The estimation of malignancy degree of prostate cancer by MRI (T2-WI, DWI, MRS and DCE)

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Nowadays the morbidity of prostate cancer remains stable and high, during last 25 years the mortality has increased for 16% [1-4].

The diagnosis of prostate cancer remains difficult due to variety of histological types with similar and non-specific clinical findings but dramatically different management [5].

Last years there is a strong tendency to use minimally invasive and organ-preserving methods of treatment [5, 6]. The choice of treatment as well as its efficacy basically depends on the stage of the process that is based on distinction of extra- and intracapsular tumor growth [3, 7].

Tumor aggressiveness is determined by Gleason grade: high grade tumors corresponds to Gleason 8-10, intermediate-high tumors - Gleason 7, intermediate tumors - Gleason 5-6 and low grade tumors - Gleason 2-4 [2, 8].

It is well-known that high grade carcinomas show "more malignant" behavior comparing with low grade cancers, it is consistent with rapid invasive growth, metastasis and high risk of relapse after the treatment [8]. Therefore, determination of tumor grade is important for treatment planning.

Typical signs of prostate cancer include impairment of glandular structure with local reduction of signal on T2-weighted images, inhomogeneous, early and rapid contrast enhancement with slow wash-out of contrast medium, local growth and metastasis [9].

The purpose of the following study was to estimate the criteria of prostate cancer malignancy grade based on MRI data.
Methods and Materials

The study enrolled 87 patients with morphologically verified 102 foci of prostatic carcinoma. Group 1 included 33 foci Gleason score 3-5 and group 2 included 69 foci of Gleason score 6-9. All the examinations were performed at 1,5 T system, protocol included T1- and T2-weighted images, diffusion weighted images (DWI), dynamic contrast enhancement (DCE) and MR-spectroscopy (MRS). In all the cases diagnosis was pathologically proved.
Results

Comparison of 2 groups showed differences of quantitative parameters (Table 1).

Table 1

Low grade vs high grade prostate cancer: quantitative parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low grade cancer</th>
<th>High grade cancer</th>
<th>Significance,</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter value</td>
<td>n</td>
<td>Me[Q_{25};Q_{75}]</td>
<td>n</td>
</tr>
<tr>
<td>Tumor area measured in axial plane, #m^2</td>
<td>33</td>
<td>1,54 [0,72; 2,29]</td>
<td>69</td>
</tr>
<tr>
<td>Signal intensity tumor / obturator muscle at T2-WI</td>
<td>33</td>
<td>2,23 [1,97; 2,5]</td>
<td>60</td>
</tr>
<tr>
<td>ADC, #10⁻⁵ mm^2/s</td>
<td>30</td>
<td>60 [40; 72]</td>
<td>61</td>
</tr>
<tr>
<td>Choline level (Cho), units</td>
<td>26</td>
<td>0,28 [0,15; 0,37]</td>
<td>61</td>
</tr>
<tr>
<td>Creatine level (Cr), units</td>
<td>26</td>
<td>0,089 [0,025; 0,114]</td>
<td>61</td>
</tr>
<tr>
<td>Citrate level (Ci), units</td>
<td>26</td>
<td>0,42 [0,21; 0,59]</td>
<td>61</td>
</tr>
<tr>
<td>(Cho+Cr)/Ci</td>
<td>26</td>
<td>0,85 [0,62; 1,43]</td>
<td>61</td>
</tr>
<tr>
<td>Signal intensity at peak</td>
<td>20</td>
<td>98,5 [82,8; 136,5]</td>
<td>40</td>
</tr>
</tbody>
</table>
enhancement, units

<table>
<thead>
<tr>
<th>Time to peak enhancement, sec</th>
<th>20</th>
<th>40</th>
<th>27</th>
<th>0,605</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[34; 36]</td>
<td>[25; 32]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signal intensity at 120 sec of DCE, units</th>
<th>20</th>
<th>40</th>
<th>148</th>
<th>0,010</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[89; 128]</td>
<td>[110; 207]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wash in rate, units / sec</th>
<th>20</th>
<th>40</th>
<th>8,45</th>
<th>&lt;0,001</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[2,46; 4,66]</td>
<td>[4,48; 9,94]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wash out rate, units / sec</th>
<th>20</th>
<th>40</th>
<th>0,57</th>
<th>0,071</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[0,06; 0,49]</td>
<td>[0,04; 0,97]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The table shows that high grade tumors have significantly larger sizes comparing with low grade carcinomas (p<0,05), consequently tumor size can be interpreted as indirect sign of its malignancy. The Gleason 3-5 tumors also demonstrate significantly lower signal intensity on T2-WI than high grade carcinomas with corresponding values of ratio tumor / obturator muscle signal intensity (#=0,011). Thos fact can be explained with higher water content in high grade tumors probably due to edema and / or dilation of the lymphatic vessels and needs further investigation.

It is noteworthy, that difference of ADC between 2 groups is close to statistically significant (#=0,053) and can be interpreted as indirect sign of dense cellularity of high grade tumors comparing with low grade malignancies.

MRS reveals significant difference of main metabolites ratio ((Cho+Cr)/Ci; #=0,002). Choline levels between 2 groups also differ (#=0,013) but the differentiation between low and high grade tumors should not be based on this parameter only (Figure 1, Figure 2).

All the quantitative parameters of DCE in the group of low grade carcinomas are lower than in high grade tumors (p<0,05).

Also the frequency of high signal intensity on the diffusion-weighted images with high b-value (> 1000 s/mm²) has been studied (Table 2).
Low grade vs high grade prostate cancer: signal intensity at DWI with b-value > 1000 s/mm²

<table>
<thead>
<tr>
<th>Signal intensity at DWI with b-value (&gt; 1000 s/mm²)</th>
<th>Gleason 3-5</th>
<th>Gleason 6-9</th>
<th>Ratio of chances</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased, n=54</td>
<td>6</td>
<td>11</td>
<td>48</td>
<td>89</td>
</tr>
<tr>
<td>Isointensive, n=37</td>
<td>24</td>
<td>65</td>
<td>13</td>
<td>35</td>
</tr>
<tr>
<td>Total, n=91</td>
<td>30</td>
<td>33</td>
<td>61</td>
<td>77</td>
</tr>
</tbody>
</table>

* - control group

Such distribution of signal intensity is shown to be statistically significant (#<0,001, df=1, Pearson index $X^2=28,7$). Consequently, it can be stated that tumor containing foci of high signal intensity at DWI with high b-values is 14,8 times [5,0-43,7] more probable to be high grade malignancy than low grade cancer (Figure 3).

Due to difference of ADC between normal gland and neoplastic tissue the borders of tumor can be accurately identified (Figure 4).

Two groups were also compared according to qualitative parameter of DCE - dynamic curve - representing summarized characteristics of contrast medium passage at tumor tissue (Table 3).

Table 3

Low grade vs high grade prostate cancer: DCE curve

<table>
<thead>
<tr>
<th>Type of curve</th>
<th>Gleason 3-5</th>
<th>Gleason 6-9</th>
<th>Ratio of chances</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>II type</td>
<td>4</td>
<td>57</td>
<td>3</td>
<td>43</td>
</tr>
<tr>
<td>slow</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
enhancement, n=7

III type 6
- rapid enhancement followed by slope enhancement, n=9

IV type 3
- rapid enhancement followed by plateau, n=14

V type 7
- peak enhancement, n=30

Total, n=60

* - control group

Such distribution of dynamic curve types is shown to be statistically significant (\#<0.036, df=3, Pearson index \(X^2=8.53\)).

According to this data, tumor with IV type of dynamic curve has probability to be high grade cancer which is 7.3 [1.1-48.3] times higher than probability to be low grade cancer. While tumor with V type of dynamic curve has probability to be Gleason 6-9 cancer which is 6.6 [1.3-33.3] times higher than for the tumor with III type of curve (Figure 5, Figure 6).

Taking into account that 95% confidence interval of chance ratio for the II type of curve contains 1, the difference between chance ratio with control group (III type of curve) has no significance (p>0.05).

The presence of tumor in the pelvic fat was also analyzed according to the tumor grade (Table 4).

Table 4

Low grade vs high grade prostate cancer: involvement of pelvic fat
The revealed difference in extracapsular growth between low grade and high grade tumors is considered to be statistically significant (#<0.002, df=1, Pearson index $X^2 = 10.23$). With the presence of tumor tissue in paraprostatic fat the probability of tumor to be high grade cancer is 5.8 [2.0-16.7] times higher than low grade carcinoma.

The difference between low and high grade cancer was also analyzed in terms of frequency of seminal vesicles invasion (Table 5).

**Table 5**

Low grade vs high grade prostate cancer: invasion to the seminal vesicles

<table>
<thead>
<tr>
<th>Seminal vesicles invasion</th>
<th>Gleason 3-5</th>
<th></th>
<th>Gleason 6-9</th>
<th></th>
<th>Chance ratio</th>
<th>95%-confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent, n=74</td>
<td>31</td>
<td>42</td>
<td>43</td>
<td>58</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Present, n=28</td>
<td>2</td>
<td>7</td>
<td>26</td>
<td>93</td>
<td>9.4</td>
<td>[2.1-42.4]</td>
</tr>
<tr>
<td>Total, n=102</td>
<td>33</td>
<td>32.4</td>
<td>69</td>
<td>67.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* - control group

Table 5 shows, that tumor involving seminal vesicles has probability to be high grade cancer 9.4 [2.1-42.4] times higher than probability to be low grade cancer (#<0.001, df=1, Pearson index=11.2).
**Fig. 1:** MR-spectroscopy of prostate adenocarcinoma Gleason 7 (4+3), (Cho+Cr)/Ci ratio = 1.74

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Fig. 2: MR-spectroscopy of prostate adenocarcinoma Gleason 5 (3+2), (Cho+Cr)/Ci ratio = 1,06

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**Fig. 3:** Patient A., 73 y.o. Adenocarcinoma within right lobe of prostate, Gleason 7 (4+3) T2aN0Mx. At T2-WI peripheral zone shows diffuse decreasing of signal intensity and it is not possible to identify tumor tissue. At ADC map tumor demonstrates moderately decreased ADC (≈ 78×10^-5 mm²/s). At DWI (b=1100 s/mm²) adenocarcinoma shows increased signal intensity (arrow).

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**Fig. 4:** Patient B., 59 y.o. Adenocarcinoma within right lobe of prostate Gleason 8 (4+4) T3aN1Mx, chronic prostatitis. At T2-WI tumor has indistinct borders, at T1-WI it shows the same signal intensity as normal parenchyma of prostate. ADC of the tumor tissue decreased (53×10^-5 mm²/s) comparing with ADC of inflammatory focus (99×10^-5 mm²/s) and tumor borders is clearly seen (arrows).

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Fig. 5: Patient C., 61 y.o. Adenocarcinoma in right lobe of prostate Gleason 8 (4+4) T2aN0M# (arrow); wash in rate =6.5 units / sec, wash out rate = 0.4 units / sec. Curve 1 corresponds to tumor, curve 2 - arterial vessel, curve 3 - inflammatory focus, curve 4 - fibro-muscular stroma

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Fig. 6: Patient D., 52 y.o; prostate adenocarcinoma Gleason 5 (3+2) T2bN0M#. Axial T2-WI shows tumor in the left prostate lobe (arrow); DCE of the tumor represented with 3 and 4 curves, wash in rate =3.1 units / sec, wash out rate = 0.1 units / sec. Curve 1 corresponds to arterial vessel, curve 2 - benign prostate hyperplasia

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Conclusion

Dense cellular distribution in high grade prostate carcinoma responsible for restricted motion of water molecules with decreased ADC and increased signal intensity on DWI with b-values higher than 1000 s/mm². At the same time decreased ADC is typical for the tissues with low water content (scar tissue, concrement, calcifications), that can misinterpreted as tumor. The disadvantages of MR diffusion are relatively low spatial resolution and artifacts consistent with endorectal coil. Increased signal intensity on the DWI is also typical for the abscesses and hematomas.

Peak enhancement of high grade tumors reflects increased vascularization and presence of pathological arterio-venous shunts, which is used to be correlated with tumor vessels growth factor production.

Predominance of invasive tumor forms in group of high grade carcinomas represents the tendency to rapid and aggressive growth.

Summing up, MRI provides reliable information for the differentiation between low and high grade prostate carcinomas.

Qualitative and quantitative parameters described in this paper can specify the type of tumor grade with definite degree of confidence.

Adenocarcinomas Gleason 6-9 comparing with Gleason 3-5 tumors are characterized with hyperintense signal at DWI images with b-value higher than 1000 s/mm² (#<0,001), shows higher signal intensity at peak of contrast enhancement (#<0,001), higher level of choline (#=0,013) and higher (Cho+Cr)/Ci ratio (#=0,002).

Besides, high grade tumors more frequently show peak type of DCE curve, extra-capsular extension and paraprostatic fat invasion (p<0,05).

Prostate tumors which demonstrate no symptoms of high grade malignancy are probably respond to low grade carcinomas.
References
