Original scientific paper

PHI AND MR SPECTROSCOPY AS GUIDELINES TO EARLY DIAGNOSIS AND TREATMENT OF CA PROSTATE IN PATIENTS IN THE GRAY ZONE OF PSA – OUR EXPERIENCES

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INTRODUCTION

Prostate cancer (CAP) is the most commonly diagnosed type of cancer in men and the second leading cause of cancer death in the world after lung cancer (1). Progress in CAP diagnosis can, in part, be attributed to the discovery of the Prostate Specific Antigen (PSA) in the 1970s. In the 1980s, PSA was primarily approved by the FDA to track patients diagnosed with CAP, and later was approved for CAP diagnostics and introduced as a screening tool for prostate cancer.This wide use of PSAled to a dramatic increase in incidence rates and prostate cancer diagnosis.Today, the prostate cancer mortality rate is approximately 45% lower than in 1992.(2). PSA has low sensitivity and low specificity for CAP. Increased PSA may not be an indicator of clinically significant cancer. The most common cause of a small increase in PSA is Benign Prostate Hyperplasia (BPH). BPH's incidence increases with age. Approximately 25% of 40-year-old men and 80% of 80-year-old men are estimated to have BPH.(3)(4). Differential diagnosis between malignant and benign disease is particularly challenging when considering that the total range of PSA is from 2ng/mL to 10 ng/mL, where there is a significant overlap between patients with benign and malignant conditions. The low specificity of PSA led to excessive diagnosis of indolent disease and excessive treatment, resulting in high costs for treating patients with elevated PSA.

MATERIAL AND METHODS:The study involved 49 patients (observed group) who had TRUS prostate biopsy, based on previousPHI (Prostatic Health Index) and multiparameter MR spectroscopy studies. In patients, an analysis of PathoHistological Postbioptic finding (PHP) from TRUS biopsy (transrectal ultrasound guided biopsy of the prostate) was performed and they were statistically processed and shown through:percentage representation, middle value, table and graphic view of parameters. In the second group of 45 patients (control group) TRUS biopsy was performed only on the basis of PSA findings, physical-digitorectal examination (DRP) and ultrasound examination. The study was conducted for a period of 2 years in patients followed by the Urological department at the City General Hospital 8th of September-Skopje.

GOAL: Determining the degree of specificity of PHI and multiparameter MR spectroscopy in early CAP diagnostics in the observed group, Analysis of postbioptic pathohistological finding according to the Glison classification in the observed group(6), Determination of the correlation of PHI and multiparameter MR spectroscopy with PathoHistological Postbioptic results, Determining the criteria for the use of PHI and multiparameter MR spectroscopy when setting an indication of TRUS biopsy according to the study analysis.

RESULTS: Of the 49 patients in the observed group with PSA valuesbetween 3.11 ngr/ml to 10.99 ngr/ml, in 63% pf the patients the PHI was with value 55+, the multiparameter MR spectroscopy was valued PIRADS 4 and 5 in 38% of patients, and TRUS biopsy had value for BPH in 61% of patients and CAP in 39% of biopsies. In the control group of a total of 45 patients with PSA values between 3.5 ngr/ml to 11.02 ngr/ml and a positive digitorectal examination, in 62% of patients the findings of TRUS prostate biopsy were as follows: BPH in 64% of patients and CAP in 36% of biopsies.

CONCLUSION: Based on the above mentioned results, we can conclude that prebioptic examination gives

better prognostics and refers us to a better treatment of the patients. Patients with negative PHI findings and multiparameter MR spectroscopy do not need to be biopsied immediately, but activlymonitored (multiparameter MR spectroscopy once a year) and just in case of a positive finding the next step is to do a prostate biopsy. These kind of diagnosed patients have a higher degree of positive diagnosis, meaning a positive PHP prostate cancer result. Using PHI and multiparameter MR spectroscopy reduces the percentage of overtreated patients, thereby reducing the cost of hospital days and the cost for TRUS prostate biopsy. With reducing the number of unnecessarily biopsyed patients there is also a reduction in the percentage of postbioptic complications in patients.

Keywords: Prostate cancer, TRUS prostate biopsy, BPH, PHI, multiparameter MR spectroscopy, PSA, PHP

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PSA has low sensitivity and low specificity for CAP. Increased PSA may not be an indicator of clinically significant cancer. The most common cause of a small increase in PSA is Benign Prostate Hyperplasia (BPH). BPH's incidence increases with age. Approximately 25% of 40-year-old men and 80% of 80-year-old men are estimated to have BPH.(3)(4).

Differential diagnosis between malignant and benign disease is particularly challenging when considering that the total range of PSA is from 2 ng/mL to 10 ng/mL, where there is a significant overlap between patients with benign and malignant conditions. The low specificity of PSA led to excessive diagnosis of indolent disease and excessive treatment, resulting in high costs for treating patients with elevated PSA.

MATERIAL AND METHODS

The study involved 49 patients (observed group) who had TRUS prostate biopsy, based on previous PHI (Prostatic Health Index) and multiparameter MR spectroscopy studies. In patients, an analysis of PathoHistological Postbioptic finding (PHP) from TRUS biopsy (TransRectal UltraSonographic water biopsy of the prostate) was performed and they were statistically processed and shown through: percentage representation, middle value, table and graphic view of parameters. In the second group of 45 patients (control group) TRUS biopsy was performed only on the basis of PSA findings, physical-digitorectal examination (DRP) and ultrasound examination.

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GOAL

-Determining the degree of specificity of PHI and multiparameter MR spectroscopy in early CAP diagnostics in the observed group,

-Analysis of postbioptic pathohistological finding according to the Glison classification in the observed group (6),

-Determination of the correlation of PHI and multiparameter MR spectroscopy with PathoHistological Postbioptic results,

-Determining the criteria for the use of PHI and multiparameter MR spectroscopy when setting an indication of TRUS biopsy according to the study analysis.

RESULTS

Of the 49 patients in the observed group with PSA values between 3.11 ngr/ml to 10.99 ngr/ml, in 63% pf the patients the PHI was with value 55+, the multiparameter MR spectroscopy was valued PIRADS 4 and 5 in 38% of patients, and TRUS biopsy had value for BPH in 61% of patients and CAP in 39% of biopsies.

In the control group of a total of 45 patients with PSA values between 3.5 ngr/ml to 11.02 ngr/ml and a positive digitorectal examination, in 62% of patients the findings of TRUS prostate biopsy were as follows: BPH in 64% of patients and CAP in 36% of biopsies.

DISCUSSION

ProstateHealthIndex

PSA can be found in the serum as different isoforms. Total PSA immune analyses reveal PSA bound to Alpha 1-antichymotrypsin, as well as the free form of PSA. Within the free fractions of PSA (fPSA), there are several isoforms, including PSA's predecessor.

-7 proPSA represents PSA's natural predecessor while -4 and -2 proPSA are abbreviated forms of -7 proPSA.In prostate cancer, there are elevated concentrations of -2 proPSA.

PSA isoforms in prostate cancer

Patients with prostate cancer have a lower %-free PSA (%fPSA) compared to patients with benign conditions. For example, when %fPSA is less than 10%, the probability of cancer is about 56%; while when %fPSA values are greater than 25% the probability of cancer is about 8%. %fPSA is used to improve sensitivity and specificity in patients with PSA between 4–10 ng/mL.

As mentioned above, the free isoform of PSA that has been shown to be increased in prostate cancer is p2PSA. P2PSA has been shown to have a higher specificity than the total and the free PSA in detecting prostate cancer. Even more so, the higher the p2PSA level, the higher the likelihood of finding high-level prostate cancer, as defined by the Gleason score equal to or higher then 7.

- The Prostate Health Index (PHI) is a blood test that includes the free PSA, total PSA and [-2] proPSA isoform of free PSA. The formula combines these test results mathematically to give the PHI result. This PHI result appears to be superior to PSA, free and total PSA and PCA3 in predicting the presence of prostate cancer.

- The Prostate Health Index (PHI) has 75% diagnostic accuracy.

- PHI is determined by a mathematical formula that uses 3 forms of PSA: totalPSA, freePSA and the isoform p2PSA. The result is expressed as a percentage:

(p2PSA / free PSA) x

In clinical practice, PHI can be used to fill the diagnostic gap between PSA screening and prostate biopsy. Combined with the patient's personal and family history, PHI can be used to create an individualized patient treatment plan. If the urologistconcludes- based on PHI and other risk factors-that there is a low likelihood of finding prostate cancer with a biopsy, the patient can be closely monitored instead od undergoing an biopsy. On the other hand, if the urologist finds that the probability for cancer is higher, then the patient is likely to undergo a prostate biopsy.

Multiparameter MR spectroscopy

Lately the Prostate MRI is becoming a standard tool in diagnosing prostate cancer. It can identify and evaluate the stage and localization of suspicious prostate nodes,it can check for extracapsular extension, it can assess seed vesicles and determine an increase in regional lymph nodes that may indicate early metastatic disease.

The combined application of morphological pre-contrast and post-contrast MR imaging and MR spectroscopy is shown as a very applicable method in the initial detection of prostate cancer, allowing preliminary acquisition of useful information in order to optimize and individualize therapeutic protocol in patients with prostate cancer.

While Magnetic Resonance Imaging (MRI) monitors anatomy,Multiparameter MR spectroscopy (MRSI) allows the evaluation of the metabolism of the tumor by determining the value of various metabolites within the tested frame of prostate tissue in vivo, primarily Citrate (Ci), Choline (Cho) and Creatine (Cr).

More specifically, Proton MRSI shows the metabolic profile of tissues. In the case of prostate cancer, three metabolites are of the utmost interest: Citrate, Choline and Creatine. Citrate is found in abundance in normal prostate tissue, but decreases in Ca of the prostate. Choline is a component of the phospholipid membrane of prostate cells and increases in Ca due to rapid multiplication of cells associated with neoplastic proliferation. Creatine is also normally present, but it remains unchanged in the presence of Ca and serves as an internal reference. The relative concentrations of these metabolites are quantified using the ratio of Choline + Creatinine/Citrate and Choline/Citrate.

Results

The tables below are showing patient results based on the following parameters:

Age (year of birth);

Result of PSA;

Result of PHI;

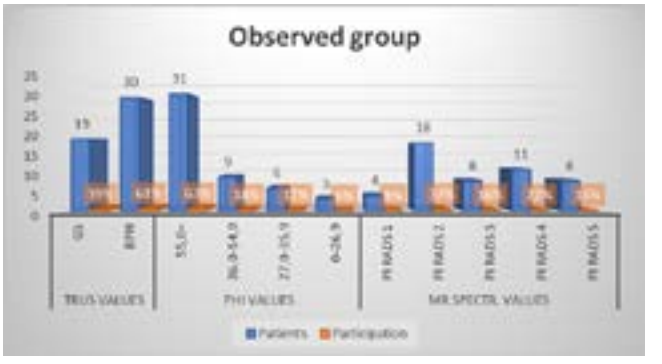
MR spectroscopy result;

Result of TRUS prostate biopsy.

Observed group

No.	Year of birth	PSA	PHI	Mrspectr	TRUS
1	1949	10,82	37,48	Pirads 3	BPH, Pros.chr
2	1950	7.3	44.71	Pirads 3	BPH, Pros.chr
3	1957	6.27	55.0+	Pirads 5	GS 4+4
4	1958	6.06	55.0+	Pirads 2	GS 3+3
5	1939	37.29	55.0+	Pirads 4	GS 4+3
6	1951	6.94	55.0+	Pirads 5	GS 3+3
7	1950	6.65	55.0+	Pirads 5	GS 3+3
8	1957	6.86	55.0+	Pirads 3	BPH, Pros.chr
9	1936	9.21	55.0+	Pirads 5	Gs 4+4
10	1942	10.99	55.0+	Pirads 5	GS 3+3
11	1946	6.16	17.42	Pirads 1	BPH, Pros.chr
12	1947	9.28	55.0+	Pirads 4	GS 3+4
13	1948	8.53	46.55	Pirads 5	GS 3+4
14	1956	7.59	43.60	Pirads 2	BPH, Pros.chr
15	1963	5.21	55.0+	Pirads 5	GS 3+3
16	1947	8.73	32.81	Pirads 1	BPH, Pros.chr
17	1951	6.08	34.85	Pirads 2	BPH, Pros.chr
18	1947	5.80	55.0+	Pirads 2	BPH, Pros.chr
19	1953	4.97	55.0+	Pirads 4	GS 3+4
20	1960	7.01	25.64	Pirads 1	BPH, Pros.chr
21	1946	6.81	55.0+	Pirads 3	BPH
22	1946	9.91	55.0+	Pirads 4	GS 3+4
23	1959	5.91	54.14	Pirads 2	BPH, Pros.chr
24	1949	10,82	37.48	Pirads 3	BPH, Pros.chr
25	1951	9.08	34.79	Pirads 2	BPH, Pros.chr
26	1942	8.33	55.0+	Pirads 4	GS 3+3
27	1949	3.42	22.59	Pirads 2	BPH, Pros.chr
28	1951	3.11	31.09	Pirads 2	BPH, Pros.chr
29	1943	4.7	42.09	Pirads 2	BPH, Pros.chr
30	1956	7.6	34.48	Pirads 2	BPH
31	1958	9.34	55.0+	Pirads 5	GS 4+4
32	1959	8.95	55.0+	Pirads 2	BPH, Pros.chr
33	1969	10,00	55.0+	Pirads 2	BPH, Pros.chr
34	1947	5,55	29,86	Pirads 2	BPH, Pros.chr
35	1949	7,84	55+	Pirads 1	BPH
36	1951	9,32	37,39	Pirads 2	BPH
37	1959	7,72	55.0+	Pirads 4	GS 3+3
38	1956	9,61	55.0+	Pirads 3	BPH,prost.chr
39	1955	8.45	55.0+	Pirads 4	GS 3+3
40	1956	9.68	49.25	Pirads 2	BPH, Pros.chr
41	1946	5.26	55.0+	Pirads 4	BPH,prost.chr
42	1950	5.33	55.0+	Pirads 2	BPH
43	1969	8.16	55.0+	Pirads 2	BPH
44	1954	6.20	55.0+	Pirads 2	BPH
45	1965	10.7	55.0+	Pirads 3	GS 3+3
46	1942	7.10	55.0+	Pirads 4	GS 3+4
47	1955	9.00	55.0+	Pirads 4	BPH ASAP
48	1963	8.93	55.0+	Pirads 3	BPH,prost.chr
49	1957	8.54	55.0+	Pirads 4	GS 3+3

PHI values			Mr Spectroscopy values			TRUS Biopsies values		
	Бр.пац	%		Бр.пац	%		Бр.пац	%
55,0+	31	63%	PI RADS 1	4	8%	CaP	19	39%
36,0-54,9	9	18%	PI RADS 2	18	37%	BPH	30	61%
27,0-35,9	6	12%	PI RADS 3	8	16%	total	49	100%
0-26,9	3	6%	PI RADS 4	11	22%			
total	49	100%	PI RADS 5	8	16%			
			total	49	100%			

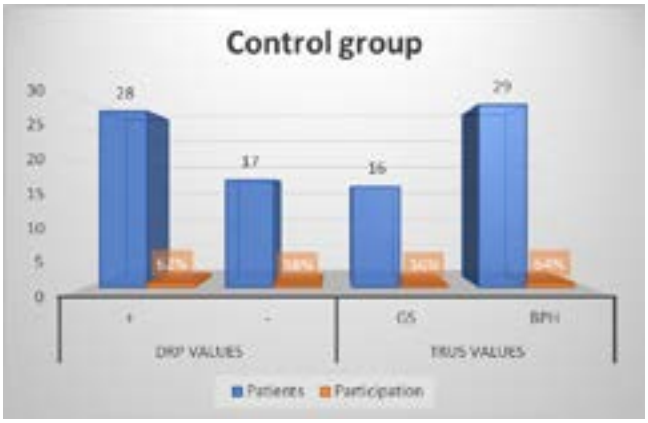


Control group

No	Year of birth	PSA	DRP	TRUS
1	1965	6.65	+	BPH.prost chr
2	1950	9.63	-	GS 3+3
3	1955	7.4	+	GS 3+4
4	1948	8.6	+	BPH
5	1954	9.56	+	GS 3+4
6	1966	6.26	-	BPH.prost chr
7	1956	10.9	+	GS 3+4
8	1951	5.42	+	BPH
9	1964	10.5	+	BPH
10	1964	9.01	+	BPH.prost chr
11	1958	6.6	-	BPH.prost chr
12	1950	9.9	+	GS 3+4
13	1956	8.6	-	BPH.prost chr
14	1948	9.4	+	BPH.ASAP
15	1957	7.2	-	BPH.ASAP
16	1947	9.8	-	GS 3+3
17	1948	8.3	+	BPH.prost chr

18	1952	7.5	+	BPH.prost chr
19	1957	7.2	+	BPH.ASAP
20	1964	9.9	+	BPH.Pros.chr
21	1954	8.9	-	CaP. 3+4
22	1945	10.2	+	CaP. 3+4
23	1956	8.9	+	CaP. 3+4
24	1963	7.6	+	BPH
25	1953	7.03	-	CaP. 3+4
26	1965	6.8	+	BPH.Pros.chr
27	1955	3.83	-	BPH
28	1948	8.7	+	CaP. 3+4
29	1954	10.00	+	BPH.ASAP
30	1949	7	-	BPH.Pros.chr
31	1948	9.32	-	BPH.Pros.chr
32	1947	6.7	+	CaP. 3+4
33	1951	5.47	-	BPH.Pros.chr
34	1957	6.35	-	BPH.Pros.chr
35	1957	9.12	+	CaP. 3+3
36	1951	10.7	+	GS 3+4
37	1954	7.6	-	BPH
38	1951	7.16	+	ASAP.BPH
39	1950	11.02	-	BPH.Pros.chr
40	1960	6.7	-	BPH.Pros.chr
41	1946	3.5	+	BPH
42	1944	10	-	GS 3+3
43	1946	6.4	+	GS 3+4
44	1950	7.34	+	BPH
45	1964	8.2	+	BPH.Pros.chr

DRP values			TRUS values		
	Number of patients	% participation		Number of patients	% participation
+	28	62%	CaP	16	36%
-	17	38%	BPH	29	64%
total	45	100%	total	45	100%



CONCLUSION

- Based on the above mentioned results, we can conclude that prebioptic examination gives better prognostics and refers us to a better treatment of the patients.

- Patients with negative PHI findings and multiparameter MR spectroscopy do not need to be biopsied immediately, but activlymonitored (multiparameter MR spectroscopy once a year) and just in case of a positive finding the next step is to do a prostate biopsy.

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