Neural Network Multiparametric Analysis in MR Detection of Localized Prostate Cancer

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Purpose

Benign prostatic hyperplasia, chronic prostatitis and prostate cancer are common diseases in 50 year old men in western countries. The identification and differentiation of such diseases constitute an important goal from the clinical as well as the social and economic viewpoint.

The purpose of this work was to study combined data obtained from spectroscopy and ADC maps deriving from prostate MR examination for a more precise cancer localization with the aim of identifying areas where to run biopsy and therapy planning. To this end, the clinical data derived from images analysis were analyzed by comparing different classification methods: Bayesian statistics, discriminant analysis and neural network.
Methods and Materials

Between November 2009 and September 2011, a population of 25 men aged between 45 and 76 (average age 66) underwent 1.5T MRI with endorectal coil at our Institution (Milan, INT). All patients had been submitted to a prostate biopsy proven tumour (cancer) tissue. Patients with prostate biopsy proven benign tissue were excluded.

The Gleason Score and the PSA value were available for each patient.

All patients of the study had a Gleason score between 3+3=6 and 5+4=9. Gleason score of 3 patients was unknown.

MR Study was performed in two phases: firstly, a morphological study (imaging) using T2-weighted images was obtained; secondly, the metabolites distribution and ADC values were evaluated.

**MR Morphological imaging** was performed on a 1.5 T MR unit (Magnetom Avanto, Siemens Medical Solution, Erlangen, Germany) using both a pelvic phased-array coil and ballon-covered expandable endorectal coil. All patients were in supine position. Sagittal, coronal and axial thin section, high spatial resolution T2-weighted images through the prostate and seminal vescicals were obtained using the following parameters: TR range 3500 milliseconds; TE 120 milliseconds; section thickness 3 mm; matrix 200x200. Axial T1-weighted images gradient-echo, TR range 500 milliseconds, TE 12 milliseconds, thin section 3 mm, matrix 200x200 were obtained. Axial T1-weighted gradient-echo images, thickness 5mm, for the pelvic region were obtained for the lymph nodes evaluation.

**MR spectroscopy imaging (MRSI)** was obtained using the following parameters: Volume of interest VOI 5x5x5mm, TR range 690 milliseconds, TE 120 milliseconds, flip angle 90°. Around the prostate 8 saturation bands were necessary to avoid the overlap of metabolic information (Fig.1). TE variation can influence the spatial distribution of metabolites. Analysis was performed using a dedicate Siemens software. Combined axial (T2-weighted image) MR image and MRSI spectral grid were used to evaluate the prostate gland and the different concentration metabolites within contiguous small volumes of interest (voxel). The spectra grid for the cellular metabolites citrate (Ci), choline (Cho) and creatine (Cr) shown in corresponds to the grid overlaid on the T2-weighted axial images. Each voxel shows the different Cho+Cr/Ci ratio (Fig2, Fig.3).

**DWI MR images** were obtained using the following parameters: 25 slices, thickness 3 mm, matrix 200x200, TR range 4300 milliseconds, TE 78 milliseconds. The volumetric resolution was 1.6x1.6x3mm. Band saturation are also necessary. (ADC values were obtained from the DWI sequences performed with different b-values- typically of 0 and 1000 s/mm). DWI images were acquired using different b-value (typically 0-1000 s/mm-3) to allow the calculation of the apparent diffusion coefficient (ADC), a quantitative parametric
map. ADC values were calculated on a matrix of 128 by 128 pixel. The mouse cursor may highlight a region of interest (ROI) and the software automatically provides the ADC value (Fig.4).

For analysis purposes, the peripheral zone of the prostate was divided into base, mid, and apex and left and right halves, thus yielding six regions. The central gland comprising the transition zone was divided into left and right halves. The base was defined as the region extending from the superior margin of the prostate to the widest transverse diameter of the prostate. The mid gland was defined as the region between the widest transverse diameter and the orifices of the ejaculatory ducts at the verumontanum. The apex was defined as the region inferior to the mid gland. 265 samples out of 300 obtained from the analysis were suitable for analysis and compared with histological findings.

We studied the correlation of ADC and spectroscopy values with Gleason Score and PSA. Than spectroscopy and ADC data were considered separately: by varying the individual discriminant thresholds where studied the sensitivity and specificity of the test. The variables were combined in different ways: using Bayesian statistics, discriminant analysis, and through the development of a neural network. To evaluate the quality of each of the statistical methods used, it was analyzed the respective ROC curves and their AUC.

**Statistical methods**

**Bayes' theorem and diagnostic information**

An effective test would allow to discriminate between cases completely healthy and sick. Bayes' theorem is the only tool that allows you to provide a quantitative measure, and therefore objective, expressed in terms of information, the added value provided by a diagnostic test.

**ROC curves**

ROC stands for Receiver Operating Characteristic. The ROC curve is constructed by bringing back to the ordinates and abscissas sensitivity (1 - specificity) of the test. In the ideal situation of complete separation of signal values from those of the noise, it has a ROC curve that rises perfectly vertical axis represents then bends at right angles horizontally, parallel to the axis of abscissas. The area under the ROC curve is an indication of goodness of the test.

**Discriminant analysis**

Discriminant analysis is a branch of statistics that deals with the problem of finding a criterion for classifying an individual within a specific population (choice between two or
more different populations known in advance), based on observation or measurement of some variables, that provide a quantitative or structural description. This technique allows us to develop a function, called discriminant function, defined by measurements made on each individual sample, which allows you to classify a new individual of its population.

**Neural network**

A neural network can be considered essentially composed of a multitude of computational elements arranged so as to recall the connection model of brain neurons. The human brain is composed of a dense network of neurons that exchange information in the form of electrical impulses. A single biological neuron works on the following principle: inputs that come to the neuron in the form of electrical signals come from the dendrites. They in turn are connected to the outputs of other neurons with junctions called synapses. The first studies on neural networks date back to the work of McCulloch and Pitts in 1943, which were proposed mathematical models based on binary systems threshold for the modeling of biological neural systems.

In this discussion will be considered only a subclass of multilayer networks: we will study only the feedforward networks. Feedforward networks are such that, once assigned to each neuron numbers in ascending order (starting from the state of inputs and gradually coming to that of outputs), each neuron (marked by a number) receives signals only from units with a labeled smaller number. This means in practice that in a feedforward network, data never return back.
Images for this section:

Fig. 1: Around the prostate 8 saturation bands were necessary to avoid the overlap of metabolic information.

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**Fig. 2:** The spectra grid for the cellular metabolites citrate (Ci), choline (Cho) and creatine (Cr) shown in corresponds to the grid overlaid on the T2-weighted axial images. Each voxel shows the different Cho+Cr/Ci ratio. The image show an examples of a normal prostate.

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**Fig. 3:** The spectra grid for the cellular metabolites citrate (Ci), choline (Cho) and creatine (Cr) shown in corresponds to the grid overlaid on the T2-weighted axial images. Each voxel shows the different Cho+Cr/Ci ratio. The image show an examples of a prostate cancer.

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**Fig. 4:** Axial TSE T2w (A), High b value (B) and the Apparent Diffusion Coefficient (ADC), a quantitative parametric map (C).

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Results

We founded a correlation between the Gleason Score and the respective value of spectroscopy, but no correlation between PSA and spectroscopy. The Gleason Score and the PSA did not appear to be correlated with the ADC. We obtained 68% specificity and 85% sensitivity with spectroscopy, while 79% specificity and 85% sensitivity with the ADC. We also obtained 81% specificity and 85% sensitivity with the discriminant analysis and 86% specificity and 85% sensitivity with the neural network.

Correlation Spectroscopy and ADC vs Gleason score and PSA

It is considered the possible existence of dependence between the ratio of the peaks (Cho + Cr) / Cit values and the Gleason score and PSA.

It was decided to carry out this study considering all the values of the ratio of the peaks (Cho + Cr) / Cit entire tumor region as a function of the Gleason for each region. The results are shown in figure 5.

The analysis of the graphs in figure 5 shows that the ratio of the peaks (Cho + Cr) / Cit mediated in each region, for any lesion, increases with increasing Gleason score, as confirmed in the literature [Kristen L. Zakian et al., 2005].

To quantify this dependence, it has been a test of significance. The p values obtained are shown in Figure 6.

Later it was considered the maximum ratio of the peaks (Cho + Cr) / Cit in every region in function of Gleason. The significance of differences between the maximum values of the peaks are shown in Figure 7.

In both cases studied we see a significant difference between the values of spectroscopic parameters of Gleason 3 +3 = 6 and the other values. This results due to the studied population it will have more patients with Gleason 3+3=6 compared to others. Comparing the values of p in the two different cases, we note that the significance is better in the first case, in fact, when we consider only the maximum, we have a smaller set of values.

Gleason Score essentially depends on the histology, so it isn't a value independent of it. Thus the parameter was not included as input data in neural network.

As it was done for the Gleason Score, it has sought a correlation between PSA and value of the peaks (Cho+Cr)/Cit.

From the distribution in figure 8 is not observed a correlation between the ratio of peaks (Cho + Cr) / Cit and PSA. The difference between the data was not significant.

-Classification with diagnostic tests and their combination
The scatter-plot of ADC values and the ratio of the peaks (Cho + Cr) / Cit is shown in figure 9. Data are divided into positive and negative according to their histology.

Looking at the distribution obtained, it can be seen to be fairly obvious where the two regions are gathering more positive and negative values. This indicates that the selected variables possess a high discriminatory power. At the level of quality is seen as mostly positive cases have a value of the proportion of high peaks and low ADC value, while negative instances are in the opposite situation.

To establish a cutoff point we proceed first considering only the values of spectroscopy and ADC separately. Then it combines the two tests considering the final test positive if and only if both tests are positive individuals (intersection) or if at least one of the two tests is positive (union).

Through the software STATISTICA discriminant analysis was performed by dividing the population of cases in 205 to train and 60 for independent testing.

At the end, the neural network that generated the best results with AUC, is limited at 3 the number of hidden neurons in order to avoid the data over-fitting.

The ROC curves for each test are show in figure 10; while in Figure 11 are reported AUC, sensibility e specificity for each case.

In Figure 12 are show p values for evaluating the differences in different statistical tets.
**Fig. 5:** Ratio of the peaks \( \text{Cho + Cr} / \text{Cit} \) in function of Gleason Score

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<table>
<thead>
<tr>
<th>Gleason</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<tr>
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<td>0.0017</td>
<td>0.1761</td>
<td>0.8057</td>
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<tr>
<td>8</td>
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<tr>
<td>7</td>
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**Fig. 6:** p values of correlation test between ratio of the peaks \( \text{Cho + Cr} / \text{Cit} \) medium and Gleason.

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Fig. 7: p values of correlation test between ratio of the peaks (Cho + Cr) / Cit maximum and Gleason.

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Fig. 8: Ratio of the peaks (Cho + Cr) / Cit in function of PSA.

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Fig. 9: Scatter-plot ADC vs (Cho+Cr)/Cit

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**Fig. 10:** ROC curves obtained for the different statistical methods.

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<table>
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<th></th>
<th>SRM</th>
<th>ADC</th>
<th>U</th>
<th>∩</th>
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<th>Neural network</th>
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<tr>
<td>Total AUC</td>
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<td>0.87</td>
<td></td>
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<tr>
<td>Specificity</td>
<td>68%</td>
<td>79%</td>
<td>51%</td>
<td>86%</td>
<td>81%</td>
<td>86%</td>
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<tr>
<td>Sensibility</td>
<td>85%</td>
<td>85%</td>
<td>96%</td>
<td>77%</td>
<td>85%</td>
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**Fig. 11:** AUC, Specificity and Sensibility for each test.

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<table>
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<tr>
<td>ADC</td>
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**Fig. 12:** P-values.
Conclusion

This method allows high accuracy in prostate cancer detection and localization and the neural network classification system results the most accurate.
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