CORRELATION BETWEEN PSA LEVEL AND GLEASON SCORE IN NEWLY DIAGNOSED PROSTATE CANCER PATIENTS IN ARAD COUNTY

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ABSTRACT. Prostate carcinoma (PCa) is the second most common type of cancer among men from North America and Europe. Histopathological diagnosis of PCa can be established by transrectal ultrasound-guided (TRUS) biopsy after an abnormal finding in digital rectal examination or finding an increased value of prostate specific antigen (PSA) in the blood. The purpose of this study is to evaluate the correlation between PSA level and Gleason score, in order to predict prostate cancer aggressiveness at time of diagnosis.

KEY WORDS: prostate, cancer, PSA, Gleason, score.

INTRODUCTION
Prostate carcinoma (PCa) is the second most common type of cancer, as well as the second most common cause of cancer-related death among men from North America and Europe \cite{1,2,3}. This disease is a serious health concern, especially in developed countries where the elderly population is growing \cite{3}. Histopathological diagnosis of PCa can be established by transrectal ultrasound (TRUS) prostate biopsy, after an abnormal finding in digital rectal examination (DRE) or finding an increased value of prostate specific antigen (PSA) in the blood \cite{3}. An elevated PSA level is not specific only for PCa, but it can also be associated with other prostate pathologies such as benign prostate hyperplasia (BPH) or prostatitis\cite{3}. Despite this disadvantage, PSA measurement remains the gold standard in clinical practice, given that no new biomarkers are currently accepted for diagnosis of prostate cancer. The purpose of this study is to evaluate the correlation between PSA level and Gleason score, in order to predict prostate cancer aggressiveness at diagnosis.

MATERIAL AND METHODS
This was a prospective study which took place between October 2015 and September 2017. The study included 59 patients who signed the informed consent, with the following inclusion criteria: abnormal DRE and PSA level (> 4 ng/dl), who underwent TRUS prostate biopsy. After PCa detection through histopathological examination, the patients were divided into 3 groups according to cancer aggressiveness, in terms of mild (<7), moderate (=7), and high (>7) Gleason score. The patients were also classified according to PSA levels, in two groups: PSA 4-10 ng/ml and PSA > 10ng/ml. This division was made in order to highlight patients diagnosed with PCa who belong in the „grey zone”(4-10ng/ml).

Furthermore, the groups were compared to each other according to age, PSA level and Gleason score.

STATISTICAL ANALYSIS
All statistical analyses were conducted using Statistica version 7 (StatSoft Inc., Tulsa, USA). In all cases, a \textit{p} value < 0.05 was considered significant. Based on the Gleason score, the men were stratified as having low-risk PCa (Gleason score < 7), moderate-risk PCa (Gleason score = 7), and high-risk PCa (total Gleason score > 7), respectively. The inter-group homogeneity of age among different groups was checked with a Median test. The blood PSA levels across different classes of PCa were compared using a Median test, with Mann-Whitney tests against the low-risk PCa group being conducted in the case of significant differences. Finally, we investigated the relationship between PSA and PCa aggressiveness using Spearman’s rank correlations.

RESULTS
Prostate cancer can be an evasive diagnostic, because of the wide heterogenity refering to age, PSA level and Gleason score. A positive biopsy result was found in all patients. The PSA level corresponded well with the diagnosis of prostate cancer. All recorded patients showed a PSA level above 4ng/ml, the majority of patients had a PSA level above 10 ng/ml (88%), the rest of patients (12%) belonged in the „grey zone” (4-10 ng/ml).
The majority of subjects who participated at this study had the age between 60 and 79 years (49 subjects, 83%), with a median age of 68.9 years, and a PSA level >10 ng/ml.

The Gleason system is used to classify prostate cancer aggressiveness. Based on the Gleason score, the men were stratified as having low-risk PCa (Gleason score < 7), moderate-risk PCa (Gleason score = 7), and high-risk PCa (total Gleason score > 7), respectively. [4]

According to prostate cancer aggressiveness, 14% of subjects had high grade PCa, the majority of subjects (69%) were recorded with intermediate grade of PCa and 17% of patients had low grade PCa. Medium level Gleason score = 7 is considered ambiguous because of Gleason Sum variability (7=3+4, 7=4+3). Pattern 4 plays a key role in differentiating cancer aggressiveness, as cancerous tissues with pattern 4 > 50%, are much closer to evolve like an high risk cancer. (7) Our study shows that 56% of patients had Gleason sum (3+4) the rest of 44% were recorded with a Gleason sum (4+3).
Table 1. Distribution of subjects according to Gleason score

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Nr. Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score Gleason 4 (2+2)</td>
<td>2</td>
</tr>
<tr>
<td>Score Gleason 5 (2+3)</td>
<td>6</td>
</tr>
<tr>
<td>Score Gleason 6 (3+3)</td>
<td>2</td>
</tr>
<tr>
<td>Score Gleason 7 (4+3)</td>
<td>18</td>
</tr>
<tr>
<td>Score Gleason 7 (3+4)</td>
<td>23</td>
</tr>
<tr>
<td>Score Gleason 8(3+5)</td>
<td>2</td>
</tr>
<tr>
<td>Score Gleason 8(4+4)</td>
<td>3</td>
</tr>
<tr>
<td>Score Gleason 9</td>
<td>3</td>
</tr>
</tbody>
</table>

When stratified based on the aggressiveness of PCa, the average age of patients were 68.80 ± 4.98 years for low-risk PCa patients; 69.65 ± 7.09 years for medium-risk PCa patients; and 65.37 ± 6.88 years for high-risk PCa patients. The measured values were homoscedastic (Levene's test, \( p = 0.604 \)) and similar among different classes of PCa aggressiveness (ANOVA, \( p = 0.257 \)), thus attesting to the homogeneity of groups in terms of patient age.

Fig.3. Median age values according to Gleason score

The highest number of patients with aggressive PCa, developed the disease earlier compared to the rest of the groups. Inspite the lack of statistical power due to the small cohort of patients, this was not a surprise for us, because Arad county is considered a hot spot for cancer, due to high concentrations of arsenic found in drinking water from ground water. [5]

Table 2. Measured values of blood PSA levels in PCa patients with different Gleason scores

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Sample size</th>
<th>Blood PSA level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median</td>
</tr>
<tr>
<td>4 (2+2)</td>
<td>2</td>
<td>34.36</td>
</tr>
<tr>
<td>5 (2+3)</td>
<td>6</td>
<td>18.95</td>
</tr>
<tr>
<td>6 (3+3)</td>
<td>2</td>
<td>44.00</td>
</tr>
<tr>
<td>7 (3+4)</td>
<td>23</td>
<td>34.00</td>
</tr>
<tr>
<td>7 (4+3)</td>
<td>18</td>
<td>31.70</td>
</tr>
<tr>
<td>8 (3+5)</td>
<td>2</td>
<td>521.50</td>
</tr>
<tr>
<td>8 (4+4)</td>
<td>3</td>
<td>93.37</td>
</tr>
<tr>
<td>9 (4+5)</td>
<td>3</td>
<td>109.00</td>
</tr>
</tbody>
</table>

Data are shown as medians with lower quartiles (Q25) and upper quartiles (Q75).
Among the patients investigated, 10 patients had low-risk PCa (16.94%), 41 had medium-risk PCa (69.49%), and 8 patients had high-risk PCa (13.57%). Figure 4 shows the median values (with Q25 and Q75 values) for blood PSA for patients belonging to different classes of PCa aggressiveness. The measured values were significantly different among the groups investigated (median test, \( p = 0.006 \)). When compared with the subjects with low-risk PCa, posthoc comparisons revealed no significant differences in serum PSA for the men with medium-risk PCa (Mann-Whitney test, \( p = 0.418 \)), but significantly higher median levels for men with high-risk PCa (Mann-Whitney test, \( p = 0.006 \)). We also note a much higher variability of serum PSA for medium-risk PCa and high-risk PCa relative to low-risk PCa.

**DISSCUTION**

Selection of patients was made by PSA cut off value of 4ng/ml, a positive biopsy result was found in all patients. The PSA level corresponded well with the diagnosis of prostate cancer. All 59 patients who participated at the study had a PSA value above 4 ng/ml, the majority of them (88%) had a PSA above 10 ng/ml. Despite that the PSA cut off value of 4 ng/ml remains the gold standard of screening and early detection of prostate cancer, studies attest Pca cases with a PSA under 4 ng/ml. This fact leaded to lowering of PSA cut off value, which resulted with elevated number of false negative biopsy punctures. PSA remains an organ specific biomarker and can present elevated values also in benign entities, like BPH or chronic inflammatory diseases. [6]

A study made by Partin, revealed that correlation exists between PSA and patologic clinical stage of prostate cancer: 80% of subjects with a PSA \(< 4 \text{ ng/ml}\) have an organ localised disease, over 50% of patients with a PSA \(> 10 \text{ ng/ml}\) have extracapsulary disease, and 75% of patients with a PSA \(> 50 \text{ ng/ml}\) have positive pelvic lymph nodes. [7]

Also world wide screening programs defined the interval of PSA value between 4-10 ng/ml, as the „grey zone”, in order to make a careful distinction between BPH and PCa, reducing this way the number of false negative biopsies. When dealing with „grey zone” values, the use of complementary biomarkers is needed, like Free PSA or PCA 3. [8]

All subjects who participated at the study had the age over 50 years, with a median of 68,9 years, the majority of them (49subjects, 83%), had the age between 60 and 79 years old. This result is in acquaintance with the scientific literature in terms that the majority of patients affected by prostate cancer are over 50 years old, most of them have between 65 and 69 years. [9]

Oesterling et al, proposed using age intervals in order to enhance early prostate cancer detection and to elarge the specificity of PSA at elderly patients, because PSA cutoff values < 4ng/ml do not reflect prostate volume changes related to age in development of BPH. Oesterling et al, reported a general specificity of 95/\%, within the following age intervals:

- Age: 40-49 years -0,2,5 ng / ml;
- Age: 50-59 years -0,3,5 ng / ml;
- Age: 60-69 years -0,4,5 ng / ml;
- Age: 70-79 years -0,6,5 ng / ml.

Using these age references in clinical practice, has lead to early diagnosis of prostate cancer with potential radical cure, in men under 60 years old, also to the increase of diagnosing insignificant (low grade) prostate cancer, which resulted in over treatment of this disease. If the purpose of using the age intervals is to identify the biggest number of prostate cancers, then all aged males should be tested. [6,12]

Our study revealed that indifferent of ages status the majority of patients had a PSA >10 ng/ml, 44% belonged in the age group 60-69-years. According to age intervals, all patients included in the study had higher age references then Oesterling et al reported.

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**Fig. 4. PSA levels according to different classes of PCa aggressiveness.**
Gleason sistem is used to classify prostate cancer aggressiveness. Based on the Gleason score, the men were stratified as having low-risk PCa (Gleason score < 7), moderate-risk PCa (Gleason score = 7), and high-risk PCa (total Gleason score > 7), respectively.

According to prostate cancer aggressiveness, 14% of subjects had high-risk PCa, the majority of subjects (69%) were recorded with intermediate-risk of PCa and 17% of patients had low-risk PCa.

Subjects with Gleason score 7 were divided in terms of cancer aggressiveness, according to Gleason sum of patterns, 7=3+4 and 7=4+3. Stamey showed that pattern 4 plays a key role in differentiating cancer aggressiveness, as cancerous tissues with dominant pattern 4 > 50%, are much closer to evolve like an high risk cancer. [7]

Our study revealed that 56% of patients had Gleason sum 7 (3+4) the rest of 44% were recorded with a Gleason sum 7(4+3).

Scientific literature published by Pietro Pepe and Michele Pennisi attests that Gleason score increases with the age of patients and they demonstrated a significant correlation between Gleason score ≥ 8 and elderly men over 80 years old. [9,13]

When discussing age values according to Gleason score, the highest number of patients with aggressive PCa, had a median age of 65.37 ± 6.88 years. This suggests an early debut of aggressive disease, compared to the rest of groups and it could be related to the fact that Arad county is considered a hot spot for prostate cancer. part 1: screening, diagnosis, and localtreatment with curative intent-update 2013. Eur Urol. 2014;65:124–137. [PubMed]


CONCLUSIONS

All patients included in the study, had higher age references then recorded age intervals used in guidelines.

The majority of subjects were recorded with intermediate PCa risk.

The dominant number of patients with high risk PCa developed the disease earlier compared to the rest of groups, with medium and low risk PCa.

According to our study, there is a relationship between PSA level and Gleason score at time of diagnosis, which suggests an overall trend towards increasing blood PSA levels with the PCa aggressiveness. Therefore, PSA remains a good indicator for predicting the Gleason score.

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