

# Prostatic specific antigen and bone scan in the diagnosis and follow-up of prostate cancer. Can diagnostic significance of PSA be increased?

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## Abstract

Prostate cancer (PC) is currently the most frequently diagnosed cancer in males and constitutes a major health issue in developed countries. On the other hand, the majority of PC cases are considered clinically not significant and certainly not lethal. These discrepancies highlight the need for the early detection of especially those cases that have aggressive features and call for early and radical intervention. The clinical use of prostatic specific antigen (PSA) towards this end is recognized as inadequate since PSA is prostate specific, but not a PC specific marker, as it is known to increase in other prostate diseases such as benign hyperplasia, inflammations, transrectal ultrasound examination, biopsy and after transurethral prostatectomy. However due to lack of other more specific markers, digital rectal examination combined with serum PSA are suggested for PC screening and diagnosis. With regard to advanced disease where bone involvement is the rule, nuclear medicine bone scan using radioactive bisphosphonates such as technetium-99m methylene-diphosphonate is quite common and reliable technique for detecting and monitoring bone metastases. The major advantage of nuclear scintigraphy is its ability to reveal bone metastases significantly earlier than the conventional X-rays imaging techniques. PSA density, velocity, doubling time and free to total PSA ratio increase the significance of serum PSA in diagnosing PC. The combination of an increased PSA (>20ng/mL) and a high biopsy Gleason score (>8) enhances the possibility of bone metastases (P<0001) and mandates a bone scan. *In conclusion*, serum PSA testing is currently recommended in symptomatic PC patients, for disease staging and treatment monitoring and in asymptomatic selected population groups aged more than 50 years. It is reasonable to suggest that PSA density, velocity, doubling time and free to total PSA ratio or combining PSA with Gleason score shall greatly increase PSA specificity in detecting PC cases. Radioisotopic bone scan by SPET or PET can demonstrate osseous metastases at later stages of PC, but should also be applied in cases falsely considered as an early stage of PC, for better staging and for periodic follow-up of the disease.

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## Introduction

Prostate cancer (PC) is the most frequently diagnosed cancer in men worldwide and is considered responsible for approximately 10% of cancer deaths with only lung cancer associated with more deaths in men [1, 2]. Men of black race or men with a family history share a higher risk for PC. The incidence of PC in European countries has been increasing lately, mainly as a result of increased screening methods, and is relatively higher in men who live in Western and Central Europe [2-4]. Switzerland has a very high frequency of PC, about twice the average with 44 cases per 100,000 men, compared with residents of the eastern and southern countries [2]. Famous personalities such as F. Mitterrand, Ayatollah Khomeini, T. Savalas, R. Moore, S. Poitier were suffering from PC.

In Greece, PC is the second most common cancer in men after lung cancer with 2.920 new cases in 2002, representing 13.2% of all neoplasms in men. It is clear that our country has one of the lowest rates in Europe with 8.7 to 12 deaths per 100,000 men [3-5]. This is probably attributed to the traditional Greek Mediterranean diet, which is rich in fiber and antioxidants and also has shown a protective role against many cancers including PC [6].

The increase in the diagnosis of PC cases that was observed mainly in the U.S.A during the so-called PSA era, was due to the systematic implementation of serum prostate specific antigen (PSA) for PC screening. This increase in PC detection is expected to sustain even further in the years to come, mainly due to the prolonged life expectancy of men in the Western World. However while the detection rate of PC is increasing, the mortality from PC is declining [7-9].

The wide implementation of PC screening has led to more cancers diagnosed in earlier stages and more "indolent" and latent forms of the disease. Greek researchers conducted

autopsy studies on 212 males aged 30 to 98 years, who died from causes other than PC. A total of 40 males were found with PC in an early or latent form, with well differentiated tumors that were less than 1cm in diameter [10]. Another study on 59 Greek patients who underwent radical cystoprostatectomy for invasive bladder cancer revealed the coexistence of latent PC in 27% of them [11].

## PSA in the diagnosis of prostate cancer

PSA is a glycoprotein (M.B: 34,000 Daltons) containing 7% carbohydrate [12], produced from the tubular epithelium of the prostate gland and diffused by the prostate tubules to the semen [13]. As an indicator of PC, PSA was first described in 1979 [13]. This antigen is considered a "marker specific for the prostate but not specific as a prostate tumor marker" because it has been shown that it increases in non-cancerous prostate disease such as benign prostatic hyperplasia (BPH), inflammation of the prostate, digital rectal examination, transrectal ultrasound, prostate biopsy, cystoscopy and transurethral prostatectomy [14].

Serum PSA is a more sensitive indicator than digital rectal examination (DRE) or transrectal ultrasonography for the diagnosis of PC [15-18]. However, when serum PSA level is combined with DRE of the prostate, then the accuracy of PC diagnosis increases. Table 1 describes the possibility for detecting PC in biopsy cores in relation to the combination of serum PSA values and negative or suspicious DRE. [18].

**Table 1.** The possibility (%) for PC diagnosis with the combination of serum PSA and digital rectal examination (DRE)

PSA	<4ng/mL		>4ng/mL	
	(-)	(+)	(-)	(+)
DRE				
PC	4%-9%	10%-21%	12%-35%	42%-72%

A recent ongoing debate is related to the excessive use of serum PSA leading to overdiagnosis of PC cases and diagnosis of clinically insignificant cancers whose clinical course would not affect patients' survival [19, 20]. The answer can be given through studies with random population samples [21]. A relatively recent study of 162,243 men aged 55-69 years showed that screening using serum PSA reduces the mortality of PC by 20% [22].

Still, the limitations of PSA as a screening tool are now well known. The low specificity of PSA, as has been reported by others, results in many unnecessary biopsies, high rates of overdiagnosis and resultant overtreatment with significant burden on the patients' quality of life. [23]. The European randomized Study of Screening for prostate Cancer (ERSPC) reported an increased ratio between incidence and mortality, further highlighting the problem of overdiagnosis. Although screening for PC with PSA can reduce cancer-specific mortality and the risk of developing metastatic disease, it does so at a considerable cost in terms of the number of men who need to be screened, biopsied, and treated [24].

These were the results of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) study where investigators indicated that most screen-detected PC cases were less aggressive and had less chances of becoming symptomatic during a patient's lifetime [25].

The challenge is to design screening programs that maximize benefits (reducing PC mortality) and minimize costs (overtreatment). Recent research has suggested that this can be achieved by: a) risk-stratifying screening and biopsy, b) increasing reliance on active surveillance for low-risk cancer, c) restricting radical prostatectomy to high-volume surgeons and d) using appropriately high-dose radiotherapy [26, 27].

## The diagnostic values of serum PSA. Low-risk and advanced PC

There is evidence that PC prevalence increases with PSA level [28]. The rate of cancer detection at PSA<3mg/mL is relatively high, although there is a false positive rate of at least 20%. Overall PSA is not very effective at detecting clinically significant tumors at such low levels of PSA and is associated, as mentioned before, with an increased risk of diagnosis of latent and insignificant forms of PC with minimum benefit for overall survival [19, 22, 28].

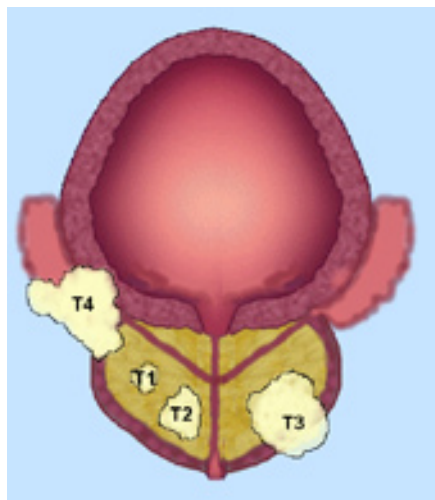
Usually, the early diagnosed PC is considered as a low risk cancer and the late diagnosed PC has an increased risk to be advanced PC. Low risk disease is considered a PC if serum PSA is less than 10ng/mL with negative DRE for stages I and II [29]. Low risk-low stage cases of PC can be managed without invasive radical treatment such as radical prostatectomy and radiotherapy because these are associated with significant complications which affect the quality of life [29, 30]. In a group of 731 men with mean age of 67 years and low risk PC, radical prostatectomy did not significantly decrease overall mortality over the next 12 years [31]. In cases of disease progression from low to high risk PC, radical prostatectomy is preferred to radiotherapy, because it has been found that in these cases the incidence of recurrence is lower for radical prostatectomy compared with radiotherapy. Recurrence in 10 years was 20%-30% in radical prostatectomy, while in only 5 years after radiotherapy the relapse of PC was around 50% [25, 32-34].

In advanced PC, radiotherapy and androgen deprivation treatment are applied in combination with or without corticosteroids [33] or systematic chemotherapy [34, 35] depending on the disease stage and the responsiveness of tumor to hormone treatment. Androgen deprivation treatment is considered palliative and while it reduces symptoms in advanced PC it is probable that the development of a castration-resistant state, resistant to androgen deprivation therapy will result in disease recurrence and death [28]. One should note that the overall survival of PC patients after initial diagnosis often lasts more than 10 years [4, 32, 33]. Certainly bone metastases worsens final prognosis and life expectancy, still, survival of 5 to 10 years has been reported for 15% of these patients [21, 36].

## PSA as a screening test for PC

Serum PSA values, especially in the U.S.A are widely used for the prosymptomatic (early) diagnosis of PC. The prosymptomatic diagnosis of PC before the age of 50 is indicated for patients at increased risk for PC, which are: those with a family history and African-Americans [37]. A recent European randomized study on routine examination of male patients found that serum PSA decreased PC mortality by 29% during 11 years of follow-up [9]. The current objections for applying

PSA are: PSA as a routine screening test shall overdiagnose and lead to overtreatment for localized, low-stage disease, the associated burden on the quality of life and cost effectiveness [38, 39]. This review may show that there are means to increase specificity of PSA and thus, its overall diagnostic significance. Figure 1 presents the different stages of PC according to the TNM system.



**Figure 1.** The PC staging system (American Joint Committee on Cancer, AJCC, T1: The tumor cannot be palpated or visualized by imaging methods such as transrectal ultrasound. T2: The tumor is palpable but is still confined to the prostate. T3: The cancer has begun to spread outside the prostate and can expand to the seminal vesicles. T4: The cancer has spread to other surrounding tissues [40].

**Ways to enhance the diagnostic accuracy of PSA (PSAD, PSAV, age specific PSA and PSA ratio)**  
Kinetics of PSA, like PSA velocity (PSAV), PSA density (PSAD), PSA doubling time (PSADT) and free-to-total PSA ratio are important predictors-indicators of risk from PC.

*The PSA density (PSAD):* is the fraction obtained by dividing the value of total serum PSA by the volume of the prostate, as measured by transrectal ultrasound. According to a study by Benson, the normal prostate tissue releases smaller amounts of circulating PSA per gram of prostate tissue (0,3ng/mL/gr) than prostate cancer (3,5ng/mL/gr) [41-44].

The annual increase in the value of PSA refers to PSA velocity (PSAV). Its use in clinical practice was proposed because the rate of increase in the serum PSA over time was significantly higher in patients with diagnosed PC compared to those with BPH [41]. A PSAV of more than 0,75ng/mL per year, is considered a threshold value in the differential diagnosis between PC and BPH with a 72% sensitivity and 95% specificity [44]. Other researchers have shown that a PSA increase of >2ng/mL during the year prior to PC diagnosis was associated with a shorter time for biochemical recurrence, and death from PC [45, 46].

**Table 2.** Age-adjusted limits of serum PSA

Age Groups	Upper serum PSA values (ng/mL)	(%) Specificity
40-49	0-2.5	95
50-59	0-3.5	95
60-69	0-4.5	95
70-79	0-6.5	95

*The age-specific PSA* was proposed in 1993 and is widely applied today. The proposed limits of the normal range of PSA in relation to age are presented in Table 2 [47].

The *free-to-total PSA ratio* is more accurate and superior to total PSA when examined in the PSA range between 2-10ng/mL. It has been shown that the use of PSA ratio might reduce the number of unnecessary biopsies while maintaining a high detection rate [48]. Analysis has shown that when serum PSA values are between 2-3.9ng/mL and free PSA is over 0.36-0.7ng/mL the risk for PC detection is less than 10%. On the contrary, serum PSA values more than 4 ng/mL and free PSA less than 0.2-0.39ng/mL, increase the relative cancer risk to more than 30% [49].

Considering the above, it is reasonable to suggest that PSA density, velocity, doubling time and free to total PSA ratio, or some of the above, shall certainly increase the sensitivity of serum PSA in diagnosing PC cases that need immediate biopsy, attention and treatment.

## Diagnosis of PC and the bone scan

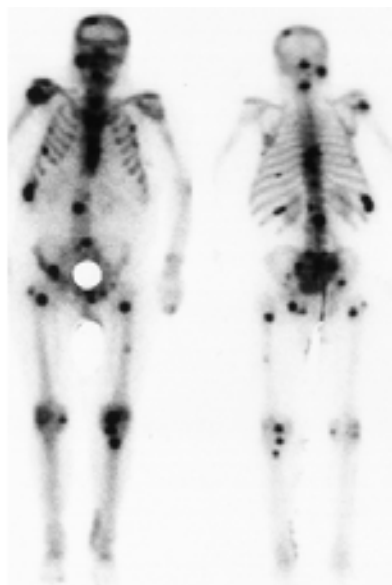
Technetium-99m methylene bisphosphonate (<sup>99m</sup>Tc-MDP) is a reliable imaging tracer to detect bone metastases from PC (Fig. 2 and 3). False positive findings are usually caused by degenerative arthritis, Paget's disease or old fractures. Bone metastases from PC are predominantly osteoblastic and to a lesser extent osteolytic. The bone scan (BS) reveals bone metastases much earlier before they appear on routine radiography and helps in disease staging [50-52].

Others do not recommend BS imaging for the initial staging of localized disease in asymptomatic patients (stages T1 and T2) and when the serum PSA is less than 20mg/mL [53]. The same cut-off level for serum PSA is set by the European Urological Association [54], while the Japanese Urological Association lowers the limit to 10mg/mL [55].

In general there is evidence that the limit of 10mg/mL for PSA is considered a valuable diagnostic threshold, since it has been shown recently that most of these men will have a low grade tumor [31].

Other investigators report that BS can be positive for osseous metastases in up to 10.5% of newly diagnosed patients with PC even with serum PSA values less than 10mg/mL [51, 52]. For PSA values between 10-20mg/mL other researchers reported positive BS in 13% to 32% of cases [48, 53-57]. The combination of high initial serum PSA (>20ng/mL) and high Gleason score (>8), enhances the possibility of bone metastases (P<0001). Gleason score grading system of prostate biopsy is based on the glandular histological pattern of the tumor as identified at relatively low magnification. The pathologist assigns a grade to the most common tumor pattern, and a second grade to the next most common tumor pattern. Both primary (predominant) and secondary (second most prevalent) architectural patterns, are assigned to a grade from 1 to 5, with 1 being the most differentiated and 5 the least differentiated pattern [58]. Grey scale color Doppler ultrasound and transrectal real time elasticity imaging (elastography) are quite useful techniques for detecting PC [56].

Computed tomography and positron emission tomography (PET) techniques may ever better detect bone metastases in PC, especially if BS is indefinite or negative.



**Figure 2.** Bone scan with 740MBq  $^{99m}\text{Tc}$ -MDP in a patient with advanced PC. Multiple, diffuse osteoblastic metastatic lesions throughout the skeleton.

### Predictors of advanced PC treated with androgens and serum PSA

Prostate specific antigen in patients undergoing radiation or androgen deprivation treatment has a prognostic value being the most significant variable associated with the progression of PC while the extent of bone metastases can be shown in the BS [33, 34].

Furthermore, falsely low PSA values are usually observed in patients with advanced PC treated with docetaxel and estramustine or mitoxantrone and prednisolone [35]. It is worth mentioning that in these cases the false positive values of PSA refer to 40% of treated patients. Four to six weeks after radical prostatectomy the value of PSA should be  $<0.1\text{ng/mL}$ . If these values remain stable or even better, undetectable for 5 years postoperatively, the risk of PC relapse is minimum. If at 6 months PSA is increased, then we have recurrence or metastases [59, 60].



**Figure 4.** Bone scan with 740MBq  $^{99m}\text{Tc}$ -MDP in the anterior and posterior projection, in a patient with newly diagnosed PC. Multiple, diffuse osteoblastic metastases are seen along the spine and in the right sacroiliac joint.



**Figure 3.** Anterior and posterior views of normal BS with 740MBq  $^{99m}\text{Tc}$ -MDP in a patient with prostate cancer at the time of initial diagnosis.

*In conclusion*, serum PSA testing is currently recommended in symptomatic patients with known PC for disease staging and treatment monitoring and in asymptomatic selected population groups aged more than 50 years. It is reasonable to suggest that PSA density, velocity, doubling time and free to total PSA ratio or combining PSA with Gleason score shall greatly increase PSA specificity in detecting PC cases that need immediate attention and treatment. Radioisotopic bone scan by SPET or PET can demonstrate osseous metastases at later stages of PC, but should also be applied in cases that may have been falsely considered as at an early stage of PC for better staging and for periodic follow-up of the disease.

*The authors declare that they have no conflicts of interest.*

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