Original research-Orijinal araştırma

Is percent free prostate specific antigen test used more than recommended by international standarts for prostate cancer screening?

Gereğinden fazla serbest prostat spesifik antijen yüzdesi test isteği yapılmakta mıdır?: Prostat kanseri taramasında uluslararası kılavuzlarla uyumsuzluk

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Abstract

Aim. For prostate cancer (PCa) screening “percent free prostate specific antigen” (pfPSA) testing is used for improving test specificity of prostate specific antigen (tPSA) and is used when tPSA is between 2.5 and 10 ng/mL, according to international screening guidelines of American Urological Association (AUA), and American Cancer Society (ACS). We evaluated the number of pfPSA testing requested in practice and the concordance to PCa screening guidelines. Method. The number of pfPSA testing performed at different age groups and different tPSA levels had evaluated, in our hospital between 2004 and 2007. Result. Twenty five thousand eight hundred and forty five pfPSA tests were performed between 2004 and 2007. Only 23.7 % of men were at tPSA levels 2.5-10 ng/mL. 9.8 % of patients were under age 45 years, and 10.2 % of them were over 75 years. Conclusion. There is no real pfPSA screening consistency with screening guidelines. Laboratories, clinicians and practitioners should overview their pfPSA requests for PCa screening.

Key words: Prostate cancer screening; Prostate specific antigen; percent free prostate specific antigen

Özet

Amaç. Prostat kanser (PCa) taramasında, “serbest prostat spesifik antijen yüzdesi” (% sPSA) ölçümü prostat spesifik antijen (tPSA) testinin özgüllüğünü arttırmakta ve Amerikan Uroloji Derneği’nin (AÜD) ve Amerikan Kanser Cemiyeti’nin uluslararası tarama kılavuzlarına göre tPSA 2.5 ve 10 ng/mL aralığında kullanılanmaktadır. Bu çalışmada, pratikte %sPSA test isteklerinin sayısı ve PCa tarama kılavuzlarına uyumu değerlendirildik. Yöntem. 2004 ve 2007 yılları arasında, hastanemizde, farklı yaş gruplarında ve farklı tPSA düzeylerinde uygulanan %sPSA test sayıları incelendi. Bulgular. Yırtına beş bin sekiz yüz kürek beş %sPSA testi 2004 ve 2007 yılları arasında yapılmıştır. Sadece %23.7’sinin tPSA düzeyleri 2.5-10 ng/mL idi. Hastaların % 9.8’i 45 yaşın altında ve % 10.2’si 75 yaşın üzerinde idi. Sonuç. % sPSA taramaları, tarama kılavuzlarına tam olarak uyum göstermemektedir. Laboratuvarlar, klinisyenler ve pratisyen hekimler %sPSA test isteklerini Pca taramasında gözden geçirmelidirler.

Anahtar sözcükler: Prostat kanser taraması, Prostat spesifik antijen, serbest prostat spesifik antijen yüzdesi

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Introduction
Prostate cancer (PCa) screening by prostate specific antigen (tPSA) has been improved over the last twenty years, and lead to dramatic increases in detection of PCa. According to guidelines from American Urological Association (AUA), and American Cancer Society (ACS), screening should begin at the age of 50 for average risk men and stop when life expectancy is less than 10 years (around age 75 years) [1]. Screening for PCa should include digital rectal examination (DRE) and tPSA measurement. The patients with abnormal DRE or tPSA >10 ng/mL are referred to prostate biopsy. The patients undergo routine screening with normal DRE or tPSA result is < 4 ng/mL (or in some institutions <2.5 ng/mL). However, for patients with tPSA 4-10 ng/mL (or 2.5-10 ng/mL), free PSA (fPSA) measurements should be used to improve specificity for PCa. Biopsy is restricted to percent fPSA (pfPSA) [ (fPSA / tPSA) x100 ] below certain cut off values (pfPSA = 20 % according to ACS guideline) [1]. There has been considerable number of studies carried out to decide the pfPSA cut off values for recommending prostate biopsies and is mostly found between 10% and 25%. Using these cut offs, most PCa will be detected and unnecessary prostate biopsies will be avoided.

After reviewing AUA and ACS screening criteria mentioned above, there is not enough evidence about how clinicians follow guidelines for pfPSA testing in clinical practice in our region. The aim of our study was to assess frequency of pfPSA testing and consistency with guidelines in clinical practice by evaluating our tPSA and pfPSA data according to Jackson et al [2] study model.

Methods
This study evaluated the frequency of tPSA and pfPSA screening between 2004 and 2007. We evaluated our data’s consistency with guidelines by performing the model that Jackson et al suggested [2].

An extended laboratory data for tPSA with simultaneous testing of pfPSA screening were accessed, but there were only limited demographic data (age at testing) and no clinical data of these patients. tPSA testing is known to be used for PCa screening, detecting recurrence and monitoring PCa. On the other hand, pfPSA is only used for accomplishing the PCa screening by being a complementary test of tPSA. The tPSA and pfPSA testing targets had clearly defined and pfPSA testing is at the intersection point of being a unique laboratory test for screening at 2.5-10 ng/mL or 4-10 ng/mL tPSA levels. In this situation, the patients’ demographics and clinical data were not necessary.

We also reviewed the frequency of pfPSA requests for both hospitalized and outpatients of all departments in our hospital and sub-grouped as Urology department, internal medicine and other departments.

We achieved the results of simultaneous requests of tPSA, fPSA and calculated pfPSA. Percent free prostate specific antigen was calculated by pfPSA = (fPSA / tPSA) x 100.

tPSA and fPSA were measured with chemiluminescence immunochemical assays on Elecsys analyzer 2010 (Roche Diagnostics, Mannheim, Germany) in 2004, Modular E170 (Roche Diagnostics, Mannheim, Germany) in 2005 - 2006 and Immulite 2000 (Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA) in 2007.

Financial disclosure and ethics
The authors had no connection with any of the companies or products mentioned in this article and no financial interest. This was retrospective study performed on unidentified patients.
data and all the products were commercially available. Thus, this study was considered exempt status from ethics committee.

**Results**

Twenty five thousand eight hundred and forty six pfPSA tests were performed between 2004 and 2007. The mean ±SD of age of this population at screening was 60.2 ± 12.5 and the range of patients’ age at pfPSA screening had shown in figure 1.

![Figure 1. Histogram of patients age at pfPSA screening.](image)

The distribution of patients screened with percent free prostate specific antigen at different ages.

The distribution of patients depending on tPSA classification shown in figure 2 and were summarized as follows. It is dramatically shown that 70.23% of pfPSA requests were at tPSA <2.5 ng/mL and a more striking data were that 46.2% of pfPSA requests were at tPSA <1ng/mL. Additionally, only 13.4% of pfPSA requests were at the proper tPSA values (4-10 ng/mL). 6.09% of pfPSA requesting was at tPSA >10 ng/mL.

![Figure 2. Distribution of patients depending tPSA values.](image)

Percentage of patients with tPSA <1 ng/mL, 1.1-2.4 ng/mL, 2.5-3.9 ng/mL, 4-10 ng/mL, >10 ng/mL.
The distribution of pfPSA test requesting frequency, according to patients’ age and tPSA values at the screening time had shown in Table 1. Overall, 76.3% of pfPSA screening were performed at tPSA values <2.5 ng/mL and >10 ng/mL. 71.46% of the patients were between 51-75 years age and at this age interval 19.28% of patients were between 2.5-10 ng/mL. 9.8% of them were under age 45, and 3.5% of them were over 80 years age.

<table>
<thead>
<tr>
<th>Total PSA</th>
<th>Age at Screening (years)</th>
<th>≤ 1</th>
<th>1.1-2.4</th>
<th>2.5-3.9</th>
<th>4-10</th>
<th>&gt;10</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ng/mL</td>
<td>45</td>
<td>46-50</td>
<td>51-60</td>
<td>61-65</td>
<td>66-70</td>
<td>71-75</td>
<td>76-80</td>
</tr>
<tr>
<td>&lt;2.5</td>
<td>7.34</td>
<td>5.69</td>
<td>15.37</td>
<td>6.00</td>
<td>4.64</td>
<td>3.5</td>
<td>2.48</td>
</tr>
<tr>
<td>2.5-3.9</td>
<td>0.32</td>
<td>0.45</td>
<td>3.11</td>
<td>2.08</td>
<td>1.71</td>
<td>1.45</td>
<td>0.74</td>
</tr>
<tr>
<td>4-10</td>
<td>0.29</td>
<td>0.33</td>
<td>3.58</td>
<td>3.04</td>
<td>2.11</td>
<td>2.20</td>
<td>1.19</td>
</tr>
<tr>
<td>&gt;10</td>
<td>0.11</td>
<td>0.14</td>
<td>1.15</td>
<td>1.03</td>
<td>0.93</td>
<td>1.20</td>
<td>0.94</td>
</tr>
<tr>
<td>Total</td>
<td>9.78</td>
<td>8.60</td>
<td>31.4</td>
<td>16.60</td>
<td>12.48</td>
<td>10.98</td>
<td>6.68</td>
</tr>
</tbody>
</table>

Gray shaded areas are recommended age and tPSA values for pfPSA testing. Moreover, pfPSA testing frequency from the departments of our hospital observed. The Urology department requests were only 18% of these patients. 34% requests were from Internal Medicine department and the remaining 48% of requests were from all the other departments of our hospital. The mean ±SD age of patients from Urology department was 60.9 ± 5.8 years, from internal medicine department was 57.2 ± 8.5 years and the other departments were 60.2 ± 12.8 years.

**Discussion**

Most of the PCa patients can be treated and cured when detected in early stages; however, PCa diagnosed generally after symptoms were occurred and metastases were present. The ACS believes that health care professionals should offer the tPSA testing and DRE yearly, beginning at age 50 and to men who have at least a 10 year life expectancy. Men with high risk of PCa, such as African-Americans and men who have a first-degree relative (father, brother, or son) diagnosed with PCa at an early age (younger than 65 years), should begin testing at age 45. Men at even higher risk (because they have several first-degree relatives who had PCa at an early age) could begin testing at age 40. Depending on the results of this initial test, further testing might not be needed until age 45 [1, 3]. So et al [4] showed that, almost 50% of Canadian men over 50 years age received tPSA screening during their lifetime and 72% of these during the preceding year. Currently, the life time risk of diagnosis of PCa is 18%, where as the mortality rate of PCa is only 3%. Critics point to evidence of high rates of over detection. Over detection leads to over treatment with the result costs, side effects, complications and increase of patient anxiety which are associated with any of the wide-ranging current treatments. Measuring the pfPSA improves test specificity for detecting PCa at tPSA levels 2.5-10 ng/mL [5]. When PCa occurs, the tPSA level is mostly >4 ng/mL, but about 13% of men with a tPSA below 4 ng/mL will have PCa on biopsy. If tPSA level is in the borderline range at 4-10 ng/mL, the patients have about a 25% chance of having PCa. If it is more than 10, the chance of having PCa is over 50% and increases more as the tPSA level increases [6]. A low pfPSA indicates increased risk of PCa among men with an elevated serum tPSA. In some studies patients with tPSA less than 2 ng/mL, pfPSA is used for PCa detection [7], but according to some studies, the power of pfPSA is poor in detection of PCa patients with tPSA less than 4 ng/mL [8].

Our data showed that 70% of the pfPSA screening was done when tPSA was less than 2.5 g/mL, and 46% was done when tPSA was less than 1 ng/mL and totally not supported by any study in literature and guidelines. In patients with tPSA >10 ng/mL, pfPSA testing is not useful because the PCa detection rate of tPSA is already quite high. Our data showed that 6.1% of pfPSA screening was done when tPSA was >10 ng/mL. All these data
indicated that for screening PCa, simultaneous tPSA and pfPSA requests resulted with highly excessive pfPSA testing. First measuring tPSA and according to tPSA levels, then testing pfPSA, “stepwise requests” are strongly needed. Similarly, in the retrospective screening study by Jackson et al [2], an exemplification model for our screening, pfPSA testing with tPSA less than 2.5 ng/mL was 29.4%, which was much less than our data, and between 4-10 ng/mL the pfPSA testing was 44.6% which was much more higher than our data. They also showed that pfPSA testing under 50 years of age was 5.7% and our data was 9.8%.

In a previous study by Barutcuoglu et al[9], in 2004-2005, 395 patients suspected PCa were screened by digital rectal examination, tPSA, pfPSA and TRUS guided biopsies were performed. 162 patients diagnosed as PCA at different stages. 10 PCa patients had tPSA < 4 ng/mL, (but not less than 2.5 ng/mL), with pfPSA ≤ 15, and this was 2.5% of all PCa diagnosed patients. Additionally, none of these patients were <50 years old. We had inferred even from this small group of patients that, screening patients with pfPSA in early ages might over diagnose PCa.

The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial found that only 1.5 % (95% CI 1.2-1.7) of men with an initial tPSA less than 1 ng/mL converted to a tPSA greater than 4.0 ng/mL after five years [10]. Similar findings for tPSA screening were noted in the European Randomized Study of Screening for Prostate Cancer (ERSPC) in which the proportion of men with a baseline tPSA below 1.0 ng/mL who converted to a level above 3.0 ng/mL was 0.9 percent after four years [11]. The estimated cancer detection rate was 0.15 percent during a four-year interval.

In the PLCO trial, a four-year screening interval in men with a tPSA below 1.0 ng/mL was estimated to result in a delay in cancer diagnosis of 15.6 months [10]. A separate report came to a similar estimate [12]. The clinical consequences of delayed diagnosis on PCa mortality and morbidity are unknown, although the majority of cancers detected after a four-year screening interval in the ERSPC were early-stage [11].

Improper laboratory testing requests do not cause detriment to patient, but lacking of essential testing leads to contribution to patient harm by under diagnosis, inappropriate medication or surgery. Contrarily, in some cases performing an unnecessary test, may be resulted with over-diagnoses. pfPSA testing on patients with tPSA less than 2.5 ng/mL may lead to unnecessary biopsies and in some cases over diagnose PCa. On the other hand, tPSA greater than 10 ng/mL may lead to excessive number of biopsies and in some cases under-diagnose PCa.

The costs of tPSA and fPSA testing also can not ruled-out in our country. We detected 46% of pfPSA testing has done when tPSA was under ≤ 1ng/mL, which was absolutely unnecessary. Inappropriate test requesting also leads to excessive testing costs, phlebotomy and unnecessary transrectal ultrasonography and prostate biopsy. Our laboratory is only a small fraction of fPSA testing in our country; the national financial effect of inessential fPSA testing is huge. In our opinion, in every health center, PCa screening guidelines should be overviewed carefully.

The main limitation of our study is that there was no clinical data in order to understand why pfPSA testing was so much in young ages (9.8% under age 45) with tPSA levels under 2.5 ng/mL (70.23% tPSA<2.5ng/mL). tPSA is also elevated in a number of benign conditions particularly benign prostatic hyperplasia (BPH) and prostatitis which are relatively rare cases in ages <50 years.

In conclusion, there is a great conflict with acknowledged worldwide-published guidelines and PCa screening requests in our region. We showed that considerable number of pfPSA data for PCa screening was redundant. All this wide extended data have suggested us that, tPSA and pfPSA screening should be carried out stepwise. All laboratories, clinicians and practitioners should revise their PCa screening requests and consistency with guidelines.
References


