THE "CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST
DOCTORAL SCHOOL
THE FIELD OF MEDICINE

THE ROLE OF MAGNETIC RESONANCE IMAGING IN THE DIAGNOSTIC ALGORITHM AND MANAGEMENT OF PROSTATE CANCER

DOCTORAL THESIS SUMMARY

Doctoral supervisor:

PROF. UNIV. DR. LUPESCU IOANA GABRIELA

Doctoral student:

MOANGĂ (m. JURCA) SANDRA-OANA

YEAR 2024

TABLE OF CONTENTS

The fundamental problem

Multiparametric Magnetic Resonance Imaging (mpMRI) is a non-invasive method that has the potential to significantly improve the accuracy, localization and characterization of prostate cancer. Also, mpMRI has the potential to distinguish between clinically significant and insignificant tumors, guiding the management of these patients and decreasing the morbidity and costs associated with unnecessary biopsies. The novelty of the subject is conferred by the rapid progress of imaging technology as well as the growing international interest in evaluating the clinical utility of this method. Also taking into account the accelerated development of high-field Magnetic Resonance Imaging, advances in diffusion imaging as well as the development of artificial intelligence algorithms, the benefits of mpMRI are invaluable in this current context. Thus, research in this field not only responds to a current need in prostate oncology, but also highlights cutting-edge technological innovations in order to advance the diagnostic and treatment potential.

The chosen topic is of current interest in an international context, as prostate cancer is one of the most common cancers in the world in men and increasingly more countries with developed health systems are adopting mpMRI to optimize patient outcomes and reduce unnecessary procedures and treatments for this category of patients. In our country, the interest in mpMRI is growing in response to the need to increase the rate of early detection and diagnostic accuracy, especially since there are major limitations at the moment in the use of traditional diagnostic methods such as PSA testing or biopsies guided by transrectal ultrasound. The research team of the Radiology and Medical Imaging Laboratory of the Fundeni Clinical Institute has a well-founded concern to evaluate and apply the latest diagnostic methods, including in the field of oncology, and to promote diagnostic methods and technologies that have the potential to bring an important contribution to patient management.

Working hypothesis and general objectives

The working hypothesis in the present doctoral study is that the multiparametric Magnetic Resonance Imaging examination has an important contribution in the diagnosis and management of patients with biochemical suspicion of prostatic adenocarcinoma, and the diagnostic efficiency can be improved by optimizing the imaging protocol and identifying new imaging markers.

The general objectives of the study are represented by:

1. Evaluation of the role of biochemical, clinical, histopathological and imaging parameters in the diagnosis of prostate adenocarcinoma;
2. Identification of a multiparametric MRI profile from a metabolic and functional point of view in patients with prostatic adenocarcinoma;
3. Application of the current prostatic adenocarcinoma diagnostic scores in the study population and evaluation of the radiological-histological correlation;
4. Evaluation of the diagnostic yield and efficiency of an extended examination protocol.

General research methodology

All patients included in the two studies of this paper gave their informed consent regarding the inclusion in the study and the performance of the Magnetic Resonance Imaging examination in the Radiology and Medical Imaging Laboratory of the Fundeni Clinical Institute. The personal data of the patients were not published or presented to third parties and the identification data was anonymized for the use of their images. Until the completion of the study, no patient withdrew from the study and no complaints were registered regarding the protection of personal data.

The software program Microsoft® Excel® 2019 (Version 2402, Build 17328.20162, 64-bit) was used for data centralization. The software programs MedCalc Version 14.8.1 64-bit as well as Stata Version 17.0 were used for statistical analysis.

In the interpretation of the data, simple statistical methods were applied, such as the calculation of the means, medians, standard deviations, standard errors, but also complex ones,

which allowed the testing of statistical differences between the subgroups as well as their superior characterization. To verify the normality of the distribution of the values of a parameter, the Shapiro-Wilk test was used with the calculation of the W statistic.

For the comparison of continuous type variables between two groups, the Student t-test was used with the prior performance of an F-test, then the display of the 95% confidence interval (CI, confidence interval), the t-statistic and the two-sided p probability (two-tailed). In the case of subgroups with a small number of subjects or with a non-normal distribution of values, the non-parametric Mann Whitney test was used with the estimation of the normal approximation, respectively the exact probability.

In order to compare categorical variables between subgroups, the Chi-squared test was used. For non-binary variables, the Chi-squared test for trends (Cochran-Armitage) was also calculated. For binary variables with a reduced total number of observations, the Fisher test was used.

The correlation between two continuous variables with a normal distribution was statistically evaluated by means of the Pearson correlation coefficient. Thus, the Pearson correlation coefficient (r), the p-value and the 95% confidence interval for r were calculated. In the case of the non-normal distribution of the variables, the rank correlation was used with the calculation of the Spearman coefficient (rho) and, respectively , Kendall (tau), the p-value and the 95% confidence interval (CI) for the correlation coefficient, respectively.

To analyze the diagnostic performance of certain functional imaging parameters, the receiver operating characteristic (ROC) curve was used, graphically presenting the classification model at different threshold values.

In the present study, the p-value was considered statistically significant at values less than or equal to 0.05.

Synthesis of chapters

The doctoral thesis comprises two parts, entitled "General part" and "Personal contributions".

In the *General Part*, are featured aspects related to the anatomy of the prostate, the pathogenesis and development of prostate cancer, current diagnostic methods, methods of screening and early detection of prostate cancer, the staging of prostate cancer, its treatment modalities, as well as the role of medical imaging in diagnosis and management of prostate cancer.

The second part of the thesis includes the *Personal Contributions* presented through two studies, the first of which refers to imaging-clinical correlations in patients with prostate adenocarcinoma, while the second study is a pilot study on the contribution of dynamic loading with contrast in multiparametric imaging of prostate adenocarcinoma.

The first study had as its *working hypothesis* the fact that the multiparametric Magnetic Resonance Imaging examination has an important contribution in the diagnosis and management of patients with biochemical suspicion of prostatic adenocarcinoma.

The specific *objectives* of study I are the following:

- presentation and illustration of the morphological and functional MRI features of suspicious prostatic lesions, classified as PIRADS 3, 4 or 5 according to the PIRADS v2.1 guide;
- establishing the contribution of multiparametric MRI in the diagnosis of prostate cancer;
- correlation of imaging parameters with clinical, paraclinical and histopathological variables;
- drawing up a standardized and optimized MRI protocol that allows the accurate assessment of prostatic tumor lesions;
- development of a set of recommendations to systematize the key points in the interpretation and structuring of MRI results in prostate cancer.

Study group I was prospectively selected from the patients who underwent Magnetic Resonance Imaging examinations in the Radiology and Medical Imaging Laboratory of the Fundeni Clinical Institute and consisted of 90 men between the ages of 40 and 84, of which 68 patients were subjected to biopsy, showing prostate adenocarcinoma in 55 cases, respectively with a negative result in 13 of the cases.

The *inclusion criteria* were represented by*:*

- Suspicious lesion revealed during the multiparametric Magnetic Resonance Imaging examination of the prostate;
- PIRADS score 3, 4, or 5 according to PIRADS v2.1;
- No other concurrent neoplasms;
- No other pathology of the genitourinary system;
- The patient provides informed consent for inclusion in the study.

The *exclusion criteria* were represented by:

- Patients with diagnosed and/or treated prostatic ADK;
- Suboptimal quality images due to overlapping artefacts (generally due to movement or hip prostheses);
- Interrupted examination;
- Examination without administration of contrast material in allergic/renal failure patients;
- PIRADS 1 and 2 prostatic lesions;
- Withdrawal of informed consent.

All patients included in the study were enrolled in the database and a series of demographic, clinico-biological, histopathological and imaging parameters were recorded for each of them. Among the imaging parameters evaluated in the study, we list: diameters and volume of the prostate, diameters and volume of tumor nodules, calculation of signal intensity in a region of interest and last but not least, the PIRADS score of suspicious lesions, according to version v2.1.

Among the most important *results* of study I, we mention:

The patients in the study were aged between 40 and 84 years, with a median age of 66 years and a mean age of 66.45 ± 8.05 years.

Of the total prostate nodules analyzed in the present study, 68 underwent biopsy. Among them, prostate adenocarcinoma was identified in 55 cases, in the remaining 13 the result was negative. For adenocarcinoma-positive nodules, the Gleason score ranged from 5 to 10, with a median value of 7.

Total PSA value did not correlate with prostate volume, neither when estimating it as an ellipsoid (p=0.6745) nor as a bullet (p=0.6745). The correlation between total PSA values and tumor nodule volume was tested, and a direct relationship was observed (coefficient r=0.5758, p<0.0001, CI 95% for r=0.4145-0.7020). The correlation is preserved for the subgroup of patients with peripheral zone tumor nodules (coefficient r=0.6822, p<0.0001, CI 95% for r=0.5051-0.8042) but not for transitional zone nodules (r=-0.0042, p=0.9820).

The correlation of the total PSA value with the PIRADS v2.1 score was analyzed for tumor nodules in the peripheral, respectively transitional zone. For the peripheral zone, statistically significant differences (p=0.007) were identified between the mean total PSA values in patients with different PIRADS scores. These differences between patients with different PIRADS scores were not identified for transitional zone nodules (p=0.300).

A total number of 35 suspicious nodules were identified in the transitional zone in 33 patients, while two of the patients in the study had 2 transitional zone nodules each. Also, among the 33 patients, another 2 presented concurrent and peripheral zone nodules. The morphology of the nodules was "focal patch" type in 42.86% (n=15) of cases, "lenticular" in 31.43% (n=11) of cases and "nodular" in 25.71% (n =9) cases. The contour of the nodules was non-circumscribed in 82.86% (n=29) of cases, well circumscribed in 14.29% (n=5) of nodules, and partially circumscribed in 2.86% (n=1) of cases. Regarding the structure of the nodules of the transitional zone, it was homogeneous in 80.0% (n=28) of the cases, respectively inhomogeneous in 20.0% (n=7) of the cases. There are statistically significant differences between the morphology (p=0.0010) and structure (p=0.0147) of transitional zone nodules and their PIRADS v2.1 score.

Nodule contour did not differ significantly between patients with different PIRADS v2.1 scores (p=0.2270).

A total of 61 suspicious nodules were identified in the peripheral zone in 58 patients, three of the patients in the study presenting 2 peripheral zone nodules each. Also, among the 58 patients, another 2 presented concurrent and similar transitional zone nodules. The morphology of the nodules was "focal patch" type in 44.26% (n=27) of cases, "nodular" in 42.62% (n=26) cases, "lenticular" in 6.56% (n= 4) of the cases, "linear" in 4.92% (n=3) cases and, respectively, “wedge-shaped” in 1.64% (n=1) cases. The contour of the nodules was diffuse in 60.66% (n=37) of the cases and well circumscribed in 39.34% (n=24) of the nodules. Regarding the structure of the peripheral zone nodules, it was homogeneous in 98.36% (n=60), and inhomogeneous in 1.64% (n=1) cases. There are statistically significant differences between the morphology (p=0.0073) of peripheral zone nodules and their PIRADS v2.1 score. Nodule outline did not differ significantly between patients with different PIRADS v2.1 scores (p=0.3304), nor did their structure (p=0.6309).

The diagnostic power of the signal intensity value on the ADC map at values b=1500 and b=2000 respectively was verified in correlation with the histopathological result from the general study group, as well as separately for each PIRADS v2.1 category. The comparative analysis of the ROC curves for the diagnostic contribution of the signal intensity on the ADC map at values of b=1500 vs b=2000 for transitional zone PIRADS 5 nodules revealed a statistically significant difference in the area under the curve, respectively 0.464 with a standard error of 0.179 , 95% CI = 0.114-0.815, z-statistic = 2.596, and a p-value = 0.0094.

Based on the results of Study I, some of the related *discussions* are presented below:

In the present study, total PSA titer does not correlate with prostate volume, neither when estimated as an ellipsoid (p=0.6745) nor as a bullet (p=0.6745). Although the study group G. Carvalhal et al. observed a correlation between PSA value and prostate volume, this was statistically significant only in the case of large prostate volumes, PSA titer remaining rather a predictive marker for tumor volume regardless of prostate size [1]. This correlation between PSA value and tumor volume was also demonstrated in the present study.

From the point of view of the morphology of prostatic tumor lesions in T2-weighted imaging, there are some distinct features depending on their location. Thus, from a total number of 35 tumor lesions identified at the level of the transitional zone during the present study, most appear structured in focal patches (n=15) and lenticular (n=11), unlike the tumor lesions identified at the level of the peripheral zone, where out of a total number of 61 tumor lesions, most appear structured in focal patches (n=27) and nodular (n=26). The data obtained are consistent with those of the PIRADS v2.1 classification [2]. Because of the significant variability in the shape of T2-weighted tumor lesions, there is an overlap in the semiology of tumor lesions with that of benign inflammatory and fibrotic lesions, leading to false-positive results and benign histopathology reports even with PIRADS scores 4-5 on the T2 sequence [3]. Also, the coexistence of tumoral and inflammatory lesions within the same focus makes it even more difficult to interpret the images, a situation in which the PIRADS score on the T2 sequence can be underestimated. The ADC map contributes to increasing diagnostic accuracy, as it is known that the signal intensity of tumor lesions on the ADC map decreases with the increase in the value of the diffusion coefficient. R. Manetta et al. manage to demonstrate the inverse correlation between the ADC value and the Gleason score ($p<0.0001$) [4]. In the present study, we did not obtain a statistically significant correlation between the ADC value at b=1500 ($p=0.223$) or b=2000 ($p=0.069$) and the Gleason score, although the ADC value is lower in tumor lesions compared to the ADC measured in healthy tissue.

The diagnostic ability of using the absolute value of signal intensity on the ADC map at b=1500 and b=2000 values, respectively, was comparatively evaluated. Thus, for patients with a PIRADS score of 3, the diagnostic sensitivity and specificity is 66.7% when interpreting ADC maps with b-values of 1500, with a cut-off of 424 x 10^{-6} mm^2/s, while when using values b of 2000 the sensitivity and specificity rises to 100% in patients from our group, with a cut-off value of 458 x 10^{-6} mm^2/s. Thus, the use of signal values at b=2000 should be considered as this allows for a more precise classification of patients with PIRADS type 3 lesions as PIRADS 4, respectively 5 lesions.

Comparative analysis of the ROC curves for the diagnostic contribution of signal intensity on the ADC map at values of b=1500 vs b=2000 for transitional zone PIRADS 5 nodules revealed

a statistically significant difference in the area under the curve, suggesting superior diagnostic power for this category of patients.

Thus, we propose the addition of diffusion sequences with b=2000 to the routine scanning protocols, as it is obvious from the data presented that they have a higher diagnostic relevance than those with b=1500.

Similar to the present study, T. Tamada and colleagues claim that the use of a diffusion coefficient b = 2000 helps to identify tumor lesions and to evaluate their aggressiveness, managing to differentiate low-risk lesions from intermediate-risk lesions [5]. The study group coordinated by G. Manenti suggests that a diffusion coefficient value of 2000 could be particularly useful for less experienced radiologists [6].

The most important *conclusions* of study I are listed below:

1. The total PSA value correlates with the volume of the tumor nodule.
2. The total PSA value correlates with the PIRADS v2.1 score for the peripheral zone only.
3. Most of the suspicious lesions in the transitional zone show a focal patch and lenticular morphology, and those in the peripheral zone more frequently show a nodular and focal patch morphology.
4. The hypointensity of the T2 signal of suspicious prostate lesions is similar regardless of their location.
5. Signal hypointensity in T2-weighted imaging is not a predictive factor for the Gleason score of prostatic lesions.
6. We recommend the use of the DWI sequence at a diffusion coefficient value of b=2000, for its superior diagnostic value.

The second study is a pilot study on the contribution of dynamic contrast enhancement in multiparametric imaging of prostate adenocarcinoma, with the working hypothesis that prostatic perfusion has an important contribution to the diagnosis and management of patients with biochemical suspicion of prostatic adenocarcinoma.

The objectives of the study are:

- presentation and illustration of the parameters obtained during the MRI perfusion examination of biopsy-confirmed prostatic adenocarcinoma;
- establishing the contribution of MRI perfusion in the diagnosis of prostate cancer.

The pilot study included 20 patients aged between 46 and 83 years, with prostate tumor nodules located in the peripheral zone (n=10) and the transitional zone (n=10), respectively.

The inclusion criteria were represented by:

- Biopsy-confirmed patient with transitional or peripheral zone tumor nodule;
- Existence of biopsy result, Gleason score and clinical history of the patient;
- Magnetic Resonance Imaging examination with dynamic perfusion sequences performed according to the protocol;
- The patient provided informed consent for participation.

The exclusion criteria for this study were:

- Suboptimal quality images due to overlapping artifacts (generally due to motion or hip prostheses);
- Interrupted examination;
- Patient with treated prostatic adenocarcinoma;
- Patient withdrew informed consent for participation;
- Patient with an allergic history of anaphylactic type, a reason for which the examination was limited to the native acquisition;
- Patient with chronic renal failure (GFR < 15mL/min/1.73m^2 body surface or dialysis), a reason for which the examination was performed natively, due to the risk of nephrogenic systemic fibrosis.

All the relevant parameters of the dynamic load with contrast were comparatively evaluated for the transitional zone, respectively the peripheral zone, respectively:

• wash-in slope (W-in);

• wash-out slope (W-out);

• time to peak (TTP);

• arrival time of the contrast (AT);

• peak enhancement intensity (PEI);

• initial area under the 60-s curve (iACU).

A number of statistically significant differences were identified between the mean values of the two groups, the most important *results* of study II being presented below.

Regarding wash-in slope, the median value in nodules in the peripheral zone was 0.059 (95% CI 0.02948 - 0.09517) versus 0.097 (95% CI 0.07710 - 0.1351) in the transitional zone (p=0.0305, Z statistic = 2.163, Mann-Whitney U value = 16).

After measuring the time interval until the maximum uptake of the contrast substance, significant differences between the two groups were revealed, as follows: in the group of patients with peripheral nodules, the median TTP value was 1.4410 minutes (CI 95% between 0.9670 and 1.9061), while for the transitional zone an average time of 1.0620 minutes was recorded (CI 95% between 0.7017 to 1.2341). The time was significantly shorter in transitional zone tumor nodules than those in the peripheral zone (p=0.0373, corrected Z statistic 2.082, Mann-Whitney U = 19.50).

The value of the initial area under the 60-sec curve was compared between the two groups. The value in the peripheral zone was 0.04150 (95% CI value from 0.03324 to 0.07357) while in the transitional zone it was 0.06250 (95% CI value from 0.05505 to 0.09670), the difference being statistically significant (p=0.0357, corrected Z statistic = 2.100, Mann-Whitney U value = 12.00).

There were no statistically significant differences between the median wash-out slope (W-out), bolus arrival time (AT) or peak enhancement (PEI) values intensity) between tumor nodules in the peripheral zone and those in the transitional zone.

The perfusion parameters studied did not correlate with the Gleason score in the patients included in the study.

Discussions related to the results are presented below.

In general, the pilot study data support the idea that transitional zone tumor nodules have particular vascular and perfusion features, revealed by higher values of wash-in slope and iAUC, respectively lower values of TTP. In this sense, a number of common factors may be involved, namely higher vascular density, more aggressive dynamic perfusion flow, as well as higher vascular permeability. The clinical implications of these data may be essential in the diagnosis and treatment of prostate tumors. The increased vascularization and enhanced perfusion of transitional zone tumor nodules may suggest that these nodules respond better to certain treatments that target blood vessels, such as angiogenic drugs [7]. Furthermore, recognition of these distinct features may help the radiologist to better identify and characterize prostate tumor nodules, leading to personalized and effective treatment strategies.

The different degree of vascularization might also reflect different degrees of prostate cancer differentiation [8]. Thus, certain well-differentiated cancers or intraepithelial neoplasms without notable vasculature may not be identified on multiparametric imaging evaluating the wash-in slope or the other parameters mentioned.

Multiple studies show that the detection of transitional zone cancer is more difficult due to some limitations, mainly represented by the concurrent existence of benign prostatic hypertrophy, and dynamic perfusion could provide additional support in this regard [9, 10]. Establishing a trade-off between temporal and spatial resolution could enable faster acquisitions with superior diagnostic sensitivity, especially for the correct identification of transitional zone tumor nodules [11, 12]. The density of microvasculature in benign prostatic hyperplasia is also increased, which may predispose to diagnostic difficulties including the use of dynamic contrast injection [13]. In this regard, some authors did not find the application of this method useful in patients with benign prostatic hyperplasia in the diagnosis of transitional zone tumor nodules [10].

In the present pilot study there were not identified statistically significant differences between dynamic perfusion MRI parameters and clinical variables such as Gleason score or tumor nodule morphology and size, or prostate volume. This may be due to the small size of the study

group, which does not provide sufficient statistical power to identify statistically significant differences. In addition, prostate cancer is recognized for its biological heterogeneity [14, 15]. Thus, tumors with the same Gleason score may exhibit markedly different vascularity, cellularity, and other characteristics and thus not directly correlate with dynamic perfusion MRI parameters. Therefore, a number of potentially useful correlations between imaging parameters and clinical variables could be masked by this heterogeneity. Another limitation could be represented by the sensitivity of the dynamic perfusion MRI imaging parameters, which coupled with the presence of other biological factors such as genetic mutations, influences of the tumor microenvironment or cell density may disturb the statistical correlations [16].

The conclusions of study II are as follows:

1. A series of dynamic MRI perfusion parameters, namely the wash-in slope, the time to peek and the initial area under the 60-s curve have significantly different values in the group of patients with transitional zone tumor nodules compared to those with a peripheral area.
2. The notable differences between the above-mentioned parameters reveal distinct peculiarities of the transitional zone, namely an increased vascularity and a more intense capture of the contrast substance in the tumor nodules at this level.
3. No significant correlations were identified between dynamic perfusion MRI parameters and Gleason score, revealing that these parameters may not accurately reflect the aggressiveness of the cancer determined by this score.
4. The lack of correlation between dynamic perfusion MRI parameters and tumor nodule morphology could be determined by study group sizes, suggesting the need for further studies with larger numbers of patients to understand the relationship between these imaging parameters and clinical variables.

Conclusions and personal contributions

The extent to which the scientific research objectives have been achieved

In the present study, a series of scientific research objectives were established in order to identify answers to the existing problems in this complex and insufficiently studied field.

One of the main objectives was to present and illustrate the morphological and functional MRI aspects of suspicious prostatic lesions, classified as PIRADS 3, 4 or 5 according to the PIRADS v2.1 guide. This objective was successfully achieved, and the present paper provides a rich description, supported by statistical data, of the morphological and functional aspects of the nodules of the patients included in the study. The situation of PIRADS 3 nodules, which represents an important problem in the management of prostate cancer, was distinctly analyzed, especially in the presence of ambiguous clinical data, which do not support a positive diagnosis.

Another proposed objective was to establish the contribution of multiparametric MRI in the diagnosis of prostate cancer. Through this paper, we have shown the role of MRI in the diagnostic management of these patients, we have analyzed the diagnostic contribution of each sequence and type of acquisition, and we have evaluated the benefit of their use in relation to the clinical and histopathological characteristics of the patients.

We also proposed the development of a standardized and optimized MRI protocol that would allow for the accurate assessment of prostatic tumor lesions. We showed that the use of diffusion imaging with high b-values has an important role especially in establishing a positive diagnosis in patients with a PIRADS score of 4 or 5, and we recommended the complementary use of this parameter in the routine protocol, as an aiding factor for diagnosis. We studied the contribution of MRI perfusion in the diagnosis of prostate cancer, and, in the same sense, we developed a series of recommendations for the parameters that revealed their importance in the superior characterization of tumor nodules in certain areas of the prostate. We have developed a set of recommendations to systematize the key points in the interpretation and structuring of MRI results in prostate cancer.

Last but not least, in the present study we proposed the presentation and illustration of the parameters obtained during the MRI perfusion examination of biopsy-confirmed prostatic adenocarcinoma. In study II, we analyzed and described all parameters, their relevance and correlations between them, and discussed their clinical importance and in future research.

Thus, all the scientific research objectives assumed at the beginning of the doctoral studies were successfully achieved.

The technical-economic advantages and disadvantages

Multiparametric MRI offers a number of technical advantages in the diagnosis of prostate cancer, such as the superior ability to provide anatomical and functional details regarding the prostate parenchyma, improving the detection rate and localization of clinically significant prostate cancer, with a reduction in the number of false-negative and false-positive results compared to other traditional imaging methods. Another advantage is represented by the role of mpMRI in guiding targeted biopsies.

A technical limitation of mp MRI is the need for adequate training and imaging expertise. The radiologist must be highly efficient in imaging interpretation and analyzing the multiple parameters provided by the different sequences, which can be time-consuming and highly complex. In addition, there may be variability in image interpretation between different radiologists, which may affect consistency and diagnostic accuracy. The PIRADS effort to standardize mpMRI interpretation aims to minimize this effect, but interobserver variability is still a challenge. Another technical disadvantage is represented by the possibility of artifacts and the application limitation of the method to certain categories of patients. Patient movements during the investigation, metal implants, or previous treatment can generate artifacts that significantly alter image quality and lead to significant diagnostic errors.

From an economic point of view, mpMRI can offer the advantage of long-term cost savings despite the apparently high initial costs, by significantly improving the diagnosis rate of prostate cancer, reducing the need for repeat biopsies and unnecessary treatments.

Issues left unresolved

Following this research, there are a number of issues that remain unsolved. First, the analysis of patients included in the study group and the correlation between clinical, histological, paraclinical and imaging parameters revealed the need for standardization of imaging protocols and the interpretation of mpMRI of the prostate. Although there are international efforts such as the PIRADS score, there is great variability between imaging methods and protocols at different institutions. In interpreting the data from the present study in an international context, referring to

studies in the literature, multiple protocols were identified and comparative assessment was often difficult due to different protocols. This lack of uniformity can affect the comparison of mpMRI data between centers and lead to inconsistent interpretations and results.

Multiparametric MRI can detect clinically insignificant cancers that do not require prompt intervention, but differentiating them from clinically significant cancers can be challenging, and may predispose to the administration of unnecessary treatments. Also, mpMRI is not an infallible method and can generate false-positive or false-negative results, leading to either unwarranted biopsies or missed diagnosis of prostate cancer.

Optimal integration of mpMRI with other diagnostic methods such as PSA tests, genomic markers, and other imaging methods is required. By combining these methods, it is possible to increase the diagnostic accuracy.

At the international level, there are few studies that analyze the impact of mpMRI on patient survival and quality of life, respectively that analyze the added value of this method on the concrete results of the clinical evolution of patients. The long-term contribution of the use of mpMRI is still unclear and longitudinal studies are needed to highlight its role in this context.

The directions in which the research should be continued

Technological progress in recent years opens up new research directions, and mpMRI could benefit from significant improvements in this regard. First, new imaging sequences could increase diagnostic accuracy and have clinical utility in prostate cancer. Among these we list diffusion kurtosis imaging (DKI), intravoxel incoherent motion (IVIM) imaging and chemical exchange saturation transfer (CEST) imaging, methods that could provide additional data on metabolism and the tumor microenvironment. In addition, the development of artificial intelligence and its integration as well as machine learning algorithms in mpMRI analysis could have significant potential in increasing diagnostic efficiency and accuracy, with AI able to assist in imaging interpretation, lesion detection, measurement and reporting of lesions with higher consistency, eliminating interobserver variability. Moreover, AI can automatically segment prostate anatomy and the identified lesions and reduce the time spent by the radiologist on these operations.

The use of advanced diffusion imaging methods such as high b-value imaging, diffusion tensor imaging and DKI can provide additional data on tissue architecture and tumor cellularity, thus revealing information on the aggressiveness of prostate cancer and having the potential to be

used as methods to assess tumor response and disease progression. There are also a number of functional MRI biomarkers that could be applied in prostate cancer such as oxygenation-sensitive imaging and MRI elastography, which could provide data on tumor vascularity, hypoxia, and tissue stiffness. Combined with conventional mpMRI sequences, these biomarkers could improve the characterization of prostate cancer phenotypes.

Own contributions

Among the own contributions made through this work are the following:

- carrying out a study regarding the illustration of morphological and functional MRI aspects of suspicious prostatic lesions and their classification according to the PIRADS v2.1 classification;
- realizing correlations between imaging and clinical, paraclinical, and histopathological features in patients with prostate adenocarcinoma and presenting the respective results;
- optimization of the MRI protocol by adding the diffusion sequence with b=2000, due to the superior diagnostic relevance over the diffusion sequence with b=1500;
- issuance of a recommendation regarding the addition of the topographic criterion within the PIRADS classification of suspicious prostatic lesions identified at the tranzitional zone level;
- carrying out a pilot study on the contribution of dynamic loading with contrast in the multiparametric imaging of prostate adenocarcinoma, with the presentation and comparative illustration of the parameters obtained at the prostatic peripheral and tranzitional zones (in the case of biopsy-confirmed prostatic tumor lesions).

Selected references

(of the total of 139 references included in the thesis)

1. Carvalhal GF, Daudi SN, Kan D, Mondo D, Roehl KA, Loeb S, et al. Correlation between serum prostate-specific antigen and cancer volume in prostate glands of different sizes. *Urology*. 2010;76(5):1072-6.
2. Turkbey B, Rosenkrantz AB, Haider MA, Padhani AR, Villeirs G, Macura KJ, et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. *Eur Urol*. 2019;76(3):340-51.
3. Żurowska A, Pęksa R, Bieńkowski M, Skrobisz K, Sowa M, Matuszewski M, et al. Prostate Cancer and Its Mimics-A Pictorial Review. *Cancers (Basel)*. 2023;15(14).
4. Manetta R, Palumbo P, Gianneramo C, Bruno F, Arrigoni F, Natella R, et al. Correlation between ADC values and Gleason score in evaluation of prostate cancer: multicentre experience and review of the literature. *Gland Surg*. 2019;8(Suppl 3):S216-s22.
5. Tamada T, Kanomata N, Sone T, Jo Y, Miyaji Y, Higashi H, et al. High b value (2,000 s/mm2) diffusion-weighted magnetic resonance imaging in prostate cancer at 3 Tesla: comparison with 1,000 s/mm2 for tumor conspicuity and discrimination of aggressiveness. *PLoS One*. 2014;9(5):e96619.
6. Manenti G, Nezzo M, Chegai F, Vasili E, Bonanno E, Simonetti G. DWI of Prostate Cancer: Optimal b-Value in Clinical Practice. *Prostate Cancer*. 2014;2014:868269.
7. Jayson GC, Kerbel R, Ellis LM, Harris AL. Antiangiogenic therapy in oncology: current status and future directions. *Lancet*. 2016;388(10043):518-29.
8. Alinezhad S, Väänänen RM, Tallgrén T, Perez IM, Jambor I, Aronen H, et al. Stratification of aggressive prostate cancer from indolent disease-Prospective controlled trial utilizing expression of 11 genes in apparently benign tissue. *Urol Oncol*. 2016;34(6):255.e15-22.
9. Rouvière O, Raudrant A, Ecochard R, Colin-Pangaud C, Pasquiou C, Bouvier R, et al. Characterization of time-enhancement curves of benign and malignant prostate tissue at dynamic MR imaging. *Eur Radiol*. 2003;13(5):931-42.

10. Oyen RH. Dynamic contrast-enhanced MRI of the prostate: is this the way to proceed for characterization of prostatic carcinoma? *Eur Radiol*. 2003;13(5):921-4.

11. Valentini AL, Gui B, Cina A, Pinto F, Totaro A, Pierconti F, et al. T2-weighted hypointense lesions within prostate gland: differential diagnosis using wash-in rate parameter on the basis of dynamic contrast-enhanced magnetic resonance imaging--hystopatology correlations. *Eur J Radiol*. 2012;81(11):3090-5.

12. Hellstern M, Martinez C, Wallenhorst C, Beyersdorff D, Lüdemann L, Grimm MO, et al. Optimal length and temporal resolution of dynamic contrast-enhanced MR imaging for the differentiation between prostate cancer and normal peripheral zone tissue. *PLoS One*. 2023;18(6):e0287651.

13. Turnbull LW, Buckley DL, Turnbull LS, Liney GP, Knowles AJ. Differentiation of prostatic carcinoma and benign prostatic hyperplasia: correlation between dynamic Gd-DTPA-enhanced MR imaging and histopathology. *J Magn Reson Imaging*. 1999;9(2):311-6.

14. Wendel M, Bazhenova L, Boshuizen R, Kolatkar A, Honnatti M, Cho EH, et al. Fluid biopsy for circulating tumor cell identification in patients with early-and late-stage non-small cell lung cancer: a glimpse into lung cancer biology. *Phys Biol*. 2012;9(1):016005.

15. Malihi PD, Graf RP, Rodriguez A, Ramesh N, Lee J, Sutton R, et al. Single-Cell Circulating Tumor Cell Analysis Reveals Genomic Instability as a Distinctive Feature of Aggressive Prostate Cancer. *Clin Cancer Res*. 2020;26(15):4143-53.

16. Barnett ES, Schultz N, Stopsack KH, Lam ET, Arfe A, Lee J, et al. Analysis of BRCA2 Copy Number Loss and Genomic Instability in Circulating Tumor Cells from Patients with Metastatic Castration-resistant Prostate Cancer. *Eur Urol*. 2023;83(2):112-20.

List of scientific papers published on the topic of the doctoral thesis

1. Multiparametric MRI evaluation in benign prostatic hyperplasia – a true challenge in prostate cancer exclusion, Sandra O. Jurcă, Gabriel Gluck, Ioana G. Lupescu, Oncolog-Hematolog.ro, 14 decembrie 2019, Nr. 49 (4/2019), DOI: 10.26416/OnHe.49.4.2019.2740.
   https://www.medichub.ro/reviste-de-specialitate/oncolog-hematolog-ro/evaluarea-irm-multiparametrica-in-hiperplazia-benigna-de-prostata-o-adevarata-provocare-in-excluderea-cancerului-de-prostata-id-2740-cmsid-68

2. Magnetic resonance imaging features of PI-RADS 5 lesions: a tertiary center experience, Sandra O. Jurcă, Gabriel Gluck, Ioana G. Lupescu, Oncolog-Hematolog.ro, No. 57 (4) 2021, 20 decembrie 2021, DOI: 10.26416/OnHe.57.4.2021.5801. https://www.medichub.ro/reviste-de-specialitate/oncolog-hematolog-ro/aspecte-irm-ale-leziunilor-pi-rads-5-experienta-unui-centru-tertiar-id-5801-cmsid-68

3. IRM MP în cancerul de prostată: de la teorie la cazuri practice. Ioana G. Lupescu, Sandra Moanga, R. Al. Capşa, Emi M. Preda, V. Herlea, G. Gluck, volumul de rezumate al Congresul Național de Radiologie și Imagistică Medicală, 2017

4. Ce trebuie să ştim despre anatomia zonală a prostatei în evaluarea IRM?. Sandra Moangă, Ioana G.Lupescu, volumul de rezumate al Congresul Național de Radiologie și Imagistică Medicală, 2017