INTRODUCTION

Prostate-specific antigen (PSA) is the most useful tumor marker in the diagnostics of prostate carcinoma (1). PSA is serin protease produced by ductal and acinal epithelial cells of normal, hyperplastic, and malignant tissue of the prostate. By the influence of pathological processes the cell integrity is destroyed leading to release of PSA into circulation, i.e. the processes inside prostate, such as hyperplasia, inflammation, tumors, lead to the increase of serum PSA value the most frequently (2-4). The investigations have revealed that every gram of cancer prostate tissue increases the value of serum PSA for 2.3 ng/ml in average, while every gram of hyperplastic tissue increases the same parameter 10 times less compared to cancer tissue (5,6). The PSA value increase is determined by histological characteristics of epithelial cells. In neoplastic processes the increase of serum PSA depends on differentiation of tumor cells. The less differentiated prostate tumors can cause lower PSA concentrations in comparison to those well differentiated (7). In prostate carcinoma (PC) evaluation there are few systems used for estimation of tumor cells differentiation i.e. histological grade of tumor. In literature the grade systems suggested by Mostofi, Broders, and Gleason are the most cited. Classical determination of histological grade according to Mostofi is based on criteria of nuclear anaplasia and formation of gland structures. According to this system prostate carcinoma could exert three histological grades: grade 1 (well differentiated), grade 2 (moderately differentiated), and grade 3 (poorly differentiated) (8).

Meanwhile, Gleason's system (GGS) is nowadays one of the most used grade systems in PC (9). The base of GGS is represented by five histological figures, which, using small microscopic magnification, encompass analysis of gland architectonics, the degree of glandular differentiation as well as stromal invasion, but not the degree of nuclear anaplasia (10,11). The aim of the work is to determine the relation between serum PSA and differentiation of prostate carcinoma using Gleason's system and classical determination of histological grade from 1 to 3, as well as to estimate comparability of these two systems.

METHODS

The investigation included 40 individuals in age from 60 to 79 years (average age, 69.9 years), who had the clinical symptoms of prostatism at digital rectal examination (DRE), established enlargement of prostate suspected to malignant process or benign prostate enlargement accompanied with PSA values above 4ng/ml. The investigation was carried out at Urology Section and Section for Pathology at the Military Hospital in Niš, at the Clinic for Urology and Institute for Pathology of Clinical Center Niš, and in the radioisotopic laboratory "Pharmacia Diagnostica" in Niš in the period from January 2002 to January 2003. Beside the basic disease the examined individuals didn’t have any other health disorder which could significantly influence the function of urinary tract. All patients have been taken a standard urological examination according to modified protocol in keeping with diagnostic protocol for prostate carcinoma (12) (Table 1).

Table 1. Modified diagnostic protocol for prostate carcinoma

<table>
<thead>
<tr>
<th>PSA (ng/ml)</th>
<th>DRE</th>
<th>Diagnostic protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 4 ng/ml</td>
<td>Negative</td>
<td>Following by PSA and DRE</td>
</tr>
<tr>
<td>&gt; 4 ng/ml</td>
<td>Negative</td>
<td>Ultrasonography and biopsy of suspected lesions</td>
</tr>
<tr>
<td>&gt;10 ng/ml or any other values</td>
<td>Positive</td>
<td>Biopsy of palpable and ultrasonographically suspected lesions</td>
</tr>
</tbody>
</table>

DRE - digitorectal examination

Using this protocol the standard diagnostic methods have been applied: DRE, transabdominal ultrasonography of prostate, determination of serum PSA, biopsy of prostate.
**Indications for biopsy**

The biopsy was performed with "Tru-cut" needle using transrectal or transperineal approach with previous preparing of patient (purification and antibiotic protection). Also, the material obtained by transurethral resection (TUR) of prostate, used in diagnostic and therapeutic purposes, was analyzed. The indications for biopsy were: changes of prostate clinically assigned as adenoma with a presence of areas suspected to malignant process, suspected malignant changes on DRE, clinically clear malignant changes, chronic indurative inflammatory changes refractory to antibiotic therapy, intermediary or high serum PSA values.

**PSA determination**

In all investigated individuals the level of PSA was determined in identical way. PSA was estimated in venous blood using two position and fluorimunnometric method based on direct "sandwich" technique. There was no immediate manipulation on prostate (DRE, prostate massage, endoscopic examination) before taking a blood sample for PSA. DELFIA PSA equipment manufactured and distributed by WALLAC was used for PSA determination. The range of PSA determination using this equipment is 0.1-500ng/ml.

**Histological verification**

Micromorphometric analysis of obtained material was done on standard HE preparations. Fixation of tissue samples has been done in 10% formaldehyde solution for 24 hours. The tissue was prepared routinely, put in paraffin, cut on microtom to the thickness of 4 microns, and then the sections were colored by hemotoxyllin-eosin (HE) method. Determination of differentiation of tumor was performed using classical determination of histological grade from 1 to 3, as well as histological grade according to Gleason. The grade determination according to Gleason means establishment of primary (dominant) and secondary (the second frequent) histological feature, as well as estimation of Gleason's score. The values of Gleason's score range from 1-5 and the total score is obtained as the sum of the values of primary and secondary Gleason's grades. The lowest value of Gleason's score is 2, and the highest is 10. The patients were divided into three groups according to the value of Gleason's score: group I (Gleason's score 2-4), group II (Gleason's score 5-7), and group III (Gleason's score 8-10).

The analysis of planned parameters was done inside the groups and according to Gleason's grades. The following statistical tests were performed: Student t test for two big and two small independent samples, Kruskal-Walls, $\chi^2$-test, Pearson's coefficient of linear correlation ($r_p$).

**RESULTS**

PSA values in individuals with prostate carcinoma ranged from 2.20 to 210.00 ng/ml. In one examined person PSA concentration was at the level of referent values, while in 11/40 (27.5%) it was in the range of intermediary values 4.01 - 10.00 ng/ml. On the other side, 28/40 (70%) of examined persons had high values of PSA (above 10.00 ng/ml) (Table 2).

<table>
<thead>
<tr>
<th>PSA (ng/ml)</th>
<th>Number</th>
<th>Carcinoma of prostate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01-4.00</td>
<td>47</td>
<td>2.50</td>
</tr>
<tr>
<td>4.01-10.00</td>
<td>11</td>
<td>27.50</td>
</tr>
<tr>
<td>10.01-20.00</td>
<td>21</td>
<td>7.50</td>
</tr>
<tr>
<td>&gt;20.00</td>
<td>21</td>
<td>52.50</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>100.00</td>
</tr>
</tbody>
</table>

The highest number of patients with prostate carcinoma, 21/40 (52.5%) had intermediary Gleason's score (5-7). In this group serum PSA values ranged from 5.00 - 60.00 ng/ml with Me = 22.0 ng/ml. One third of treated persons - 12/40 (30.0%) had a high Gleason's score (8-10). These persons had PSA value in the range 5.00 - 210.00 ng/ml with Me = 41.50 ng/ml. The smallest number of persons had a low Gleason's score (<5), i.e. 7/40 or 17.5%, PSA concentration was the lowest in this group with Me = 7.50 ng/ml (Table 3).

Table 3. Gleason's score and PSA level in serum of examined persons with prostate carcinoma

<table>
<thead>
<tr>
<th>Gleason's score</th>
<th>Number (%)</th>
<th>X ± SD</th>
<th>min - max</th>
<th>Me</th>
<th>Interquartile difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 - 4</td>
<td>7 (17.5%)</td>
<td>10.47 ± 6.99</td>
<td>2.20 - 22.00</td>
<td>7.50</td>
<td>6.70 - 18.00</td>
<td>0.0188</td>
</tr>
<tr>
<td>5 - 7</td>
<td>21 (52.5%)</td>
<td>28.68 ± 17.25</td>
<td>5.00 - 63.00</td>
<td>22.00</td>
<td>10.23 - 39.45</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>8 - 10</td>
<td>12 (30.0%)</td>
<td>58.45 ± 58.09</td>
<td>5.00 - 210.00</td>
<td>41.50</td>
<td>11.13 - 90.65</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Total</td>
<td>40 (100.0%)</td>
<td>34.09 ± 37.94</td>
<td>2.20 - 210.00</td>
<td>22.00</td>
<td>8.85 - 48.825</td>
<td></td>
</tr>
</tbody>
</table>

PSA values in serum of patients with prostate carcinoma were statistically significantly different between the three groups of examined persons, where the leading criteria was the value of Gleason's score (low, intermediary, high).

Kruskal-Walls test was used and its value was $\chi^2=7.9522$, and the statistical significance was p < 0.05. Looking at data in Table 3 it could be noticed that the average values (arithmetic mean and median) of serum PSA in patients with prostate carcinoma are higher in groups with higher Gleason's score. To investigate possible relations between Gleason's score and PSA concentration, we calculated the coefficient of linear correlation and constructed the regression line (Figure 1).

**Figure 1. Regression line and a coefficient of linear correlation between PSA (ng/ml) and Gleason's score**

It is documented that there is statistically highly significant positive correlation between PSA and Gleason's score in prostate carcinoma ($r_p=0.4619$; p=0.003; $<0.01$) (Figure 1). Determination coefficient ($r_{xy}^2=0.213$) points out the fact that Gleason's score is one of the factors that influence serum PSA concentration in patients and that its part is 21.3%. Beside Gleason's score, the classical determination of tumor histological grade (1-3) was used for the estimation of tumor cell differentiation. The most patients had tumor grade 2 and 3 (35/40 or 87.5%). Only 5 persons with prostate carcinoma had grade 1. In the group of patients with well-differentiated adenocarcinoma of prostate (G1) the values of PSA were the lowest. PSA concentration in serum of patients with prostate carcinoma with differentiation grade 1, ranges from 2.20-22.0 ng/ml with Me=7.50 ng/ml. In the group of patients with tumor grade 2, the value of Me for PSA was higher (Me=22.0 ng/ml), as well as the variation interval (min-max) and interquartile difference (9.60-42.27 ng/ml). The individuals, whose tumor cell differentiation grade was estimated as 3, had the highest values of serum PSA (Me=33.00) (Table 4).

Table 4. Tumor grade and the level of serum PSA in patients with carcinoma

<table>
<thead>
<tr>
<th>Grade</th>
<th>Number (%)</th>
<th>X ± SD</th>
<th>min - max</th>
<th>Me</th>
<th>Interquartile difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 (12.5%)</td>
<td>11.28 ± 8.33</td>
<td>2.20 - 22.00</td>
<td>7.50</td>
<td>4.45 - 20.00</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>2</td>
<td>28 (65.0%)</td>
<td>28.33 ± 19.91</td>
<td>5.00 - 75.00</td>
<td>22.00</td>
<td>9.60 - 42.27</td>
<td>p = 0.0572</td>
</tr>
<tr>
<td>3</td>
<td>9 (22.5%)</td>
<td>83.41 ± 65.92</td>
<td>6.00 - 210.00</td>
<td>33.00</td>
<td>13.75 - 97.50</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Total</td>
<td>40 (100.0%)</td>
<td>34.09 ± 37.94</td>
<td>2.20 - 210.00</td>
<td>22.00</td>
<td>8.85 - 48.825</td>
<td></td>
</tr>
</tbody>
</table>

Using Kruskal-Walls $\chi^2$ test it was established that the differences in PSA values between these three groups are at the border of statistical significance ($\chi^2=5.7234$; p=0.0572; p > 0.05). Table 4 clearly shows that the increase of PSA in serum of patients with prostate carcinoma is followed by less differentiation of tumor. To establish whether this relation is accidental or not, we had used regression and correlation analysis. It was proved that there was statistically significant positive correlation between prostate carcinoma cell differentiation grade expressed through grade and the concentration of PSA in serum of examined persons ($r_{xy}=0.4325$; p = 0.005; $<0.001$) (Figure 2).
DISCUSSION

PSA is tumor marker, which serum levels are under the influence of physiological and pathological processes, meaning that PSA is not highly specific for prostate carcinoma. Clinically applicable referent values for this marker are from 0 - 4.0 ng/ml, but they don't point out the absence of carcinoma always. Intermediary PSA values, i.e., value interval from 4.0 - 10.0 ng/ml, could be present in patients with benign hyperplasia of prostate, prostatitis, intraepithelial neoplasia as well as prostate carcinoma (3,13).

The results of our investigation show that PSA values in patients with prostate carcinoma ranged widely, i.e. in the interval of referent, intermediary and high values. Approximately one third of examined persons had serum PSA levels in the interval of intermediary values, where it was necessary to distinguish whether it was prostate carcinoma or benign disease, which was only possible to determine by biopsy of prostate. This is one of examples of limited use of PSA test.

Our choice of standard clinically changeable PSA intervals with cut-off value of 4 ng/ml and not age-specific referent values had been based on studies of authors who proved that PSA didn't correlate with age. There are also numerous studies in which the usage of different levels of age-specific referent values has been reported (14-16). In the last years, the attention was paid on lowered cut-off value for PSA, i.e. 2.5 ng/ml, where inside the value interval of 2.6-4.0 ng/ml (20%) to 25% of biopsied patients had prostate carcinoma (17,18).

Our results show that serum PSA level is in positive correlation with Gleason's score, as well as that two thirds of our patients have intermediary Gleason's score which is in accordance with other authors' studies (19-21).

Literature data point out that the highest number of patients with prostate carcinoma has intermediary value of Gleason's score (5-7) (22). For example, in a big study of Roehl et al., related to 241 patients with prostate carcinoma confirmed by biopsy, more than half of intermediary value of Gleason's score (5-7) (22). For example, in a big study of Roehl et al., related to 241 patients with prostate carcinoma confirmed by biopsy, more than half of examined patients had clinically localized carcinoma and moderate differentiation with predominant Gleason grade (Histological grade), while 81.3% represent other factors (age, etc.).

The results of study of correlation between PSA and tumor differentiation grade determined by classical determination of histological grade, while 81.3% represent other factors (age, etc.).

Determination coefficient is low $r_{xy2} = 0.187$ pointing out the fact that PSA level in men with prostate carcinoma is determined in 18.7% by tumor cell differentiation histological grade (histological grade), while 81.3% represent other factors (age, etc.).

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This study showed that there was high positive correlation between serum PSA value and carcinoma differentiation grade determined by Gleason's system, as well as low correlation between PSA and tumor differentiation grade determined by classical determination of histological grade from 1 - 3. Dominant histopathological finding during revealing of prostate carcinoma is the presence of carcinoma of high Gleason's grade and score.

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Predictive ECG coding using linear time-invariant models

Aleksandar Bošković¹, Miroslav Despotović², Dragana Bajić²

ABSTRACT

Electrocardiogram (ECG) signal compression suffers of lack of standards for analogue-digital conversion. Results of this study have shown that 8 bits/sample, although frequently in use, does not satisfy quality criteria for medical doctors. This paper also presents predictive technique for lossless ECG compression using linear time-invariant models. Tests on clinically measured ECG signals confirm a very good performance in terms of compression ratio.

KEY WORDS: Electrocardiography; Signal Processing, Computer Assisted; Analog-Digital Conversion; Linear Models

INTRODUCTION

A typical ECG signal requires less storage capacity than for medical images. However, ECG monitor devices are used frequently, even on a regular medical exams, while the medical images are recorded only when is necessary. Nowadays, electrocardiograph represents a necessary diagnostic device. Consequently, large amounts of data have to be stored. A need for efficient coding of ECG signals is continually increasing with modern use of long-term monitoring and telemicine. Modern medical telemetry systems with low bit-rate channels require signal compression for efficient functioning.

For example, high-resolution electrocardiogram monitoring device, records 12-channels ECG with 11-bit resolution and sampling rate of 1000 samples per second, and therefore it generates over 56 MB per hour (about 1360 MB per day), or charges the network with constant flow of 132 kb/s. Thus, the ECG signal compression is not only desirable and useful, but also necessary.

Signal compression methods fall into two common categories: lossy and lossless. Lossless ECG compression is essential for storage and transmission of electrocardiographs. The purpose of ECG compression should not be only to transmit or store the signal with fewer bits, but also to preserve the clinically significant information. According to the law regulations in many countries, medical signals after lossy compression cannot be used in diagnostics.

Predictive methods are a subclass of the lossless techniques. These methods exploit redundancy between samples, beats and leads of ECG signal, so that only new information has to be coded. Correlation of ECG samples is significant, and it is illustrated in Figures 3. and 4. In this paper, predictive techniques for lossless ECG compression are introduced. In combination with entropy coding, they achieve very good results.

The Massachusetts Institute of Technology and Beth Israel Hospital (MIT-BIH) ECG Compression Test Database and the MIT-BIH Arrhythmia Database were used for testing the different compression methods. The MIT-BIH ECG Compression Test Database contains 168 short ECG two-lead recordings (20.48 seconds each). The recordings were digitized at 250 samples per second per lead with 12-bit resolution over a 10 mV range. The MIT-BIH Arrhythmia Database contains 48 half-hour excerpts of two-lead ambulatory ECG recordings. The recordings were digitized at 360 samples per second per lead with 11-bit resolution over a 10 mV range.

The amount of compression is often expressed with the compression ratio (CR)

\[ CR = \frac{b_{orig}}{b_{comp}} \]

that is defined as the ratio between the bit rate of the original ECG signal and the bit rate of the compressed one. In this way, compression ratio shows how much the ECG data is being compressed compared to the original.