Magnetic resonance spectroscopy imaging in the diagnosis of prostate cancer: initial experience*

Espectroscopia por ressonância magnética no diagnóstico do câncer de próstata: experiência inicial

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Abstract **OBJECTIVE: To report an experiment involving the introduction of a protocol utilizing commercially available three-dimensional 1H magnetic resonance spectroscopy imaging (3D 1H MRSI) method in patients diagnosed with prostatic tumors under suspicion of neoplasm. MATERIALS AND METHODS: Forty-one patients in the age range between 51 and 80 years (mean, 67 years) were prospectively evaluated. The patients were divided into two groups: patients with one or more biopsies negative for cancer and high specific-prostatic antigen levels (group A), and patients with cancer confirmed by biopsy (group B). The determination of the target-area (group A) or the known cancer extent (group B) was based on magnetic resonance imaging and MRSI studies. RESULTS: The specificity of MRSI in the diagnosis of prostate cancer was lower than the specificity reported in the literature (about 47%). On the other hand, for tumor staging, it corresponded to the specificity reported in the literature. CONCLUSION: The introduction and standardization of 3D 1H MRSI has allowed the obtention of a presumable diagnosis of prostate cancer, by a combined analysis of magnetic resonance imaging and metabolic data from 3D 1H MRSI.**

Keywords: Magnetic resonance spectroscopy imaging; Prostate; Prostatic neoplasm.

Resumo **OBJETIVO: Demonstrar a experiência na implantação de um protocolo de espectroscopia por ressonância magnética do 1H tridimensional (3D 1H MRSI), disponível comercialmente, aplicando-o em pacientes com suspeita de neoplasia prostática e com diagnóstico estabelecido de tumor prostático. MATERIAIS E MÉTODOS: Estudo realizado de forma prospectiva, em 41 pacientes com idades entre 51 e 80 anos (média de 67 anos). Dois grupos foram formados: pacientes com uma ou mais biópsias negativas para câncer e antígeno prostático específico elevado (grupo A) e pacientes com câncer confirmado por biópsia (grupo B). Procurou-se, a partir dos resultados da ressonância magnética e espectroscopia por ressonância magnética, determinar a área-alvo (grupo A) ou a extensão do câncer conhecido (grupo B). RESULTADOS: No diagnóstico de câncer de próstata a espectroscopia por ressonância magnética apresentou especificidade abaixo da descrita pela literatura, cerca de 47%. Já para o estadiamento do tumor diagnosticado, houve correspondência com a literatura. CONCLUSÃO: A implantação e padronização da espectroscopia por ressonância magnética permitiram a obtenção de informações importantes para o diagnóstico presuntivo da existência de câncer de próstata, combinando as imagens por ressonância magnética com os dados metabólicos da espectroscopia por ressonância magnética.**

Unitermos: Espectroscopia por ressonância magnética; Próstata; Neoplasia prostática.

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INTRODUCTION

The increase in the incidence of prostate cancer from 86,000 cases in 1985 to 218,890 cases in 2007 in the United States alone, has transformed this disease not only into an important medical problem, but also into a public health and socioeconomic[1,2] one. In Brazil, 49,530 new cases are estimated in 2008, according to Instituto Nacional de Câncer[3].

However, in spite of the fact that digital rectal examination is considered as the first diagnostic tool, it is limited as it presents negative results for non palpable nodules (T1c stage)[4].

The uncertainty with respect to the upper limit value for cancer screening with prostate specific antigen (PSA) and its low

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specificity contribute for two current clinical challenges: only one in four men with PSA > 4 ng/ml actually present cancer at biopsy, and approximately one third of the prostate cancers are detected in men with normal PSA[5].

Ultrasonography is widely utilized because of its relatively low cost, and when used with the transrectal probe this method offers the best opportunity to guide the gland biopsy[6,7] . However it is limited to local staging due to the difficulty in the early diagnosis of the extracapsular extent and high operator dependency, which limits the reproducibility of the technique[8,9]

Amongst the other radiological techniques, magnetic resonance imaging (MRI) is the most useful diagnostic tool for evaluation of tumor stages, mainly on cases where endorectal coil is utilized[8] . Magnetic resonance imaging has a significantly higher sensitivity (51–89%) in the detection of the tumor when compared with transrectal ultrasonography (TRUS) (27–86%). However, both methods present a low specificity (58–94%)[8,9].

Recently, magnetic resonance spectroscopy (MRS) brought a new diagnostic hope. Based on anatomical data generated by MRI, this method can demonstrate the metabolic indicators detected in the prostate gland, enhancing the accuracy in the probable localization of the tumor[8,10–14]. In Brazil, there are still only few MRI centers with the technical background required to perform prostate examinations with spectroscopy. Additionally, this technique is not covered by health insurance plans or by the Sistema Único de Saúde (SUS) (Brazilian Public Health System).

With the real perspective of a significant improvement in prostate cancer diagnosis utilizing MRSI, a protocol for the acquisition of spectroscopic data was implemented at the Department of Imaging Diagnosis – Universidade Federal de São Paulo/Escola Paulista de Medicina (Unifesp/EPM).

MATERIALS AND METHODS

The present prospective study was developed between February of 2004 and December of 2005, with 41 male patients with ages ranging from 51 to 80 years, and mean age of 67 years, selected by the Nucleus of Prostate Research (Nuppro) of Unifesp/EPM. Throughout this period, Nuppro assisted approximately 2,000 patients.

The patients were divided into two groups: group A – patients with clinic-laboratory diagnostic suspicion of cancer, including 28 patients selected due to the fact that they had one or more negative biopsies, and persistently high PSA levels and/or altered digital prostate examination results; group B – patients with confirmed diagnosis of prostate cancer, including 13 patients selected due to the fact of having positive biopsies (one Gleason 3, one Gleason 5, three Gleason 6, six Gleason 7, two Gleason 8).

The patients from group A with diagnostic suspicion presented indication for prostate biopsies because of persistently high PSA levels. For these patients, MRSI was performed in order to identify the possible altered areas to be approached at US guided biopsy.

In the case of Group B patients, besides the identification of tumor site, locoregional staging of the prostate cancer was performed by MRI. Patients included in this group were not submitted to biopsy after MRSI, as the previously performed biopsies were positive.

This study protocol was previously submitted to and approved by the Committee for Ethics in Research of Unifesp/EPM. All patients signed a term of free and informed consent.

Examination protocol

Preparation and positioning of the patient

The patients preparation for examination consisted of four-hour fasting and intravenous administration of antispasmodic drug. No intestinal lavage was performed. All patients were previously instructed on the examination procedures.

The endorectal coil introduction was performed with the patient in left lateral decubitus. The coil characteristics indicate that the blue line on its shaft should be positioned towards the ventral direction in relation to the patient, and the first portion of the shaft should be positioned at the level of the anal border. The extremity of the endorectal coil was protected with an unlubricated condom externally lubricated with Xylocaine® gel. Then, the balloon at the end of the coil was inflated with 100 ml of air to distend the rectum wall, keeping the safety support to avoid displacement of the coil and loss of the condom. After completion of this operation, the patient was slowly positioned in dorsal decubitus, holding the coil shaft.

The positioning consisted in connecting endorectal, phased-array and column coils (SP's), with the objective of optimizing the image acquisition and spectroscopy.

With these maneuvers, the patient remained in dorsal decubitus, with the feet entering the equipment first, and with the arms towards the floor. Finally, the patient was asked to remain still during the whole examination process, breathing normally, and without contracting the rectal channel.

Exam technique

Protocol for magnetic resonance image acquisition

All examinations were performed in a 1.5 T Magnetom Sonata unit with a gradient of 43 mT/m (Siemens Medical Systems; Erlangen, Germany), at the Department of Imaging Diagnosis of Unifesp/EPM.

The radiofrequency body coil, present in the equipment itself, was utilized for excitation, the endorectal coil, combined with the matrix coil, in the prepubic region of the patient; the SP's, located in the presacral region of the patient, were utilized for MR signal reception.

The MRI examination programming was performed as recommended in the literature, as demonstrated on Figure 1. Chart 1 includes a summary of the sequence parameters applied.

In the sagittal plane, the positioning was performed following the longest axis of the prostate, aligning the pubic symphysis with the lumbar spine. In the coronal plane, the block was angled according to the longest axis of the prostate. In the axial plane, the angle was according to the longest prostate axis, in such a manner to position the images from the pubic symphysis to the end of the seminal vesicles.

Paramagnetic contrast injection (10 ml) was systematically performed in the patients, after spectroscopy, on T1-weighted sequences with fat saturation.

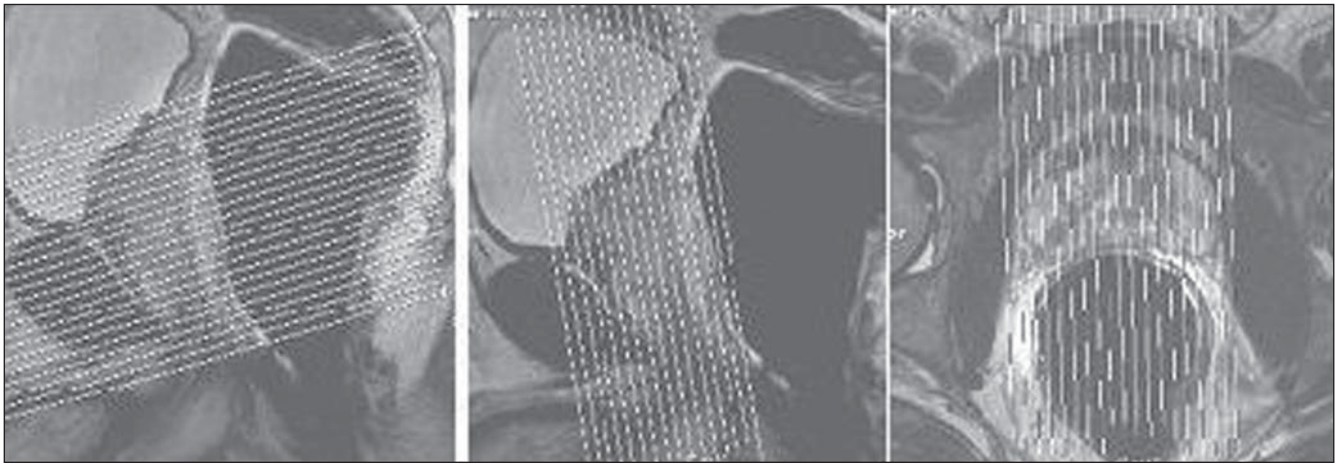

Figure 1. Programming of MRI of prostate. Programming representation in the axial, coronal, and sagittal planes.

Chart 1 MRI sequence parameters utilized in the protocol.

Sequence	No. of images	Thickness (mm)	TR (ms)	TE (ms)	Matrix
Axial T2 FSE	24	3.0	3,000–3,900	94–100	480 × 512
Coronal T2 FSE	16	3.0	3,000–3,900	94–100	512 × 512
Sagittal T2 FSE	19	3.0	3,200–4,200	94–100	512 × 512
Axial T1 FSE	24	3.0	500–650	12–14	464 × 512
Axial FS Gd	24	3.0	500–650	12–14	464 × 512

FSE, *fast spin echo*; FS, fat saturation.

Protocol for spectroscopic data acquisition

A multiple-volume system was utilized in the selection of the spectroscopic volume of interest, acquired by the commercially available sequence PRESS CSI 3D hybrid (TR 1,300 ms/TE 120 ms; FOV 60–100 cm^2; voxel 0.10–0.22 cm^3, 4–5 acquisitions) (Siemens Medical Systems; Erlangen, Germany), so as to minimize possible artifacts of the periprostatic structures.

The MRSI programming included T2-weighted sequences so as to evaluate the whole prostatic volume as shown on Figure 2. Besides being freely angled, without any limitations for the spectroscopic acquisition, the MRSI sequence offered the possibility of using eight external saturation bars, thus minimizing the effects of the non homogenization of the field by the effect of magnetic susceptibility, originated from the air within the coil, bone structures, periprostatic fat, and presence of urine in the bladder and in the penile urethra.

For the prostate spectroscopy, spectral suppression was utilized both for water and fat, according to recommended in literature[8,10–13,15–18], making it possible for the lipids present in the prostate, not to interfere in the acquisition.

The total examination time, including the patients positioning, MR image and spectroscopic data acquisition, was approximately 45 minutes.

Image and spectroscopic data analysis

The studies were consensually evaluated by two observers with regards to the morphology, and by one observer with respect to the spectral analysis.

The first phase consisted of the sequences analysis for evaluation of the prostate morphology, areas of signal alteration (peripheral zone and transition zone), iden-

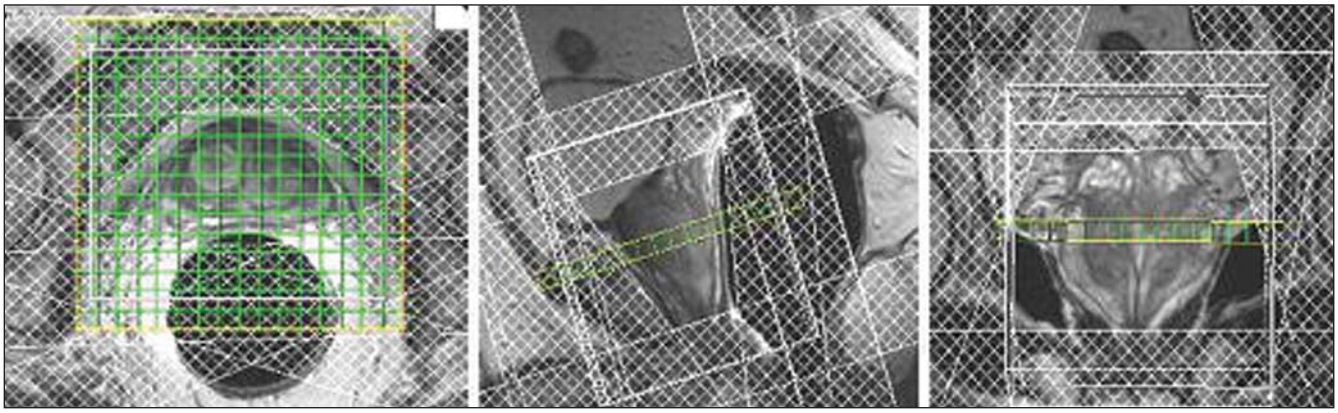

Figure 2. Model of prostate MRSI programming. Utilization of the three orthogonal planes with free *multi-voxel* angulation and eight saturation bars positioned in such a way to minimize artifacts.

tification of possible blood residues, evaluation of periprostatic fat and seminal vesicle integrity.

The second phase consisted of the analysis of spectroscopy acquisition. The postprocessing was made in a Leonardo® workstation (Siemens Medical Systems; Erlangen, Germany). The spectroscopic data were measured after baseline correction, of the chemical deviation, with water as reference and T2-weighted in the three orthogonal planes to evaluate the positioning of the voxel. The Fourier transformation was prioritized in three spatial directions, applying the Hamming filter.

The whole prostatic volume was qualitatively evaluated. Initially, the regions of interest were identified as those that presented an increase in choline levels and decreased citrate levels, therefore nominated target areas. Then a qualitative and quantitative evaluation was performed, identifying the relationship between metabolite peak amplitude ratios target area.

Upon conclusion of the two phases, the analyses results were compared in consensus and classified into three groups: 1 – areas detected by MRI in agreement with MRSI; 2 – areas detected by MRI in disagreement with MRSI; 3 – areas not detected by MRI but characterized by MRSI.

Biopsy of the target area

Based on MRI and MRSI results, TRUS-guided biopsies were performed in the Ultrasonography Sector of the Department of Imaging Diagnosis at Unifesp/EPM, utilizing a Philips SD 800 unit (Philips Medical Systems; Eindhoven, The Netherlands) and 18 G needle.

The radiologists were informed on the position of the target areas according to the McNeal's nomenclature[19]. In patients with no suspect areas at MRI and MRSI, randomized biopsies were performed obtaining 18 fragments.

Statistical analysis

A descriptive study was developed, considering the small number of patients. Even with this limitation, one tried to demonstrate the most relevant findings by association measurements (sensitivity, specificity, accuracy, positive predictive value and negative predictive value).

RESULTS

In relation to alterations identified at MRSI and /or MRI, compared with biopsies after MRSI in the 28 patients included in group A (high PSA levels and negative biopsies), 12 presented alterations both at MRI and MRSI , 8 only at MRSI , in 7 no alteration was observed, and in one, alteration was observed only at MRI.

In group A, the relationship between citrate/choline ratio (positive: 0.221 ± 0.166; negative: 1.441 ± 0.562) and (choline + creatine)/citrate ratio (positive: 7.922 ± 4.976; negative: 2.151 ± 1.089) amplitudes was established. These data were measured in a systematic manner, utilizing the same analysis protocol in the target area of all the patients included in the present study.

In the group A, for patients with alterations both at MRI and MRSI, presented 100% sensitivity, 47% specificity, 58% accuracy, 37% positive predictive value, and 100% negative predictive value (Figure 3).

All of the 13 patients from group B presented alterations both at MRI and MRSI.

Citrate/choline ratio (mean: 0.369 ± 0.231) and (choline+creatine)/citrate ratio (mean: 5.471 ± 4.355) amplitudes of group B were measured in a systematic manner, with the same analysis protocol, in the area affected by cancer of all the patients included in the present study.

For the group B, sensitivity, specificity, accuracy, positive predictive value and negative predictive value were 100%.

DISCUSSION

Prostate cancer screening fundamentals are based on the fact that patients diagnosed at screening tend to present a more favorable stage as compared with those clinically diagnosed, with a possible decrease in the rate of specific mortality due to prostate cancer.

Magnetic resonance imaging is commonly utilized for the tumor staging after a diagnosis is established by prostatic biopsy. When the disease is confined to the prostate, the capsule will appear intact, even if there is an extensive contact or regular bulging between the capsule and the tumor[8,20].

Additionally, MRI can also demonstrate the prostate anatomy, identifying areas with alteration of signal intensity, which may represent focal lesions in the gland. Thus, this method provides an extensive evaluation of patients with prostate cancer, for its capacity of observation of the primary disease and locoregional lymph nodes involvement[20,21]. On T1-weighted images, the prostate appearance is homogeneous with isosignal, and the zonal anatomy and intraprostatic diseases are not demonstrated. These are observed on T2-weighted images, as the cancer presents itself as an area with signal hypointensity at peripheral zone, which is hyperintense[21].

Technical advances for better signal detection by MRI antennas, have led to the development of endorectal coils[22]. Magnetic resonance imaging endorectal coil presents > 97% accuracy in the localization of known prostate lesions; however, the method performance is poor in the detection of focal tumors with < 5 mm in diameter[23].

Magnetic resonance spectroscopy of the prostate increases the diagnostic probability in cases of cancer, by adding metabolic data on the gland to the morphological information. The sensitivity of this method ranges from 68% to 95% and specificity, from 70% to 91%[21,24].

Advantages of the utilization of this technique in the determination of prostate cancer include: accurate spectral localization of each small morphologically abnormal region; precise correlation between the spectral mapping and the high-resolution magnetic resonance imaging; evaluation of the abnormal metabolism extent; three-dimensional coverage of the entire gland[17].

A variation is observed when MRI results and MRSI metabolic data are combined. Together, they result in 56–94% sensitivity and 70–98% specificity[10,24,25].

In 2004, Yuen et al.[26] observed that MRI data in association with those of MRSI, presented 100% sensitivity and 70.3% specificity in the determination of suspicious areas.

Most recently, in 2005, Prando et al.[27] observed that MRI combined with MRSI presented high sensitivity (84% to 100%) and low specificity (44% to 71%) in the identification of target areas.

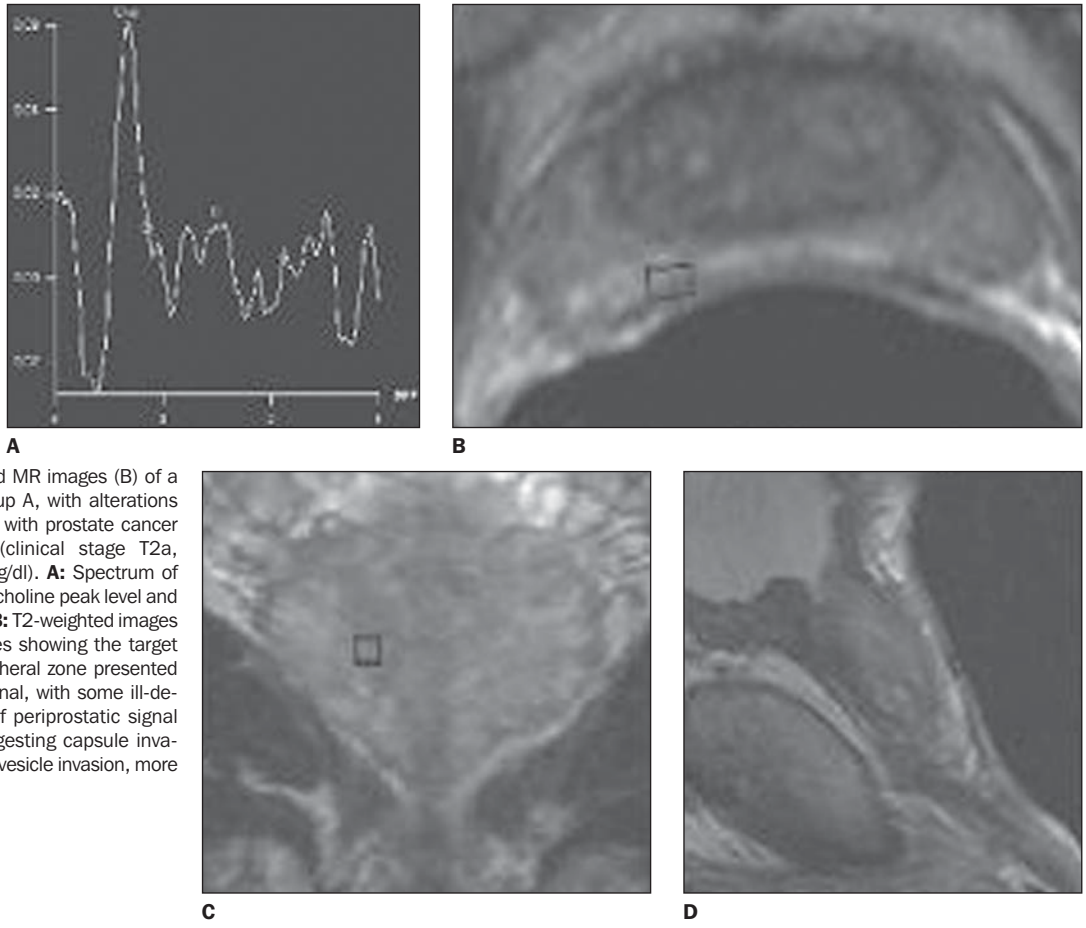

Figure 3. MRSI graph (A) and MR images (B) of a 72-year-old patient from group A, with alterations at MRI and MRSI, diagnosed with prostate cancer after TRUS-guided biopsy (clinical stage T2a, Gleason 6 and PSA of 2.5 ng/dl). **A:** Spectrum of the voxel of interest with high choline peak level and decreased citrate peak level. **B:** T2-weighted images in the three orthogonal planes showing the target area voxel. AT MRI, the peripheral zone presented a diffusely heterogeneous signal, with some ill-defined nodular areas. Signs of periprostatic signal alteration are observed, suggesting capsule invasion, besides signs of seminal vesicle invasion, more evident to the right.

In the present study, alterations at MRI or at MRSI alone presented very low specificity. Thus, the findings should be considered when both peripheral zone hypointense signal at MRI and metabolic inversions at MRSI are present (58% accuracy).

As regards sensitivity of MRI in association with MRSI in the detection of prostatic cancer (group A), the results of the present study are in agreement with previous studies. However, with respect to specificity, the results were below (47%) those described in the literature, and agreeing only with Prando et al.[27], including in what refers to the group in study.

Therefore, information detected by MRSI with respect to the probable localization of prostate cancer may be useful in the programming of TRTRUS-guided biopsies, particularly in patients with PSA levels indicating cancer and with previous negative biopsies. It can also improve the stratification of patients in clinical screening, and also their monitoring, from a simple clinical follow up to a minimally aggressive treatment[17].

The study protocol implementation underwent several phases. The first one occurred in 2004, with the installation of the Magneton Sonata MRI in the Department of Imaging Diagnosis, where commercially available Siemens MRI and spectroscopy pulse sequences were adapted to the working conditions.

The second phase of prostate MRSI protocol set up corresponded to the elaboration of spectral analysis criteria. Based on these criteria, spectral data analysis was standardized, involving both qualitative and quantitative studies adapted according to recommendations in the literature[8,10–13,15–18,21,24–27,28]. Additionally, efforts were made to standardize studies reports and the TRTRUS-guided biopsies programming based on MRI and MRSI data.

However, these phases were modified to better adapt to diagnosis requirements, not to mention the aspect of one being at the beginning of the learning curve. The valuation of certain metabolic inversions in the first patients contributed to the fact that accuracy results of the method fell short of the literature ones, approximately 58%.

This difficulty in the diagnosis may be explained by the fact that MRSI as well as MRI results may be influenced by inflammatory processes (prostatitis), postbiopsy hemorrhages, and by several types of treatments such as hormone therapy, radiotherapy, cryotherapy among others[21,25,29].

Concerning the mathematical relation, our study demonstrated that the utilization of creatine must be better evaluated, verifying to what extent its amplitude is being influenced by choline and spermidines. This was demonstrated by the higher number of false-positive results, with the mathematical relation (choline + creatine)/citrate.

CONCLUSION

The implantation and standardization of magnetic resonance spectroscopy imaging allowed the acquisition of relevant data for

the presumptive diagnosis of the presence of prostate cancer, combining the MR images with metabolic data from MRSI.

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