IMAGISTIC EXPLORATIONS IN THE PATHOLOGY OF THE PROSTATE. A COMPARATIVE APPROACH

DOCTOR'S DEGREE THESIS

ABSTRACT

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**KEY-WORDS:** prostate pathology, imaging
INTRODUCTION

Prostate cancer is a public health problem worldwide, constituting the second cause of cancer induced death in men in industrialized countries. Part of the arsenal of more modern imaging diagnostic methods are for one ultrasonography (US), which through the use of spectral Doppler examinations, color or power Doppler ultrasonography and contrast agents allows the analysis of vascular architecture of lesions, magnetic resonance imaging (MRI), with the possibility of MR spectroscopy, computed tomography (CT), positron emission tomography, scintigraphy. Imaging allows targeted biopsies under ultrasound guidance or by magnetic resonance imaging, increasing diagnostic accuracy significantly.

KNOWLEDGE

Chapter 1 - Anatomy and physiology of the prostate and vesicles

The particular anatomy of the prostate and seminal vesicles offers large possibilities to the imaging techniques of diagnosis. The prostate is structured into two parts, namely the glandular portion, which represents two-thirds of the gland, composed of the lateral lobes, located laterally to the urethra, representing most of the prostate, the posterior portion situated behind urethra and bellow ejaculatory ducts and the median portion around the urethra and the fibro-muscular portion which represents a third of the gland, consisting of the anterior lobe, located anterior the urethra, which contains no glandular tissue. Classical lobar anatomy is less useful in terms of clinically and pathologically significance that is why zonal anatomy is used more frequently. In terms of histology three zones are described: central, transitional and peripheral [3].

Chapter 2 - Imaging methods used in prostate pathology

Imaging examination of the prostate includes excretory urography and cysto-urethrogram, ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) [1]. All these methods, their principles and guidelines in assessing prostate pathology, are presented in this chapter.

Chapter 3 - Aspects of normal prostate imaging

In transrectal US prostate delineation of periprostatic fat can be easily seen, but in case of areas located at the periphery of the acquisition or away from the transducer the delineation may be less well defined [3]. CT shows the prostate as an oval, homogeneous, finely delineated soft tissue. Prostate zones can not be individualized [3]. When using MRI techniques, T2-weight sequences show the zonal anatomy of the prostate.

Chapter 4 - Clinical, epidemiological, histopathological and therapeutic aspects in prostate pathology

In prostate cancer we followed the epidemiology and etiology; local and general clinical manifestations; digital rectal examination; biomarkers, prostate-specific antigen (PSA) in particular; WHO histological classification of prostate tumors, the most common being adenocarcinomas; the Gleason score; diagnosis and staging (TNM, Whitmore-Jewett); prognostic factors; the natural development and treatment of prostate cancer [6]. High-intensity focused ultrasound (HIFU) is a non-invasive therapeutic method in prostate cancer [5].

In benign prostate diseases clinical-biological aspects are customized in acute and chronic prostatitis and benign prostatic hyperplasia [1, 3].

Chapter 5 - Imaging aspects in prostate pathology

Inflammatory diseases of the prostate don’t have a characteristic US appearance. A particular aspect is seen in granulomatous prostatitis. In benign prostatic hyperplasia we can identify either the presence of nodules or the diffuse increase in size of the transitional zone, or both. The US appearance of prostate cancer is variable [2], 70% of them being hypoechoic, located in the peripheral area. They can’t be identified only by US if they are not big enough to deform the contour of the gland [3].
Acute prostatitis can not be distinguished clearly by CT of a normal prostate or benign prostatic hyperplasia. In benign prostate hyperplasia, CT shows the glandular enlargement, usually symmetrical, homogeneous or heterogeneous. Malignant lesions that do not exceed the prostate capsule, particularly those located deep can not be distinguished from normal glandular tissue. Peripheral tumors may show focal or diffuse enhancement after contrast medium [4]. Lymph node and distant spread can be detected. In acute prostatitis magnetic resonance examination highlights the overall increase in prostate volume, with an edematous aspect. In chronic prostatitis MRI examination reveals diffuse or focal T2 hypo signal in the peripheral area and small cystic lesions in showing T2 hyper signal. MRI in benign prostatic hyperplasia emphasizes different aspects according to histological subtypes, depending on the amount of stromal and glandular tissue. Tumor detection is better accomplished on T2-weighted sequences, occurring as a focus of low signal intensity within an otherwise high-signal intensity peripheral zone [4]. One can identify capsule penetration, seminal vesicle invasion, tumor extension to the bladder and rectum, lymph nodes and distant metastases.

**ORIGINAL CONTRIBUTIONS**

**Chapter 6 - Aim and hypotheses**

The aim of this retrospective research is to establish the role of imaging examinations in the diagnosis of prostate diseases. I also wanted to present an analysis of neovascularity issues in prostate cancer through Doppler ultrasound, computed tomography and magnetic resonance. I also presented some aspects regarding the procedure for high-intensity focused ultrasound (HIFU). In achieving this objective we started from the assumption that modern imaging methods, particularly spectral Doppler, color or power Doppler and magnetic resonance imaging have a much greater role than currently recognized, particularly by clinicians, namely the assessment of the extension of prostate cancer and the detection of recurrence, through the ability to detect infracentimetric malignant lesions and to investigate the vascular architecture of lesions.

**Chapter 7 - Materials and methods**

**7.1. Material**

We studied 1601 patients, of which 1590 were investigated using imaging methods. They were divided into two groups. The first batch consisted of 1396 patients investigated for diagnostic purposes by one or more of the methods represented by US, CT and MRI, divided into seven subgroups on the basis of imaging investigations carried out. The second group included 194 patients with prostate cancer investigated after treatment, divided into seven subgroups, according to the same criteria as the first batch. To the 1590 investigated patients were added 11 patients diagnosed with prostate cancer who were treated by the procedure of high-intensity focused ultrasound.

**7.2. Imaging diagnostic methods in prostate pathology**

Ultrasonographies were performed on ALOKA PROSOUND DIGITAL equipment, using the convex transducer or the endorectal probe with the achievement of axial, sagittal and oblique sections. Protocol ultrasound examination included the detection of a suspect prostatic mass, determination of the gland volume, calculation of predicted PSA and excess PSA. Ultrasound examinations included color/power Doppler and spectral Doppler. Computed tomography was performed using a Siemens SOMATOM Emotion 6 device and a multi-slice Presto Basic System, Hitachi Medical Systems. Computed tomography examinations include native abdominal-pelvic scans post i contrast acquisitions in the arterial and venous phases, with multiplanar reconstructions. Magnetic resonance imaging examinations were performed using a Siemens Magnetom Symphony 1.5 Tesla unit, a permanent magnet AIRIS Mate, Hitachi and a General Electric Signa Horizon unit of 1 Tesla, using standard protocols.

**7.3. Methods of statistical analysis**

For the statistical analysis we used Epi Info2000 and SPSS programs, specializing in scientific statistical calculations. Recording and processing of patient data was performed using Excel and Data
Analysis module. Comparison of averages was performed using ANOVA test, Student, Wilcoxon or Kruskal-Wallis.

7.4 High-intensity focused ultrasound procedure

High-intensity focused ultrasound was performed with Sonablate ® 500, which combines its own technology for multi-focal transducer in a probe unit performing both transrectal imaging and ultrasound therapy.

Chapter 8 - Results

8.1 Results in diagnostic imaging in prostate pathology

Of the 1396 patients investigated for diagnostic purpose, the imaging appearance of 937 patients called for benign pathology and that of 459 for malignancy.

Of the 937 cases with benign pathology, 69 patients were diagnosed using imaging methods with inflammatory diseases of prostate and the remaining 868 with benign prostatic hyperplasia.

We found that the most affected age groups were, in descending order, 61-70 years old, 51-60 years old and 71-80 years old. Cases with inflammatory prostatic diseases and benign prostatic hypertrophy came predominantly from urban environment.

Most patients were investigated by US and transrectal or US associated with CT.

The 459 patients diagnosed with malignant pathology consisted of 432 prostate cancer cases and 27 cases with other pelvic malignant tumors extensive to the prostate.

For the 432 patients with the imaging diagnosis of prostate cancer we found that the majority belonged to the age groups 61-70 years old and 51-60 years old and came from urban areas.

Most cases have been investigated by US and US + MRI, in equal proportions.

We divided the cases diagnosed with prostate cancer in cases with lesions confined to the prostate and cases with locally extensive lesions, within each category seeking the number of patients for which the imaging diagnosis was correct, depending on the imaging method or methods used.

In lesions limited to the prostate the accuracy of diagnostic imaging methods was as follows: US + CT + MRI, MRI + US, MRI, CT + MRI, US, CT + US and CT.

Regarding prostate cancer with local extension the order was: US + CT + MRI, US + MRI, US + CT, MRI, CT + MRI, CT and US.

Taking into account both lesions confined to the prostate, as well as those extensive locally the order was as follows: US + CT + MRI, MRI + US, MRI, US + CT, CT + MRI, US and CT.

I have found regional lymph node metastases in 22 cases, most evidenced by the association of US with MRI.

Distant metastases were detected in 179 patients, that are, in descending order of frequency: bone metastases, metastases in other areas than bone, bone metastases associated with those in other areas than bone metastases, other than regional lymph node metastases, and other than regional lymph node metastases associated with bone metastases. The detection of bone metastases was made using MRI, CT or the combination of the two, and that of the other metastases or association of metastases by using US combined, in most cases, with MRI, CT or both.

The 27 cases of other pelvic malignant tumors extensive to the prostate, most of them rectal tumors were depicted by CT, MRI, followed in equal proportions by US + CT, US + MRI, the last place being occupied equally by US, CT + MRI and US + CT + MRI.

8.2 Results in post-therapeutic imaging explorations in prostate cancer patients

Most patients in this group belonged to the age groups 61-70 years old and 51-60 years old and came from urban areas.

In descending order of frequency of use, the seven subgroups formed by imaging investigations carried out, were as follows: US + CT, US + MRI, MRI, US, CT, CT + MRI and US + CT + MRI.

We followed the presence of residual or recurrent lesions, distant metastases and distant metastases associated with recurrent disease. For this lot we included in the metastases category only those undiagnosed before treatment.
Of the 194 persons investigated, we found changes in 54, of which in 43 we found residual or recurrent lesions associated with distant metastases, in 6 distant metastases and in the remaining residual or recurrent lesions.

Distal metastases were, in descending order of frequency, bone metastases, metastases in other areas than bone, bone metastases associated with those in other areas than bone, metastases in other than regional lymph nodes, and metastases in other than regional lymph nodes associated with bone metastases. Bone metastases were found using MRI, CT or CT + MRI, and the other metastases and associations of metastases using US + CT, US + MRI, US + CT + MRI, CT + MRI, and CT.

8.3. Aspects regarding prostate cancer treatment by high-intensity focused ultrasound

During HIFU a very small volume of ablation is created, oval shaped, with each pulse of energy. Treatment of prostate cancer is achieved through systematic energy pulses through the target volume until the whole volume of the tumor is removed. Treatment volume is predefined in the planning phase.

Chapter 9 - Discussions

9.1. Diagnostic imaging explorations in prostate pathology

Although chronic prostatitis and benign prostatic hyperplasia are common, the number of cases in this study is not very high because of the exclusion criteria of this lot, particularly the lack of symptoms, because chronic prostatitis can often be asymptomatic. In benign prostatic pathology most affected age groups were, in descending order, 61-70 year olds, 51-60 year olds and 71-80 year olds, justified by the predominant distribution of benign prostatic hyperplasia in these age groups.

Most patients were investigated by US and US + CT.

In acute prostatitis imaging aspects varied, the diagnosis being made, usually in a clinically evocative context. In benign prostatic hyperplasia there was shown either the presence of nodules or diffuse increase in size of the transitional zone, or both.

The study by age distribution of patients diagnosed with prostate cancer using imaging methods revealed data consistent with the literature.

There is no parallelism between the number of patients in each subgroup divided according to the method or combination of imaging methods used and the number of cases correctly diagnosed by these methods or combination of methods, for both lesions confined to the prostate, as well as those extensive locally.

Imaging flow assessment has become increasingly important for the preoperative non-invasive diagnostic and treatment of prostate cancer.

In half of cases, regional lymph node metastases were detected by using US + MRI, although the number of patients in whom these methods were carried out was only 31.49% of patients with cancer, which underlines the significant value.

The presence of distant metastases was detected in a significant percentage through imaging methods. There is no parallelism between the number of cases with detected metastases and the total number of patients who underwent explorations using one method or combination methods, which allows us to conclude that the combinations US - MRI, US - CT and CT - MRI were the best in detecting distant metastases.

In 5.88% of all cases diagnosed by imaging methods with malignant lesions, these were other pelvic tumors extensive to the prostate. Most of these were detected by CT and MRI.

9.2. Post therapeutic imaging explorations in patients with prostate cancer

The continuing increase in the incidence and mortality of prostate cancer motivates redirecting efforts to adopt effective strategies for secondary prevention.

Early postoperative evaluation allows the detection of complications and residual lesions and late evaluation detects recurrent disease. The aim is early detection of recurrence and significant reduction of the number of biopsies for the diagnosis of benign lesions, through post-therapeutic imaging evaluation of the greatest possible accuracy.

I found a very high percentage of changes (27.84%), most of them residual or recurrent lesions associated with distant metastases, that justifies the need for imaging in these patients.
Regarding distant metastases, the survey shows increased frequency of bone metastases, 21.65% respectively, detected by MRI, CT and the combination of the two methods. In contrast, metastases in other areas than bone accounted for only 1.54% of all cases assessed, unlike in group which underwent imaging investigations for diagnostic purpose, where they represented 6.14%.

9.3. Prostate cancer treatment using high-intensity focused ultrasound

Due to the low number of cases to which I had access, I included in the lot just the patients in whom post therapeutic evaluations at intervals of less than an year showed the absence of residual lesions, aiming to show just the aspect of the prostate at the beginning of the procedure, the changes during the procedure, and the aspect at the end of it. It is very important to respect the criteria for patient selection.

CONCLUSIONS

Benign pathology was the most commonly diagnosed through imaging, representing 67.12% of cases. The most affected age groups were, in descending order, 61-70 year olds, 51-60 year olds and 71-80 year old, the distribution being justified by the predominance of benign prostatic hypertrophy, occurring in these age groups. Most patients were investigated by US (46.53%) and US + CT (16%), in opposition to US + CT + MRI, which was used in only two patients.

What concerns malignant lesions, these were in most cases prostate cancers and only in 27 cases were other pelvic malignant tumors extending to the prostate.

The goal of the management of prostate cancer is an as earlier possible diagnostic with a non-invasive, repeatable, accessible and low cost technique.

The study by age distribution of patients diagnosed with prostate cancer by imaging showed predominant impairment of people between 61 and 70 years of age, followed by the 51-60 years old group.

Diagnostic accuracy differences between these methods were very small so I believe that the combination of several imaging methods should not be used so frequently in the diagnosis of prostate cancer. As the exclusive use of CT allowed correct diagnosis of localized prostate lesions in a much smaller number of cases compared with other methods or combination of methods, I believe that it should not be the first choice examination.

In prostate cancer with local extension US occupied the last place. Their use as first choice is however justified by their wide availability, relatively low cost and the lack of harm.

US has a relatively high accuracy in detecting cancers located in the peripheral area, which are the most common. Transrectal US provides high resolution imaging, by placing the probe near the prostate, allowing a detailed study of regional anatomy. US detection of capsular extension is limited in early cases, but the accuracy in identifying the seminal vesicles is higher. US allow us determination of the gland volume, calculation of predicted PSA and excess PSA.

Gland volume can be accurately calculated by MRI as well, due to multiplanar acquisitions and also by CT, by making multiplanar reconstructions.

CT has a low diagnostic accuracy in lesions confined to the prostate. Its value is higher when assessing prostate cancer extension, due to the detection, in particular, of damage to the lymphatic system, and also to the seminal vesicles. It also has the advantage of assessing bone structures included in the acquisition plan.

The main role of MRI in prostate cancer consists of extracapsular extension evaluation, periprostatic fat and seminal vesicle invasion assessment, pelvic lymph node and bone metastases evaluation.

Of the imaging methods magnetic resonance has the best sensitivity, but it is possible that ultrasound, through Doppler examination, 3D/4D acquisitions and sonoelastography, becomes the best non-invasive, available and cost-effective imaging method of detection, follow-up and guided biopsy in prostate cancer. MRI has several advantages, namely, being non-irradiating, obtaining images in multiple planes and having the best tissue contrast.
Malignant lesions show a higher blood flow than that of normal tissue, aspect revealed by Doppler US, spiral CT with intravenous contrast and MRI. Even in the early stages, when no imaging may reveal the presence of tumor mass, cancer is suspected when pericapsular vessels have increased size or flow. Usefulness of blood flow assessment is proven, even in cases of discordance between digital rectal examination and prostate biopsy or in cases of lesions not completely removed during the surgical treatment of benign prostatic hyperplasia. Angiogenesis is crucial for tumor growth and metastasis, being an important indicator in the differential diagnosis, evolution and prognosis of tumors.

Imaging exploration differentiated, in 5.88% of all cases diagnosed by imaging methods with malignant lesions, other pelvic tumors extensive to the prostate. The majority of these were detected by CT and magnetic resonance imaging. Most of the cases consisted of rectal tumors extended to the prostate.

In follow-up investigations, CT and MRI are particularly useful for detecting local recurrence, extension of the tumor through the capsule, invasion of the seminal vesicles and bladder wall, damage to pelvic lymph nodes, bone and liver metastases, CT having as well an increased sensitivity in detecting lung metastases.

Post-therapeutic follow-up by imaging is essential, allowing the evaluation of regression or stability of changes, or, on the contrary, showing the appearance of early complications, of recurrences and relapses, justified by the high percentage of changes (27.84%), particularly residual lesions or relapse associated to remote metastases.

One of tissue ablation technologies is high-intensity focused ultrasound, which is a non-invasive surgical procedure, of high accuracy and efficiency. It is very important that the criteria for selecting patients are respected, in order to obtain desired results.

The study confirmed the hypothesis from which we started in achieving this objective, the fact that modern imaging methods, particularly spectral Doppler, color or power Doppler and magnetic resonance imaging have a much greater role than currently recognized, namely the review of extension and detection of prostate cancer recurrence by allowing detection of infracentimetric malignant lesions and investigating the vascular architecture of the lesions.

Although imaging methods are extremely useful to clinicians in managing patients suspected of prostate cancer or with confirmed cancer, there are still many opportunities for development.

**SELECTIVE BIBLIOGRAPHY**

CURRICULUM VITAE

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**Papers published in magazines** – 3: 1 first author; 2 co-author


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- National Congress of Radiology and Medical Imaging Constanţa, 23-25 September 1999.
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- The 9th Congress of Endocrinology, Craiova, 5-7 June 2003.
- Musculoskeletal Sectional Imaging Group Meeting, Timişoara, November 2009
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