use of PSA testing led in the short term to a clinical stage migration and prostate cancer was diagnosed at earlier stages. The proportion of patients diagnosed at local stages increased significantly and diagnoses of disseminated disease were drastically reduced. The effects of prostate cancer screening with PSA also spread soon to our field. Only 3% of cancers are currently diagnosed with disseminated disease, whereas this rate reached 40% in the 80s. In our field, we have also gone from 20% in the 80s to a current 70% when diagnosing prostate cancer at local stages.\textsuperscript{14}

In the early 2000s, two events occurred and the effectiveness of PSA as an efficient tool for early diagnosis of prostate cancer began to be questioned. Stamey et al.\textsuperscript{15} studied the correlation between serum PSA levels and tumor volume for a period of 20 years, and saw a significant decrease in tumor volume and its correlation with PSA. On the other hand, Thompson et al.\textsuperscript{16} analyzed the behavior of PSA in the control arm of the Prostate Cancer Prevention Trial (PCPT) and saw a gradual incidence of prostate neoplasia in men with PSA <4 ng/ml. Rates of cancer ranged from 6% in men with PSA <1 ng/ml to about 25% in men with PSA between 3 and 4 ng/ml. These studies showed that the specificity of PSA for cancer was limited, and therefore the need for new markers that would increase it was disclosed.

Nevertheless, the origins of this effort to increase the specificity of PSA go back much further, since it was never considered to be a specific marker of the disease. Since its purification in 1979, it became known that PSA is a kallikrein specific to prostate tissue synthesized in the acinar and ductal epithelium of the gland, and it is exocrine-secreted to seminal fluid, where its physiological function is to liquefy semen. Elevation of serum PSA is caused by abnormal discharge into the bloodstream, as a consequence of inflammatory and neoplastic neovascularization processes, ruptured basement membrane and neoplastic stromal invasion, benign growth, prostate manipulation, etc.\textsuperscript{17}

During the 1990s, PSA density was described as a method to increase its predictive value at intermediate levels, age-specific PSA ranges with the goal of adapting the indication for biopsy to PSA levels for each age group and the usefulness of the free PSA percentage to avoid unnecessary biopsies was demonstrated. These and other more recent tools can be used to rationalize indications and avoid unnecessary biopsies. The most recent advances to increase the specificity of PSA have focused on new markers detected in post-prostatic massage urine such as PCA\textsuperscript{1} or a combination of several genes.\textsuperscript{18} The Phi index, which is the combination of different isoforms of PSA determined in serum and integrated in a mathematical formula.\textsuperscript{19} Finally, multiparametric magnetic resonance imaging brings about significant advances in imaging the location of cancer which would allow in the future to perform targeted prostate biopsies and change the paradigm of randomization.\textsuperscript{20}

Finally, we must mention the studies that are analyzing the influence of population-based screening with PSA in the death rate for this disease. The U.S. Preventive Services Task Force (USPSTF) has recently taken a stand against population-based screening for prostate cancer with PSA. This institution concludes that there is moderate or high certainty that this service moderately reduces or does not reduce cancer-specific mortality, and that the damage associated with diagnostic procedures and treatment outweigh the benefits.\textsuperscript{21} Schröder explains the scientific deficit in the interpretation of the meta-analysis carried out by the USPSTF and advocates for the stratification of cancer risk and the individualization in the decision to perform prostate biopsies, as well as in therapeutic decisions.\textsuperscript{22}

Prostate-specific antigen after radical prostatectomy

PSA levels after radical prostatectomy establish the oncological situation of the patient so that its persistence or increase above undetectable levels indicates active disease except in exceptional cases. That increase may precede clinical relapse in months or years. The clinical challenge precisely involves trying to discriminate those patients whose quality of life and life expectancy will be affected by this relapse, due to the onset of metastatic disease, in order to modify its natural history. Thus, options would include salvage radiotherapy at the site of surgery or ganglion surgery, starting androgen deprivation (AD) or expectant surveillance.

A PSA rise above 0.2 ng/ml is defined as relapse or biochemical failure (BF) in several determinations.\textsuperscript{23} This is the case observed in 15–50% of patients who had undergone radical prostatectomy.\textsuperscript{24} The risk of BF is related to the pathologic stage, the presence of positive margins, preoperative PSA velocity and PSA level, and the Gleason grade. Predictive models which incorporate genetic profiles of prostate cancer into clinical factors seem to have a greater capacity to discriminate the risk of BF although,
nowadays, have little practical use.\textsuperscript{25} It has been suggested that a PSA nadir >0.03 after surgery is an important predictive factor of BF. Also, the higher the previous Gleason score, PSA and BMI levels, the higher the risk of BF.\textsuperscript{26}

The first decision in case of BF is considering whether it is a probable local or systemic relapse. In the former case, rescue maneuvers might be suitable; in the latter case, immediate or deferred AD might be suitable until the appearance of symptoms or signs of metastatic disease. Taking into consideration the length of time until the appearance of metastases, time elapsed from metastases to death, the patients' life expectancy adjusted according to their comorbidities and their preferences in shared decision-making will be determining factors in the treatment decision.

15-year cancer-specific mortality in patients who had undergone radical prostatectomy is very low in the current series, varying from 2% in low-risk patients (PSA < 10; Gleason ≤ 6; T1c-T2a) to 19% in high-risk patients (Gleason > 7, PSA > 20 and T2c-T3).\textsuperscript{27} The median time from BF to the appearance of metastases can be 8 years, and the median time from metastases to death can be 5 years.\textsuperscript{28} The Gleason grade (>7), time until BF (less than 1–2 years), and a short PSADT (less than 6–10 months) correlate to early onset of metastases and death.\textsuperscript{29}

Late BF (>3 years), the presence of positive margins and Gleason <7 predict local relapse. On the contrary, BF <12 months, Gleason >7 and the presence of negative margins are highly suggestive of distant disease. If local recurrence is suspected, salvage radiation treatment tends to be more effective if it is started at the lower PSA level. Radiation therapy at the site of surgery (doses of 64–66 Gy), with or without ganglion fields, should be given with PSA <0.5 ng/ml.

No response with biochemical normalization suggests the presence of disseminated disease. In such cases, PSA is again a significant factor when determining if it is worth starting AD therapy, although it is unclear who could benefit from it, since prolonged survival without AD has been observed and no randomized prospective studies are available.\textsuperscript{30} In principle, it should be reserved for those cases with worse prognosis, which may jeopardize their life expectancy and their quality of life, taking into consideration short- and long-term side effects of AD in a personalized way. Immediate AD – versus deferred AD – offers survival advantages in node-positive disease after surgery, regardless of postoperative PSA levels, versus deferred AD with regard to the appearance of symptoms.\textsuperscript{31} Early AD after BF may not delay the development of metastases except in those patients with Gleason >7 or PSADT <12 months.\textsuperscript{32} In any case, although a certain reduction in cause-specific mortality has been suggested, no benefit in overall survival has been proven yet.\textsuperscript{33}

Prostate-specific antigen after radiation therapy

Although initially criteria of the American Society of Therapeutic Radiology and Oncology (ASTRO) were applied, which required 3 consecutive increases of PSA to confirm PSA biochemical relapse, the new definition provided by this Society indicates that there is BF when the PSA increase is >2 ng/ml higher than the PSA nadir value after treatment.\textsuperscript{34}

PSA concentration slowly decreases after radiation therapy when compared to radical prostatectomy. The optimal cut-off value for a favorable PSA nadir after radiotherapy is somewhat controversial. Achieving a PSA nadir <0.5 ng/ml seems to be associated with a favorable outcome.\textsuperscript{35-37} The interval before reaching the nadir PSA may be very long and can sometimes take up to 3 years or more. Also, after radiotherapy, the PSA doubling time has been shown to correlate to the site of recurrence; patients with local recurrence had a doubling time of 13 months compared to 3 months for those with distant failure.\textsuperscript{38-40}

In the prediction of BF after external radiation therapy, the most commonly accepted model (external validation) is that of the Memorial Sloan Kettering Cancer Center, which evaluates recurrence-free survival at 5 years. Pre-treatment PSA is one of the main variables used in this model, along with the Gleason score of the biopsy, clinical stage, adjuvant hormonal blocking, and radiation doses.

Prostate-specific antigen after focal therapy

Focal therapy consists of trying to eliminate prostate carcinoma cells, preserving normal (or unaffected by the tumor) prostate tissue, keeping its functionality. That effect shall be accomplished by eliminating the largest tumor focus (index tumor), which is a conditioning factor in the total tumor volume of the prostate, the Gleason grade, as well as in its biological aggression.

The sources of energy capable of achieving this effect are brachytherapy, cryotherapy, high-intensity focused ultrasound, photodynamic therapy, and laser-induced interstitial thermotherapy. The patients who may benefit the most from any of these focal therapy techniques are those with life expectancy >10 years, a good staging of the disease determined by saturation prostate biopsies and, if necessary, prostate remapping using 20 cylinders and cutting-edge imaging techniques, along with information provided by skilled radiologists ensuring that there is low or intermediate risk of prostate carcinoma.\textsuperscript{34-36}

Brachytherapy, which is available in many urology departments, has been the most commonly used focal therapy in Spain and, less frequently, cryotherapy, so we will concentrate on PSA behavior after these 2 techniques. The other techniques are still considered experimental therapies, and their oncological results are difficult to interpret because several PSA thresholds have been defined as response criteria, and no international consensus has been reached on them.

Prostate-specific antigen and definition of therapeutic failure

In past decades, treatment failure in prostate cancer was defined as local relapse determined by a digital rectal examination or imaging tests or by the development of distant metastases. PSA elevation after treatment is currently the main variable to define it. Nowadays this is a generally accepted fact and the Pound et al. study supported this conclusion.\textsuperscript{41} These authors presented a study which showed
that none of the patients followed for more than 5 years developed recurrence without an elevated PSA.

**Prostate-specific antigen after brachytherapy**

The definition of BF is the same as that after external RT: a PSA rise by 2 ng/ml or more above the PSA nadir achieved after treatment. A general recommendation consists in waiting about 18 months after brachytherapy to get the PSA nadir. We can also calculate the probability or the prediction of BF after brachytherapy with the Kattan nomogram. Pre- and post-treatment PSA is one of the main variables included in it, along with the Gleason of the biopsy, time elapsed since implant and the kind of isotope (iodine 125 or Pd-103).

**Prostate-specific antigen after cryotherapy**

An objective evaluation of PSA evolution after this technique is not a simple affair, because there are different criteria among the different authors who use it. While some of them use the value of PSA <0.1 ng/ml as a response value to regard it as a therapeutic success and, thus, any rise above this value would be a BF, other authors apply the criteria provided by the ASTRO, which require 3 consecutive increases of PSA to confirm PSA biochemical failure.

With third-generation cryosurgery the clinical follow-up still remains short, and achieving a PSA nadir <0.4 ng/ml within 3 months is generally regarded as a success criterion. Anything above this value is considered biochemical progression.

**Conclusions**

PSA is directly related to prostate volume and the risk of progression. PSA helps the urologist stratify those patients with BPH and decide which the most appropriate treatment is in each case. In a patient treated with dutasteride PSA rise, from the PSA nadir >0.3 ng/ml, must be taken into account due to possible coexistence of prostatic adenocarcinoma. Population-based screening for prostate cancer with PSA should be aimed at young, healthy men, and always in conjunction with the patient. An indication for prostate biopsy should be determined by stratifying the risk of prostate cancer detection and of insignificant cancer. Active surveillance should be part of the therapeutic offer to those patients with insignificant prostate cancer. Post-RP biochemical failure is defined as a PSA level >0.2 ng/ml on at least 2 evaluations. PSA kinetics may guide us when estimating the possibility of local disease or distant dissemination. BF after radiation therapy or brachytherapy is defined as a PSA rise >2 ng/ml above the nadir achieved. There is no consensus on defining BF after emerging therapies.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**References**

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