The Analysis of Some Factors That Influence on Serum PSA Level in Localized Prostate Cancer Patients: Mathematical Model

Introduction: Serum prostate specific antigen (PSA) concentration in localized prostate cancer (PCa) patients depends on numerous factors related to tumor, prostate and the patient. Tumor factors include tumor volume, localization, growth rate and aggressiveness. Prostate factors include prostate volume, the activity of dihydrotestosterone (DHT) and PSA synthesis. Host factors include androgenic status and total blood volume.

Objective: To discuss all the possible factors that influence on serum PSA levels in localized PCa patients. To present the mathematical model that predicts serum PSA concentration in localized PCa patients.

Methods: Mathematical model is based on the hypothesis that tumor-related PSA molecules are released from the epithelial prostatic cells around the tumor, so called "Destruction Zone" around the tumor (DZ). The amount of PSA is dependent on DZ volume. Moreover, DZ volume depends on tumor volume, tumor localization in the prostate and tumor growth rate.

Results: The study offers the wide spectrum of PSA values, dependent on tumor, prostate and patient characteristics. These values are comparable with the empirical results in the literature, especially if tumor-volume doubling time of three years is entered into the calculations.

Conclusion: Although with some limitations, this mathematical model can explain the great variety of PSA serum concentrations in PCa patients.

Key words: mathematical model, prostate cancer, tumor volume, tumor position.

INTRODUCTION

Prostate-specific antigen (PSA) is a kallikrein-like serine protease produced by the epithelial cells of the prostate and male urethra. The serum levels of PSA may be elevated in the presence of benign prostatic hypertrophy (BPH), prostatitis and other non-malignant conditions. So, it is said that PSA is organ-specific but not cancer-specific. Although the level of PSA as an independent variable is a better predictor of PCa than suspicious findings on DRE or TRUS. PSA lacks specificity and sensitivity for the ideal tumor marker. Moreover, PSA level cannot predict tumor volume and stage; there is a great percent of tumors with PSA lower than historical upper limit of 4.0 ng/ml. Today, it is clear that there is no optimal PSA threshold value for detecting non-palpable, but clinically significant PCa. In addition, there is no universally accepted cut-off or upper limit: PSA is a continuous parameter: the higher the value, the more likely is the existence of PCa (Table 1.)

PROSTATE SPECIFIC ANTIGEN: THE MAIN PRODUCT OF THE PROSTATE SECRETION

Prostate specific antigen is the main product of the prostate secretion. Normal prostate contains 100 mg of PSA. Average PSA concentration in seminal plasma is 0.3-3 mg/mL. Prostate specific antigen was detected for the first time in the seminal plasma, in 1966; its first use was the identification of rape victims. Later, in the 1981, Wang predicted the potential use of PSA as a prostate tumor marker.

PROSTATE SPECIFIC ANTIGEN IN THE PROSTATIC CELLS

The PSA molecule is a glycoprotein with 240 amino acids. The molecular weight of PSA is 34 kDa. The gen for PSA is located on XIX chromosome, near the genes for pancreatic and glandular kallikrein (hK1and hK2). The synthesis of PSA is influenced by testosterone, adrenal androgens and dihydrotestosterone (DHT). Treatment with either testosterone or DHT in LNCaP cells produces dose and time-dependent increases in PSA levels in the cell media and in PSA messenger RNA (mRNA) levels in
After the synthesis in cytosol, PSA molecules are stored in prostatic secretory granules (PSG). These granules, 1 µ in diameter, fulfill the cytosol; during so-called apocrine decapitation, great numbers of PSGs are emptied from the cell to the prostatic acini lumina. Average PSA concentration in prostatic tissue is 15 mg per gram of tissue, as calculated by Kuriyama. However, the expression of PSA is the highest in the epithelial cells of BPH, moderate in normal epithelial cells and the lowest in PCa cells. In addition, PSA expression is higher in well-differentiated PCa cells, than in poor-differentiated high-grade PCa cells.

**THE TRANSFER OF PSA MOLECULES INTO PROSTATIC DUCTS AND THE BLOOD**

Prostatic epithelial cell secretes precursors of PSA into the lumen. This precursor is called pro-PSA, with 244 amino acids and it is enzymatically inactive. In the lumina, hK2 removes polypeptide and transforms pro-PSA into active PSA. Active molecules pass into the circulation, where they are quickly bounded with alpha-1-antichymotripsine (ACT). However, one percentage of active PSA molecules underwent proteolysis and become inactive; these inactive molecules are detected in blood as free PSA.

In normal prostate, PSA molecules enter the circulation through the prostate-blood barrier, consisted of basal cells, basal membrane, stroma, capillary basal membrane and endothelial cells. The common reason for increased PSA shunting into the blood is the damage of pro-state-blood barrier; so, increased serum PSA often follows acute inflammations of the prostate, prostate cancer, prostate infarct and various prostatic tissue traumas, like after biopsy or surgery.

In PCa, the damage is located most probably around the tumor and followed by PSA leakage of PSA from extracellular space, dead cells and ruptured acini to small prostatic or tumor-induced blood vessels. The decreased concentration of free PSA molecules in PCa is the consequence of the same process; due to damaged prostate-blood barrier, the "maturation" of PSA is impaired and just a small percent of PSA is processed into inactive forms. Thus, the larger percent of active molecules enter the circulation where they are almost immediately bounded by ACT. The average half-life of PSA in plasma is 65 hours.

**THE FACTORS THAT INFLUENCE ON PSA BLOOD CONCENTRATION**

All factors that could influence on PSA blood concentration can be divided into three categories: factors related to tumor, prostate and the patient.

1. **Factors related to tumor**

The factors related to tumor that influence on PSA blood level are tumor volume, tumor growth rate and tumor histological type.

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**TABLE 1**

<table>
<thead>
<tr>
<th>PSA level (ng/mL)</th>
<th>Risk of PCa</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.5</td>
<td>6.6</td>
</tr>
<tr>
<td>0.6-1</td>
<td>10.1</td>
</tr>
<tr>
<td>1.1-2</td>
<td>17.0</td>
</tr>
<tr>
<td>2.1-3</td>
<td>23.9</td>
</tr>
<tr>
<td>3.1-4</td>
<td>26.9</td>
</tr>
</tbody>
</table>

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**FIGURE 1:**

The DZ volume represents the difference between concentric spheres TO and TO + T. (TO represents initial tumor volume, TO + T represents final tumor volume after the period of time T; period T equals 65 hours)

1.1 **Tumor volume**

Tumor volume is very important parameter; Stamey was the first that estimated the average PSA/tumor volume ratio of 3.6 ng PSA per milliliter of the tumor, although some other authors had different results. However, this model had significant errors in the single patient evaluation. As PCa secretes low amounts of PSA, it is not the source of elevated PSA, but the damaged tissue around the tumor. In addition, tumors with equal volumes could be associated with various and very different PSA values.

1.2 **Tumor position**

The majority of PCa rise in peripheral zone, due to its richness in glandular elements. It is proved that centrally positioned tumors have higher PSA than its peripheral counterparts. Possibly, central tumors have more neighboring epithelial tissue than peripheral ones.
1.3. Tumor growth rate and tumor grade

According to McNeal, organ-confined PCa has constant volume-doubling time. In addition, tumor grade or cell differentiation is related to tumor volume: the larger the tumor, it is older and therefore, with more poorly differentiated cells. Following this concept, there is no tumor latency; the "latency" is the consequence of small volume and late beginning of the malignant process. For example, if the average tumor doubling time is three years, 30 years are needed for the growth of 1 ml volume tumor, from the first malignant transformation. It is known that high-grade intraepithelial neoplasia (HG-PIN) is discovered in the very young men, in the third decade of life. Conversely, if the first malignant transformation takes place in the man aged 50-60 years, probably he will not live so long to develop significant PCa.

2. Factors related to the prostate

The prostate is glandular organ with intracrine activity and the synthesis of its own hormone, DHT, from testosterone and adrenal androgens. In BPH, due to increased DHT activity, the synthesis of PSA is increased and PSA=1.6 ng/ml is significant predictor of the progression of the BPH. In addition, the PSA concentration in urine is also associated with BPH. The reason for elevation of serum PSA in patients with BPH is more likely DHT hyperactivity and PSA synthesis, than PSA production in hyperplastic, mainly stromal, transition zone. As the majority of glands are localized in the peripheral zone (PZ), it is the main origin of the elevated PSA in BPH. If the PCa appears in the PZ rich in PSA, its growth will follow significant increase of PSA concentration.

3. Factors related to the patient

It seems that hormonal milieu does not affect PSA production. Namely, older men that have BPH, PCa or both diseases, usually have low serum testosterone, but normal or elevated DHT. Elevated DHT levels are probably correlated with decreased serum testosterone. The second factor is the total blood volume. As the blood volume is 7% of total body weight, a man weighted 60kg has 4.2L of blood, while man weighted 120kg has 8.4L of blood. That means, if both men have PSA level of 3.0ng/ml, the heavier man has double amount of PSA than his smaller counterpart.

METHODS

The mathematical model was used in the attempt to explain the great varieties in PSA values, emerged due to various factors and conditions. At first, it was necessary to enter various theoretical mathematical data, like prostate-tumor model, "destruction zone around the tumor" (DZT), position of the tumor, prostate volume, DZT volume etc.

Prostate-tumor model

The prostate and the tumor were presented like ideal spheres. Destruction zone around the tumor (DZ) is the model of PSA-containing tissue around the tumor; it is defined as the volume inside the prostate, which represents the difference between two concentric spheres (Fig. 1).

Tumor volume

Various tumor models were entered, with volumes ranged continuously from 0.01 ml to 15ml.
The position of the tumor in the prostate

Five points were chosen to represent the center of the growth of the tumor models: $r/6$, $2r/6$, $3r/6$, $4r/6$ and $5r/6$, from the center of the prostate model (C) (Fig. 2).

The shape and the volume of the DZ depend on the volume and the position of the tumor: identical tumors can be followed by different PSA levels, due to different volumes of their DZ. (Fig. 3.)

Prostate volume

The different volumes of the prostate model were entered into the calculation: 20ml, 40ml, 60ml, 80ml, 100ml and 120ml.

The calculation of DZ volume

Mr. A. Marjanovic is the author of the software for this mathematical model. The model included general geometrical formulas for the calculations of sphere volumes, and complex equations for the calculation of the calotte, transverse spherical section, section bases and coordinates of intersection of inner spheres and outer sphere.

The growth of the tumor model was analyzed using three possible volume-doubling rates of 2, 3 and 4 years. However, the interval $t$ was constant and equals 65 hours, what is the average PSA half-life in the blood. Therefore, during 65 hours, tumor with volume-doubling time of 2 years produces greater DZ than the tumor with doubling time of 4 years.

The calculation of serum PSA concentration

From the calculated DZ volume, during 65 hours, PSA molecules with the average tissue concentration of 15 mg/ml enter the blood. This result was divided with 2, due to the value of PSA half-life in plasma, and with various blood volumes, in various virtual patients.

Various blood volumes and PSA concentration

Various blood volumes, i.e. body weight were entered into the calculation, ranging from 50kg, continuously to 100kg. The last calculation stresses the need for new PSA derivate, "weight-corrected PSA". It could be calculated as serum PSA multiplied with coefficient $k$: $k = \text{actual weight}/70\text{kg}$ (average weight).

Graphical presentation

On the graphs, PSA serum concentrations are presented on the ordinate and tumor volumes on the abscissa. Every curve on the graph represents tumor volume to serum PSA ratio. Numerous curves represent various prostate volumes, from 20ml to 120ml. On the every particular graph, there is one body weight (i.e. blood volume) and one tumor-volume doubling time. In the graph 1, the patient weighted 70kg, with the prostate of 20ml and the tumor sized 5ml can have serum PSA of 8 ng/ml. On the other hand, the patient weighted 70kg, with the prostate of 120ml and the tumor of 5ml can have serum PSA of 20ng/ml.

RESULTS

The huge number of results and the combinations of different multiple parameters can be presented in the graphs; particular graphs than could be used for particular patient, according to his weight. The best match between graphical values and the literature data was achieved in the graphs with tumor doubling time of 3 years (Graph 2)\textsuperscript{44}. The simpler graphs can be made with the use of minimal curve and the maximal curve. "Minimal curve" represents tumor volume/PSA ratio for the peripheral tumors, arising
from 5r/6 from the prostate model center (C), with the smallest prostates (20ml) and the highest body weights (100kg). Maximal curve represents tumor volume/PSA ratio for the central tumors, arising from r/6 from C, with the largest prostate (120ml) and lowest weight (50kg).

The graphs enable virtual observation of tumor natural history and the rise of tumor volume and the PSA. It is consistent with epidemiological and clinical data that prostate tumors have long period to become "significant".

DISCUSSION

The use of PSA dramatically changed prostate cancer (PCa) detection and treatment strategies. The definition of PSA cut-off of 4.0ng/ml made the PCa diagnosis very easy. Unfortunately, the great number of organ-confined PCa with PSA < 4.0ng/ml emerged, so the cut-off was lowered to 2.5ng/ml. However, new data show that the patients with PSA from 1.1-2.0ng/ml have the risk of harboring PCa of even 17%. So, adored urological marker started to lose its popularity! Some claimed that PSA era is finally completed and PSA-terror ended.

However, there are so many factors that could influence PSA concentration in blood. At the first place, some prostates are DHT-active and rich in PSA, while others are not. On the other side, there is a large number of men with late onset hypogonadism; in the USA, they comprise 43% of men aged = 65 years. These men most probably have lower PSA values than their counterparts. Different tumor volumes also contribute to different PSA values, but not due to their own PSA production, but due to local influence on the surrounding PSA-producing tissue. It is well known that tumors which occupy entire peripheral zone of the prostate can be followed with surprisingly low PSA. In addition, different blood volumes may significantly influence PSA serum levels, due to dilution effect.

This mathematical model had the aim to show the variety of factors that can influence of PSA level; some of these factors can be practically applied, but there is lot of limitations, as well. At the first place, the position of the tumor or multiple tumors can be estimated. The center of the tumor and its volume and boundaries can be measured on whole-mount pathological specimen, as shown in the Fig. 4.

Second, blood volume can be calculated for every patient from its body weight. The insufficiently clarified factors are tumor volume-doubling time, PSA tissue concentration and PSA half-life in plasma. While tumor doubling-time is still hard to measure, PSA half-life can be estimated more precisely. Moreover, tissue PSA could be obtained for every single patient from the biopsy specimen.

CONCLUSION

In the future, with the inclusion of all listed factors, the interpretation of PSA could be more precise and its sensitivity acceptable, again.

SUMMARY

Uvod: Koncentracija prostata specifičnog antigena (PSA) u serumu kod lokalizovanog karcinoma prostate (PCa) zavisí od mnogih faktora. Ovi faktori se mogu podeliti na faktore vezane za tumor, prostatu i pacijenta. Tumorski faktori su zapremina tumora, lokalizacija i brzina rasta tumora. Faktori vezani za prostatu su zapre-
min prostate, activism dihydrotestosterona (DHT) u prostati i jačina sinteze PSA. Faktori vezani za pacijenta su androgeni status i ukupna zapremina krvi. 

Cilj rada: Analiza i diskusija svih navedenih faktora koji mogu da utiču na nivo PSA kod lokalizovanog PCa. Takodje, predstaviti matematički model koji predviđa koncentraciju PSA u serumu kod lokalizovanog PCa.

Metode: Matematički model se zasniva na hipotezi da serumski PSA koji je posledica rasta tumora, potiče iz epitelnih čelija iz neposredne blizine tumora, takođe Zone destrukcije (DZ). Zapremina DZ zavisi od zapremine tumora, njegovog položaja u prostati i njegovih brzine rasta. Sa druge strane, količina PSA koja ulazi u krvotok zavisi od zapremine DZ i koncentracije PSA u DZ.

Rezultati: Ova studija nudi široki spektar vrednosti PSA u zavisnosti od karakteristika tumora, prostate i pacijenta. Ove vrednosti je moguće uporediti sa vrednostima iz literature. Najbolje slaganje sa podacima iz literature se dobiha ako se za period udvostručavanja zapremina tumora uzme period od tri godine.

Zaključak: Uz izvesna ograničenja, ovaj model može da objasni velike raznolikosti koncentracije PSA u serumu.

Ključne reči: matematički model, karcinom prostate, zapremina tumora, položaj tumora

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