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Role of the Apparent Diffusion Coefficient (ADC) values analysis in Diffusion Weighted Imaging (DWI-MR) in the characterization of prostatic disease on Multiparametric Magnetic Resonance Imaging (Mp-MRI) of the prostate.

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INDEX.

I. INTRODUCTION

Prostatic diseases are a very common male pathology, affecting every year millions of men around the world. These pathologies group include benign conditions, such as prostatitis, fibrosis and benign prostatic hypertrophy (BPH), and malignant pathologies such as prostate cancer (PCa). PCa is currently the most common neoplasm in men and the second leading cause of cancer-related death in male patients [1].

In addition to PCa, there are at least two other potentially malignant pathological conditions: prostatic intraepithelial neoplasia (PIN) and atypical small acinar proliferation (ASAP).

PIN is characterized by atypical proliferation of premalignant foci of cellular dysplasia and carcinoma in situ within the prostatic ducts, ductules and large acini [2]. It is possible to differentiate low (LG-PIN) and high grade (HG-PIN) PIN depending on the severity of the histopathological anomalies. HG-PIN is usually accepted as the most likely precursor lesion to adenocarcinoma of the prostate [3].

ASAP is a pathological definition indicating areas composed of several glands with atypical epithelium. Although these findings are not considered definite pre-neoplastic lesions, like HG-PIN, several studies showed that ASAP is associated with an increased incidence of prostate cancer at follow-up biopsies [4].

Despite conflicting opinions, magnetic resonance imaging (MRI) is currently considered the best imaging modality for studying prostate disease [5]. Multiparametric MRI (mp-MRI) combines anatomic and functional techniques (diffusion-weighted imaging, dynamic contrast enhanced imaging and MR spectroscopy) allowing significant improvement in the diagnostic value of this imaging modality that is fundamental in detection, localization, and staging of prostate cancer [6]. Among functional techniques, the diffusion-weighted imaging (DWI) has a very important role as it allows evaluation of the degree of diffusion of water molecules in biological tissues. This

microscopic information can be quantified by calculating the apparent diffusion coefficient (ADC). Several studies confirm that it is possible to distinguish between malignant and benign prostate tissue based on relatively lower apparent diffusion coefficients of cancer tissue [7-8]. To our knowledge, no study has specifically investigated the possibility of distinguishing between the different prostatic diseases using only diffusion sequences.

Therefore, the purpose of this study was to evaluate if normal and pathological prostate tissue can be distinguished using ADC values on MRI. We also try to understand if it is possible to differentiate among pathological prostate tissues (prostate cancer, atypical small acinar proliferation, prostatic intraepithelial neoplasia, fibrosis) using ADC values.

PURPOSE OF THE STUDY

The purpose of the study was first to evaluate if normal prostate tissue and prostate cancer (PCa) can be distinguished by using apparent diffusion coefficient (ADC) values analysis on magnetic resonance imaging (MRI) obtained applying DWI sequences with 1400 s/mm2 *b value*. Secondary purpose of the study was to evaluate the ability of the apparent diffusion coefficient (ADC) values analysis in differentiating between normal prostatic tissue, prostate cancer (PCa), precancerous pathologic prostatic conditions, including intraepithelial neoplasm (PIN) and atypical small acinar proliferation (ASAP), and prostatic post-radiotherapy fibrotic changes.

III. MATERIAL AND METHODS

III.1. Population

Our institutional review board approved this retrospective study and waived the informed consent requirement for our retrospective study.

We examined the MRI studies of 123 patients who underwent prostate MRI between 2015 and 2016.

Exams were performed for at least one of the following reasons: (a) elevated PSA level (> 4 ng/mL), (b) abnormal digital rectal examination and/or transrectal ultrasonography and (c) follow-up post radiation therapy (post-RT).

We excluded patients who underwent radical prostatectomy before MRI examination (12 patients). Moreover, no suspicious regions were detected on MRI in 18 patients. So our final population consisted in 93 patients between the ages of 50 and 81 (mean: 65.4 ± 8.9).

III.2 MR study protocol

To reduce possible sources of diagnostic errors, MRI studies were performed at least 6 weeks after prostate biopsies to allow any hemorrhage to resolve.

Before the exams, we suppressed intestinal peristalsis with an intravenous administration of 20 mg of butylscopolaminebromide (Buscopan®; Boehringer-Ingelheim, Ingelheim, Germany).

All MRI examinations were performed using a 1.5-T MR scanner (Signa Excite, General Electric Medical Systems, Milwaukee, WI) equipped with a phased array surface coil (8-channel HD Torso, General Electric Medical Systems, Milwaukee, WI) and an endorectal coil (e-Coil; Medrad,

Pittsburgh, PA, US), filled with 60–90 mL of air on the basis of patient tolerance. After a single-shot sagittal sequence was obtained to verify the position of the endorectal coil, morphological images of the prostate gland were obtained using T2-weighted turbo spin-echo sequences on sagittal, axial, and coronal plans. We also acquired axial T1-weighted images to exclude hyperintense areas of post-biopsy hemorrhage.

The diffusion study comprises 7 different b values (0-10-20-50-100-700-1400 s/mm2) acquired by a single-shot echoplanar imaging (EPI) sequence. For the present study 2 b values of diffusion whole study have been considered, of 0 and 1400 s/mm2.

The DWI sequences were then post-processed by using software integrated into the MR imaging acquisition console to obtain the ADC map of the prostate gland. Image acquisition details are summarized in Table 1.

We also performed a perfusion study after intravenous injection of paramagnetic contrast agent.

Dynamic contrast-enhanced MRI (DCE-MRI) studies were performed to detect highly vascular lesions and to evaluate the wash in/wash out rate perfusional parameter. Axial 3D T1-weighted sequences have been acquired after intravenous administration of approximately 1 mmol/Kg of body weight of gadoterate meglumine (Dotarem®; Guerbet, USA) at a rate of 3.0 mL/sec, followed by a 20-30 mL saline flush.

III.3 Image analysis

Images were evaluated by two radiologists in consensus with 7 years and 4 years of experience in prostate MR imaging.

The high-spatial resolution axial T2-weighted images were used as the basis for evaluation of the prostate, and all other functional imaging modalities were interpreted in relation to these. The readers considered areas with at least one of the following characteristics to be suspicious: a) low intensity on T2-weighted images, b) diffusion restriction on DWI and/or hypointensity on ADC

maps, c) anomalous contrast enhancement on DCE-MRI images. The radiologists placed a region of interest (ROI) over these areas on the ADC map to perform a quantitative assessment. ADC values were also calculated in the prostatic region of the peripheral zone (PZ) with normal appearance on mpMRI in order to compare numerical values.

In our study population, 12 patients underwent radiotherapy for PCa. It was only possible to evaluate the images after treatment because pre-therapy MRI was performed at other hospitals. In all these cases, the readers were not able to identify the known tumor; therefore, they placed ROIs over the peripheral zone on the ADC maps.

III.4 Statistical analysis

Data were processed with Excel (Microsoft Corporation, Redmond, WA, USA). ADC values of the different prostate areas were reported as mean ± standard deviation (SD). The *t test* for paired data was used to evaluate statistical differences between ADC values of the pathological findings (PCa, ASAP, PIN, and fibrosis) among them and compared to healthy PZ. The significant level was set at a p value of less than .05.

IV. RESULTS

In the 12 patients who received radiotherapy we identified just one area in PZ and targeted MRI\Ultrasound fusion biopsy was performed. From these patients we obtained 12 specimens.

In the other 81 patients, 84 suspicious areas were identified. In three patients, in fact, two distinct suspicious areas were recognized (PCa of peripheral zone and transition zone in two patients; PCa and HG-PIN in one patient). Moreover, 81 other areas were identified as normal prostate tissue on mpMRI.

Every patient underwent to targeted MRI\Ultrasound fusion biopsy in the areas considered suspicious and normal; so, in total, 177 specimens were obtained in order to correlate histopathological diagnosis to the ADC values. Among our population, 42 patients with bioptic diagnosis of PCa subsequently underwent radical prostatectomy that confirmed prostate cancer.

Among suspicious areas, histopathology revealed PCa in 58/84 specimens (69.1%), ASAP in 10/84 specimens (11.9%) and HG-PIN in 16/84 specimens (19%). Among mpMRI normal prostate tissue (81 specimens), histopathology revealed normal prostate tissue in all cases.

Histopathology showed histologic changes of acinar distortion and atrophy as well as stromal fibrosis with granulation tissue in all 12 specimens obtained from patients who underwent radiotherapy.

Patients and biopsy characteristics are summarized in Table 2.

Normal prostate tissue, PCa, HG-PIN, ASAP and histologic alterations after radiotherapy had a mean ADC of 1.50 ± 0.26 mm^2/sec, 0.74 ± 0.24 mm^2/sec, 0.91 ± 0.12 mm^2/sec, 1.04 ± 0.1 mm^2/sec and 0.96 ± 0.31 mm^2/sec, respectively. The linear mixed-model analyses revealed significant differences between mean ADC values of the groups with normal prostate tissue versus PCA ($p<.01$), HG-PIN ($p<.01$), ASAP ($p<.05$) and post-radiotherapy changes ($p<.05$). Significant differences were also observed between mean ADC values of the groups with PCa versus HG-PIN

($p<.05$) and ASAP ($p<.01$). The difference between the mean ADC values of the groups with HG-PIN and ASAP was not significant ($p=0.17$). Differences between the mean ADC values of post-radiotherapy histologic alterations versus PCa ($p=0.24$), HG-PIN ($p=0.76$) and ASAP ($p=0.69$) were not significant. Table 3 shows ADC values and p-values for normal and pathologic tissue.

V. DISCUSSION

V.1. Overview on PCa, ASAP and HG-PIN

V.1.a. Prostate cancer

Prostate cancer is a disease of increasing significance worldwide. In many industrialized nations such as the United States, it is one of the most common cancers and among the leading causes of cancer deaths [9]. In developing countries it may be less common, however its incidence and mortality has been on the rise [21]. The progressive increasing prostatic specific antigene (PSA) screening test determine a parallel huge huge increase in prostate cancer incidence [22]. PSA suffers of several limitation due to the low specificity of the test (36%), because benign conditions can cause elevated PSA. Thus, increased PSA is not equivalent with a tumor, and normal PSA does not exclude a tumor [12]. In patients with elevated PSA associated to the clinical suspicious of PCa, routine nontargeted TRUS biopsy was in the past the main diagnostic choice, but TRUS is directed toward the peripheral gland and can miss some tumors, particularly those located in the anterior prostate. In fact TRUS biopsy has a negative predictive value (NPV) of 70–80%, and up to 20–30% of patients with a negative biopsy may still have prostate cancer [13]. In addition there is a progressively lower diagnostic yield from subsequent repeat prostate biopsie in those patients with a false-negative biopsy [14]. Patients affected by prostate cancer should have actually access to different options of treatment. A recent study of the primary treatment received by 11.892 men with newly diagnosed prostate cancer showed that approximately elected 50% radical prostatectomy, 14%, androgen-deprivation therapy, 13%, brachytherapy, 12%, external-beam radiation therapy (RT) 7% active surveillance and 4% cryoablation [9]. In addition other minimal invasive treatment options have become recently avalaible, such as high-intensity focused ultrasound and photodynamic therapy [15]. Continuous improvements and refinements in these treatment

strategies, together with a trend toward earlier detection and a decrease in prostate cancer stage at the time of diagnosis, have resulted in a 99% relative survival rate 5 years after initial diagnosis [15] .

V.1.b. Atipical small acinar proliferation (ASAP)

The Atypical small acinar proliferation (ASAP) represents a suspicious glands in which histologic atypia for a definitive diagnosis of prostate adenocarcinoma is not adequate [16]. The diagnosis of atypical small acinar proliferation (ASAP) occurs in about 1-2% of prostate biopsies [17] . Previous studies have suggested that 17–70% of patients with ASAP have adenocarcinoma present on subsequent prostate biopsies [18]. ASAP generally surrounds marginally sampled adenocarcinomas or benign acini with reactive atypia or partial atrophy. In order to the clinical managing of patients affected by ASAP current recommendations suggest a repeated the biopsy within 3–6 months of the initial biopsy basing on the evidenced that most (80-90%) PCas found in patients with ASAP are detected within the first 6 months after the initial biopsy [19]. Recently the trend for low risk PCa is the adoption of active surveillance (AS) in which serum PSA, digital rectal exam (DRE) every 4-6 months and a repeat biopsy in 1 year are performed. However, there is concern with the potential for undersampling of intermediate risk PCa (GG 3+4). Recent evidence suggests that AS may be an acceptable treatment option in select patients with GG 3+4 PCa in order to the evidence that when patients do progress, the progression rate is slow and delayed intervention does not impact overall survival [20]. Patients with ASAP can be followed with parameters similar to AS for very low risk or low risk PCa [21].

V.1.c. High grade prostatic intraepithelial neoplasia (HG-PIN)

The high grade prostatic intraepithelial neoplasia (HG-PIN) is considered a precancerous condition, defined by neoplastic development of epithelial cells among pre-existing benign prostatic acini or

ducts, appearing as a sort of intermediate stage between benign epithelium and malignant carcinoma. Pathologically, prostatic intraepithelial neoplasia involves a continuum of intra-luminal proliferation of atypical secretory cells lining pre-existing ducts and acini in the prostate [22].

The main difference that differentiate HG-PIN from prostate carcinoma is the preservation of the basement membrane, which orients pathologists in indicating an HG-PIN. The incidence of HG-PIN on prostatic biopsy averages approximately 15%, increasing with patient's age. Some areas of HG-PIN are frequently found around prostatic cancerous lesions and evolution into carcinoma is estimated in about 30% of cases [23]. Recent literature states that 30% of men with HG-PIN would develop prostate cancer within 1 year after repeated biopsy[24].

V.1.d. ASAP & HG-PIN patients management

Despite previous reserch indicates a predictive potential of PSA [25], prostate volume [26], PSA density [25] and number of positive cores [27] on subsequent development of adenocarcinoma to adenocarcinoma of ASAP/HGPIN patients on repeat biopsy, these evidence have been recently disconfirmed [9]. In recent literature, in fact, the reported rates of prostate adenocarcinoma on re-peat biopsy are significantly variable, ranging between 30 and 55% [25-27] for ASAP and 45% [22] for HGPIN. Differing indications for re-biopsy, biopsy techniques including core sampling techniques and dissimilar study populations between studies indicates that actually there isn't agreement on ASAP/HGPIN patients management. It is crucial that the mission of re-biopsy is to identify carcinoma with clinically significant consequences rather than all carcinomas. The relevance of an initial diagnosis of ASAP or HGPIN with respect to future significant prostate cancer is unclear and the evidence remains conflicting [28], and even for HGPIN there is a considerable debate as to whether HGPIN is a truly precancerous lesion with potential to progress to cancer, thus there is conflict, with variable advice, on timing of repeate prostate biopsy. A review article reported no increased risk of prostate cancer compared those with benign deseas, indicating

as not reccomended a repeated biopsy within 1 year of the diagnosis of HGPIN [20]. Contrariwise another article suggested repeat biopsy at 1 year for patients with multifocal disease and active surveillance thereafter [22] .

In order to the definition of the best management choice between active surveillance, timing of re-biopsy and treatment options (surgical, minimal invasive and RT), the definitive discrimination between different prostate pathologies, spacing from benign to precancerous and cancerous tranformation, is crucial.

V.2 Multiparametric MRI in Prostate Cancer

Multi-parametric MRI (mpMRI) has begun to occupy an increasingly central role in the management of patients suspected of prostate cancer, as it generates both the best spatial resolution and soft tissue contrast for characterizing lesions in the prostate gland. The multiparametric technique combines anatomic MR imaging sequences (turbo spin echo T1 and T2 weighted) with functional MR imaging sequences, including diffusion weighted magnetic resonance imaging (DW MRI) and dynamic contrast enhanced MRI (DCE MRI). This combination of different imaging modalities have proven successful in identifying clinically significant cancers while under-diagnosing low grade cancers that do not require treatment. Recent studies suggested that mpMRI can be also used in the evaluation of recurrent or residual disease even if treatment induced changes including distorted anatomy, fibrosis, artifacts from surgical clips, and alteration of the signal characteristics on MRI can complicate the interpretation. Therefore, it is essential to distinguish expected post-therapy changes from local recurrence.

V.2.a. Mp-MRI in PCa detection

Multiple studies have now shown that multiparametric MRI can help to identify tumors missed on biopsy, thus increasing biopsy yields with fewer core samples. Many of these tumors are deep in the

prostate further from the rectal wall than typically reached with a standard TRUS biopsy approach. [29-31]. In these studies have been demonstrated the role of the mp-MRI in detecting clinically significant tumor foci and in the guiding repeat of prostate biopsy after an initial negative TRUS biopsy for patients with a high clinical suspicion of prostate cancer. The sensitivity of the repated biopsy is higher applying MRI-guided prostate biopsy which offers the possibility of a more precise targeting, because MRI is the most accurate imaging modality for localization of prostate cancer [27]. Mp-MRI, toghether with PSA, DRE, and TRUS biopsy, play a key role in active surveillance in those patients affected by a low-grade PCa, HG-PIN and ASAP, conditions in which patients are monitored with the intention to intervene if the disease progresses. Mp-MRI has an emerging role in patients on active surveillance and there is a parallel increasing interest in using MRI before performing a biopsy in patients with elevated PSA. The use of MRI before biopsy in patients with elevated PSA levels could identify patients who require a biopsy because of a significant cancer identified on MRI or those who only require observation and thus can avoid a biopsy. In several studies patients with low-grade disease on initial biopsy have reported a Gleason upgrading in 19% and 34% on repeat random extended biopsy, probably due to an undersampling by the initial biopsy [33-37]. Therefore, these patients may be put on active surveillance (AS) and thus be denied appropriate treatment of an occult higher Gleason grade tumor. In addition MRI has recently shown that apparent diffusion coefficient (ADC) is correlated with Gleason grade, thus MRI should be useful in ensuring that most aggressive tumors in the gland will be biopsed by TRUS. Thus, there is a potential role for MRI not only in localizing tumor but also in identifying the areas of more aggressive cancer that could be targeted by TRUS- or MRI-guided biopsy [29, 38-41]. The NPV of MRI in the screening population is still unknown.

V.2.b. Mp-Mri in PCa local staging and pretreatment planning

Digital Rectal Examination (DRE), Prostatic Serum Antigene (PSA) and the Gleason Score are

validated tools in Partin tables to predict the stage of cancer in PCa. They predict the risk of extracapsular extension (ECE) but do not provide information regarding localization or extent of ECE, which is of benefit to optimize further treatment. Prostate MRI has been shown to add value in all risk groups in the prediction of ECE; the greatest incremental value of MRI to the Partin tables has been found in high-risk patients [42]. For potential surgical candidates, regional imaging is crucial for surgical planning [43]. It is important to differentiate between stage T2 (disease confined to the prostate, for which curative therapy can be considered) and stage T3 (ECE). MRI can evaluate for ECE (stage T3), involvement of the neurovascular bundle (NVB), seminal vesicle invasion (SVI) (stage T3), and invasion of adjacent structures, such as the bladder or rectum (stage T4), the presence of which may prevent curative surgery. Recent studies have found high sensitivity and specificity for preoperative MRI in evaluating for ECE (0.78 and 0.96) and SVI (0.88 and 0.98), respectively [44, 45]. Therefore, MRI offers the most accurate imaging assessment of local prostate cancer and regional metastatic spread. In addition, the presence of advanced local disease at diagnosis determined by MRI has a worse prognosis with a higher risk of developing relapse and metastases after treatment [45]. Pretreatment knowledge of lymph node metastases (LNM) is important for appropriate treatment planning. PSA screening has resulted in stage migration with more patients presenting with earlier-stage disease. The incidence of LNM at the time of diagnosis is low at approximately 5%, but prognosis is worse because of a higher probability of progression to distal metastatic disease after treatment [46]. For node-negative versus node-positive disease at the time of diagnosis, the risk of metastatic disease at 10 years is 31% versus 83%. MRI has high specificity but low sensitivity for the detection of LNM [46]. Treatment of prostate cancer is patient specific and is based on clinical stage, Gleason score, and PSA levels, which stratify patients into low-, intermediate-, and high-risk groups. TNM stage is most optimally determined by MRI, which can therefore help correctly stratify patients into the best therapy option and rarely a patient with clinically low-risk disease be found to have advanced disease on MRI [46]. Therefore, for patients

with low-risk disease clinically determined, MRI can confirm early-stage tumor, thus correctly stratifying patients into active surveillance while ensuring the few patients with more aggressive disease are not being denied further appropriate treatment.

As previously discussed, multiparametric MRI correlates with Gleason grade. Therefore, if required, multiparametric MRI can help guide repeat biopsy in these patients for more accurate tumor grading. Multiparametric MRI can stratify intermediate risk patients into high- and low-risk groups on the basis of the presence or absence of ECE to influence further treatment.

Treatment options are surgical and nonsurgical. For surgical candidates, because only carcinomas confined within the prostate gland are potentially curable by radical prostatectomy (RP), findings of ECE and SVI on preoperative MRI may preclude curative surgery. Involvement of the NVB will preclude NVB sparing surgery. It is important for the patient to be counseled in this regard preoperatively because of the implications for the recovery of urinary and sexual function. Conversely, in patients who may otherwise have undergone radical surgerywith excision of the NVB, MRI can accurately show lack of invasion of the NVB, thus enabling the patient to undergo NVB-sparing surgery [32]. A significant improving of MRI have been found in the surgeon's decision to preserve or resect the NVB during radical prostatectomy (RP) [47].

In preoperative treatment planning there different non surgical options that have to be considered including radiation therapy (brachytherapy, external-beam radiation therapy [EBRT]), hormone therapy, and minimally invasive ablative therapies that use physical energy to cause tumor destruction, such as cryotherapy and high-intensity focused ultrasound (HIFU). In order to the selection of the best treatment option, mainly in surgical or non surgical choice, the extact localization of the prostatic disease and an affordable preoperative staging are mandatory, and multiparametric MRI represent the best non invasive diagnostic modality. In planning of EBRT for locally advanced disease MRI represent an invaluable tool to determine tumor location, volume, and extent, helping direct maximal therapy to the largest focus of tumor while minimizing

surrounding radiation-induced tissue damage [48].

In patients with a minimally invasive desease (T1/2 NO MO) brachitherapy should be considered as treatment choice and MRI provides first to determine the extension of the tumor within the pseudocapsule and secondary aids in the placement of brachytherapy seeds to target the tumor site within the prostate for more focal therapy while avoiding periprostatic toxicity to the rectum and urethra [49].

Recently focal ablative therapies in treatment of PCa have been applied, particularly referring to cryotherapy and HIFU that have been widely used in the treatment of localized PCa. MRI aid to guide focal minimally invasive ablative therapies for these patients and the role is on one hand similar to the ones before radical prostatectomy, in which MRI is used to assess local staging including ECE and NVB invasion, and on the another hand MRI should provide a real-time guidance with an ablation margin of 1 mm, allowing higly targeted therapy and minimizing the periprostatic injury [49].

V.2.c. Post treatment monitoring. Radical Prostatectomy (RP) and Radiotherapy (RT)

Most of patients affected by PCa are eligible to surgery by radical prostatectomy (RP), which represents the first line treatment with curative intent, or by radiotherapy (RT) treatment (interstitial or external beam) which is becoming a valid alternative to surgery in patients with low to intermediate-risk PCa and a long life expectancy [50]. Both, surgery and RT, are definitive treatments for localised PCa and offer long-term tumour control in most patients, but residual or recurrent local disease is a critical issue because it may greatly influence the subsequent therapeutic strategy and patient management. Post treatment changes induced by therapy, including artifacts from surgical clips, fibrosis, distorted anatomy, and alteration of the signal characteristics on MRI, can complicate the interpretation, and a wrong interpretation of MRI findings should affects the managing of patients affected by a recurrence of PCa. Therefore, it is essential to distinguish

expected post-therapy changes from local recurrence.

V.2.cI Post radical prostatectomy (RP) monitoring

RP is the most frequently utilized treatment option for patients with PCa. In about 40-50% of patients with localized PCa RP represent the definitive therapy (20, 51). In RP is conduced by removal of the entire prostate gland and both seminal vesicles, with the goal of negative surgical margins, and consensually the procedure is accompanied by resection of pelvic lymph node. Following RP, PSA levels fall to undetectable levels (<0.01 ng/mL). About 15 to 20% of patients goes to a biochemical recurrence (BCR) following RP [52-53]. Positive surgical margins, high grade tumors, extra-prostatic extension of tumor, seminal vesicle invasion, increased tumor volume, perineural invasion, and PSA doubling time (PSADT) prior to and after surgery are all associated with increased risk of recurrence [51]. It is validated as BCR an increase of PSA over 0,2 ng/ml confirmed in two consecutive levels [54]. In the clinical practice, it is not so easy to identify the origin of the PSA relapse and sometimes many risk factors for both local and distant recurrence are present in the same patient. Moreover it should be taken into account that the PSA level does not always correlate well with the tumour burden and that there are numerous examples of metastatic PCa in the absence of significantly elevated PSA levels, particularly when the tumours are poorly differentiated. Therefore in patients with increasing of PSA levels <2ng/ml, the so called biochimical failure (BF), after surgical treatment, a diagnostic imaging procedure is often performed to distinguish between local cancer recurrence and distant spread of disease. In the absence of systemic metastases salvage RT could theoretically be assumed to be the first line treatment offering a potential chance of cure. Cross-sectional imaging modalities (ultrasound, computed tomography, and morphologic MRI) have previously been evaluated in the detection of local recurrence following RP, but each of them evidenced as poorly sensitive for detecting a small-sized relapse and is unable to distinguish between local recurrence and postsurgical scarring

[55,56]. The technological advances in imaging field have recently allowed the feasibility of links anatomic, functional, and biological information together. Positron emission tomography/computed tomography (PET/CT) and multiparametric MRI have proven to be useful in the early diagnosis of PCa recurrence74.

When PSA levels are > 1 ng/mL and PSAdt is < 6 months, PET/CT with 11C- or 18F-Cho compounds are more affordable in identification of local neoplastic recurrences, distant metastases and metastatic nodes, in restaging patients with PCa after RP [57,58]. Although PET/CT is recommended in patients with high PSA serum values, in patients who experience low biochemical alterations after RP (PSA serum values between 0.2 and 1 ng/mL) it is very important to exclude the presence of locoregional recurrence, being this information essential for radiation oncologists [59]. PET-CT due to the limited spatial resolution (5- 6 mm) of PET scanners, suffers of a poor detection rate of small lesions in detecting local recurrence in post-prostatectomy bed in patients with BF and low PSA values, and its role is still undefined. The greater contrast and spatial resolution of MRI, maximized applying the endorectal coil, allows a useful tool in evaluation of prostatic fossa after RP, and functional applications in MRI added value to the accuracy of the detection and characterization of small recurrent PCa. Mp-MRI allows a useful tool in discriminating between scar/fibrosis, granulation tissue, residual glandular healthy tissue and locoregional relapse after RP. ADC values analysis may even be able to assess the aggressiveness of nodule recurrence [59]. One third of patients with a BCR will ultimately develop metastatic disease, and approximately one in five will die of PCa [60]. Thus identification and carachterization of relapse of PCa after RP in patients with BCR represent a crucial objective to intercept early stage of pathology.

V.2.cII Post radiotherapy monitoring

Radiation therapy (RT) targets high doses of ionizing radiation to the prostate through several forms

of external beam radiation therapy (EBRT) and/or brachytherapy. The discrimination between normal post RT changes of the gland and recurrence of PCa is very hard on MRI due to a radical change of the entire prostate which shows a decreased size and a diffuse descrease of signal intensity on T2 eighted imaging involves both peripheral and central zone, with indistinct margins of the transition zone. Parallely the RT influence the structure of foci of PCa and decreased size, reduced capsular bulging, capsular irregularity, or decreased extracapsular extension are observed. Cho and acetate labeled PET/CT has shown promise in the identification of regional and distant metastases but cannot allow precise location of the intraprostatic post-RT recurrent cancer due to its poor spatial resolution [61]. Actually MRI is widely considered to be the state of the art in detecting and localizing PCa recurrence in patients with BP after definitive RT [59]. The prostatic tessutal variations induced by RT affects the signal intensity of normal and pathologic prostate, and are consequent to the parenchimal fibrotic changes and atrophy. In this perspective is evident the difficulty in identifing a focus of PCa recurrence inside the fibrotic atmosphere of the post RT prostatic gland. Thus T2WI alone is of a limited diagnostic accuracy because the recurrent tumor and the normal surrounding parenchyma both appear hypointense [62]. In nodular pattern on T2W MRI, recurrent PCa after RT appears as a nodular lesion which hypointense relative to normal prostatic tissue and it is usually located at the same of the pre-treatment tumor, with only 4-9% of lesions recurring in a previously unidentified area [63]. In addition to T2W the evaluation of tumor contrast uptake, vascularity, and permeability is obtained by applying of functional imaging technique of DCE, and DCE showed a relative increase of tumor vascularity, with an early enhancement and high peak enhancement due to the tumoral angiogenesis, in comparison to surrouniding prostatic fibrotic tissue. In head-to-head comparisons with T2W MRI, DCE MRI consistently performed with a higher level of accuracy and reproducibility [64].

DW MRI holds particular promise in evaluation of PCa recurrence after RT when combined with T2W MRI [65]. An increase of sensitivity from 25 to 62% in BCR after RT have been observed by

combination of DW MRI with T2WI [66]. At the same time other studies report a disappearing of significant difference in ADC values between the tumors and benign tissues after treatment RT, affirming that after Rt the benign tissues might show histological changes such as acinar distortion, atrophy, stromal fibrosis with granulation tissue formation, and inflammatory swelling of prostate cells,which might result in a decrease in ADC values, whereas the tumour shows an increase of ADC values [59]. The role of the DW-MRI and of the ADC analysis in identification of recurrence of PCa after RT remain actually controversal and the results non definitive, and one of the purpose in of this research have been to explore the ability of the ADC analysis in DW-MRI in discriminating between Post-RT fibrotic changes and recurrence of PCa.

V.3. Technique principles of mp-MRI: DCE & DWI

In order to risk stratification and staging of prostate cancer the multiparametric-magnetic resonance imaging (mp-MRI) demonstrates significant results in detection, localization and characterization of PCa. The combinations of morphologic T2-weighted imaging with funcitional informations, derived by diffusion imaging of DWI and perfusion imaging of dynamic contrast-enhanced (DCE) have been used in mp-MRI assessment of prostate cancer and post treatment monitoring of patients84. Combining the morphological assessment of T2-weighted imaging (T2WI) with diffusion-weighted imaging (DWI), dynamic contrast-enhanced (DCE) has been extensively studied in recent years [67,68]. The espansion of the role of the MRI in the diagnosis and in the risk stratification of patients derived, partially, by the inaccurate risk stratification and selection of therapeutic options of the systematic TRUS in addition to an underestimation of the TRUS about final Gleason grade of tumor on histology following radical prostatectomy [69].

T2 morphologic assessment and functional assessment by diffusion weighted imaging (DWI) remains the mainstay for prostate cancer diagnosis on mp-MRI, and the ADC analysis had shown as an affordable tool in discrimination between benign and malignant conditions [70,71]. In this

research work over the first purpose based on the validation of the ability of the ADC analysis in mp-MRI in discriminating between PCa and normal prostate tissue, have been also evaluated the the ability of the ADC analysis in discriminate between different pathological conditions such as precancerous condition and post RT fibrotic changes. Even if this research have been mainly based on ADC analysis in DWI, anyway the contestual evaluation of the functional information about perfusion, derived by dynamic contrast enhanced (DCE) imaging, have been mandatory. Altough the role of the perfusion analysis on DCE imaging in this research work have been marginal, it was crucial in other research acticity that have been personally conducted [72], in which the DCE demonstrated to be a useful tool in cancer detection and in the evaluation of post treatment response in head and neck and prostate tumors conditions, indicating a whole role of the DCE in functional imaging analysis, with significant results.

For completeness the technical aspects of both functional imaging, DCE and DWI techniques, are shortly described below.

V.3.a Dynamic Contrast Enhanced (DCE) Imaging

Dynamic contrast enhanced (DCE) magnetic resonance imaging (MRI) is influenced by the micro-vascular characteristics of tissue, such as blood flow/volume, surface area/permeability of vessel walls, and micro-vascular density. These characteristics are associated with the expression of potent cytokines (such as the vascular∗ endothelial growth factor) that support the development of tumour vessels. This makes DCE-MRI a valuable diagnostic tool in oncology [72]. The activation of the angiogenesis in cancerous tissue determine an increasing of vessels number and permeability with a consequent greater contrast enhancement rather than non pathologic tissue. Dynamic contrast enhanced quantify tumor angiogenesis and provides direct depiction of tumor vascularity. The data obtained from DCE reflect the tissue perfusion, the microvessel permeability, and the extracellular

leakage space.

The DCE imaging is performed acquiring a rapid set of consecutive gradient-echo T1-weighted 3D images immediately before and during administration of gadolinium contrast agent, obtaining data about temporal variation of tissutal enhancement. This effect is derived by the shortening of T1 relaxation time of water induced by Gadolinium, resulting in high signal intensity on T1-weighted imaging. The differentiation of cancerous to benign tissue is based on the analysis of different aspects including a qualitative method based on detection by identification of areas of enhancement on early contrast-enhanced images (30-60 seconds after administration of contrast medium) and a quantitative method which is based on the evaluation of parameters such as wash out time, time to enhancement, peak enhancement, relative peak enhancement and time to peak enahancement. In the literature the sensitivity of DCE-MRI varying from 46-96%, while the specificity is quite higher varying from 74–96%, and DCE-MRI improves sensitivity and specificity of the T2-weighted imaging evaluation [40,73]. In fact T2-weighted imaging alone has range of reported sensitivity and specificity of 75–94% and 37–53% while combined T2-weighted imaging and DCE-MRI have been reported of 70–96% and 88–97% respectively [74, 75]. Thus DCE-MRI play a role mainly in improving specificity in the detection of lesions, because T2-weighted imaging alone already has high sensitivity. DCE-MRI is not useful in the detection of further lesions that are not seen on T2-weighted imaging but to it is used as an adjunct to T2-weighted imaging to determine whether a lesion seen on T2-weighted imaging is cancerous or benign [74], and therefore, tumors can be detected with higher accuracy. DCE-MRI also provides information regarding prognosis and response to treatment. It is a useful prognostic marker and indicator of tumor aggressiveness because the degree of angiogenesis correlates with pathologic staging of prostate cancer [74].

V.3.b Diffusion Weighted Magnetic Resonance Imaging (DW-MRI)

Diffusion-weighted magnetic resonance imaging (DW-MRI) is increasingly being used to study the

abdomen and pelvis, and more specifically, the prostate [76-77]. Diffusion-weighted imaging si based on the quantification of the random motion of free water molecules known as Brownian movement.

When used in conjunction with apparent diffusion coefficient mapping, diffusion-weighted imaging provides information about the functional environment of water in tissues, thereby augmenting the morphologic information provided by conventional MR imaging.

V.3.b1 DWI technical principles

Biological tissues are composed of intra and extracellular compartementes. In these tissued water molecules are in a state of continuous exchange between these two compartements. The random diffusion of water, as described in Brownian model of diffusion, is not feasible in normal biological tissue, due to a restriction to the free diffusion exerted by macromolecules, fibers and membrane. There are many factors that should influence water molecules movement including shifts of water from extracellular to intracellular spaces, restriction of cellular membrane permeability, increased cellular density, and disruption of cellular membrane depolarization. These findings are commonly associated with malignancies [78]. To perform the diffusion-weighted imaging the most common method is to incorporate two symmetric motion-probing gradient pulses into a single-shot spin-echo (SE) T2-weighted sequence, one on either side of the 180° refocusing pulse, so called Stejskal-Tanner sequence [81]. A diffusion gradient induces a phase shift to vary with position, with all spins that remain at the same location along the gradient axis during the two pulses returning to their initial state. As consequences of the application of diffusion gradient the spins protons that have moved, live free water molecules, will be subjected to a different field strength during the second pulse and therefore will not return to their initial state, but will instead undergo a total phase shift, resulting in decreased intensity of the measured MR signal. Contrarly the spins that have not moved along the gradient axis, in restricted diffusion microenvironment, will be totally subjected

to the rephasing gradient with subsequent recover of the initial MR signal [79]. DW-MRI is performed without administering contrast medium, and requires less time than other functional MRI techniques.

V.3.b.II The parameter b value

The b value is a parameter that influences the intensity of gradient diffusion, and it depends proportionally to the amplitude of the gradient at the time of applicationd of the gradient and during the interal elapsed between application of first dephasing and second rephasing gradient. The b value intensity is measured in square per millimeter [80]. By varying the amplitude of the b value, the sensitivity of the diffusion sequence is modified. Applying a b value equal to 0 sec/mm2 the sequence is simply T2 weighted. Applying lower b values (50-100 sec/mm2) the effect is a MR signal loss of the higly mobile water molecules, like in vessels (Intravoxel Incoherent Motion model). At high b values (500-1000 sec/mm2) the signal loss is characteristic of higly restriction movements of water molecule [81].

V.3.bIII Apparent diffusion coefficient. The DW-MRI quantitative value.

The apparent diffusion coefficient (ADC) value represents the magnitude of molecular movement in biological tissues as a quantitative parameter of DW-MRI. The restriction of diffusion results in decreased ADC values on ADC maps generated from DW images [82]. ADC value represents gradient of a line drawn in a cartesian system and it's derived from the logarithm of relative intensity of the examined tissue signal. Increasing the number of b values a parallel increases of the realibility of the ADC is obtained, and it derives a increasing of MR scanning time. The ADC value is indipendent of the magnetic field and is measured for each individual pixel. The obtained ADC values are used for the construction of the related maps that reflect the tissue diffusivity corresponding to different values of b [83].

V.4. Rationale and evidences of the study

It is assumed that the restriction in the diffusion of water molecules is related to the degree of cellularity of the tissue with a directly proportional relationship. This restricted diffusion is observed primarily in malignancies, hypercellular metastases, and fibrosis, which contain a greater number of cells with intact cell walls than does healthy tissue. The rationale of this research work is strictly linked to the relationship between variation of the water molecules movement in biological tissue and variation of cellular density, and in particular is based on the hypotesis that the modification of tissutal composition during the cancerogenesis process, like in HGPIN and ASAP, should be detectable by the quantification of differences of movement of the water molecules at various transformation steps. A relationship between ADC values and tumor aggressiveness have been report in different studies. Sun Y et al. identified a relationship beteween decreasing of ADC values and tumor aggressiveness in application of DW-MRI model to rectal cancer, with implications on the previsional outcome of patients affected [84]. There's an increasing inteerest in literature about the application of Mp-MRI in pretreatment definition of the tumor aggressiveness. Starobinets et al. have recently studied the relationship between ADC analysis on DW-MRI, DCE and magnetic resonance spctroscopy (MRS) with tumor aggressiveness related referred to histologic Gleason score, concluding that Mp-MRI provides excellent separation between benign tissues and PCa, and across PCa tissues of different aggressiveness [85]. Dwivedi DK et al. have recently explored the potential of Mp-MRI in the identification of HG-PIN in patients with previous negative biopsy, to predict the progression to prostate cancer, and in order to the ADC analysis the ADC value for HG-PIN have been reported as significantly lower (1.01±0.16×10-3mm2/s) mm2/sec rather than normal prostate tissue 1.69±0.25×10-3mm2/s [86]. To date few papers in literature explore the effects of precancerous transformation on the ADC analysis in the intrapathologic group in prostate pathology such as ASAP and HG-PIN, which are proven cancer

precursor. In this perspective the research of affordable tools that helps in identification and characterization of precancerous condition od the prostate, togheter with the discrimination of normal prostate tissue, post-treatment fibrotic changes, from PCa, is crucial in order to the recent many different treatment or surveillance options of patient affected, as previous discussed (see also V.2.b, V2.c.)

V.4.a. ADC values in PCa vs normal prostate tissue

In our study cohort, we found a statistically significant difference between ADC values in abnormal areas, neoplastic or not, and in healthy prostate tissue ($p=0.05$). This result is particularly evident if we consider PCa ($p<.01$). There are many publications related to the significance of DWI and ADC in prostate cancer diagnostics [76, 77]. For example, Tamada et al [87] reported that mean ADC values of tumor regions in both PZ (1.02±0.25x10-3 mm^2/sec) and transition zone (0.94±0.21x10-3 mm^2/sec) were significantly lower than those in the corresponding normal regions (1.80±0.27x10-3 mm^2/sec and 1.34±0.14x10-3 mm^2/sec, respectively). Our results are consistent with this report even though, in our study, mean ADC values were lower for both malignant (0.74±0.24 x10-3 mm^2/sec) and healthy (1.50±0.26 x10-3 mm^2/sec) prostate tissue. These differences can be explained in several ways. Tamada et al. took into account the different tumor sites, PZ and transition zones, whereas we have not considered this distinction to be necessary for the purpose of the study. Some authors have also demonstrated [88] that lower ADC values are correlated with higher Gleason score. The values we found in PCa could be justified by a worse histological differentiation, even though we have not considered the ADC-Gleason score correlation in this study. Another variable is the different degree of BPH; the PZ compressed by the hypertrophic transition zone usually has lower ADC values [89] Finally, the different values found in healthy prostate parenchyma may be related to the intrinsic characteristics of DWI: ADC value, in fact, may be markedly different in adjacent regions related to the physiological heterogeneity of the prostatic

parenchyma - caused by the close intermingling of high and low-cellularity regions - and deteriorations due to aging, structural fibrotic changes, and variations in cellular composition [89].

V.4.b. ADC values in PCA vs PIN

Referring to PIN, in our study cohort, histopathology revealed exclusively HG-PIN. These histopathological findings can probably be explained by the fact that lower grade alterations (LG-PIN) are not associated with significantly abnormal findings on mpMRI, so radiologists are not able to identify them. We are not aware of previous studies regarding LG-PIN imaging. In our population, mean value of ADC for patients with HGPIN was 0.91 ± 0.12 x10-3 mm^2/sec. This result shows a statistically significant difference compared to mean value of ADC calculated in healthy prostate tissue, without overlapping values. To our knowledge, there are no previous studies that consider this differentiation. We can conclude that DWI is helpful to individuate HG-PIN; however, by itself, it does not allow a correct characterization. In this regard, we compared ADC values of HG-PIN to values calculated in PCa. We observed that ADC values of PCa were on average lower than those calculated in HG-PIN ($p<.05$); but we also noticed that there was a high degree of overlap between these values. These observations are in agreement with previous studies that emphasize the role of other functional techniques. For example, Sciarra et al [90] demonstrated the role of DCE-MRI and, above all, the spectroscopic study for the characterization of HG-PIN foci as well as Dwivedi et al. in a more recent study [86].

V.4.c ADC values in ASAP vs PCA/PIN/Normal Gland

Referring to ASAP the mean value of ADC was 1.04±0.1 x10-3 mm^2/sec. Although there was a statistically significant difference compared to the mean value of ADC calculated in healthy and neoplastic prostate tissue, we noticed that there were many overlapping values. It is questionable whether such small differences in mean ADC values between these groups, although statistically

significant, are also clinically useful. We can conclude that a differentiation between ASAP vs PCa and ASAP vs normal prostate parenchyma cannot be based solely on the ADC values in routine clinical practice. The same conclusion was reached when comparing ASAP and HG-PIN; both lesions, in fact, had very similar ADC values.

V.4.d ADC values post-RT

Referring to the evaluation of ADC values in patients with PCa treated with RT, the present study only included patients in follow-up post-RT, because no pre-RT MR scan was available. Even though this shortfall surely affects the possibility of obtaining a comparison between pre-RT and post-RT treatment, in the present study we focused on ability of the ADC differentiating residual/recurrence of PCa post-RT by radiation therapy changes in normal glands. Several clinical studies for the evaluation of changes of ADC values after radiotherapy in localized PCa have been reported [91]. Lysing neoplastic cells, the radiotherapy causes an increase in free water molecule movement resulting in an increase of the ADC values. A lack of the increase on ADC or a further reduction of ADC values, after RT, have been reported to be highly suspicious for residual PCa or recurrence [92]. Song et al. studied patients with PCa who received radiotherapy [93] observing that the mean ADC value calculated in PCa after RT was increased compared with the mean ADC value before therapy (1.61 × 10−3 mm2/s vs 1.0 × 10−3 mm^2/s). They also noticed that the mean ADC values of benign PZ and the transition zone were statistically significantly decreased compared with those before radiotherapy, due to histologic alterations of normal prostate tissue. In conclusion, no significant difference of ADC values between the tumors and benign tissues after radiotherapy have been depicted in previous studies. In our post-RT PCa population, results are substantially in agreement with this last observation. In our population, post-RT PCa patients had a mean value of ADC of 0.96 ± 0.31 x10-3 mm^2/sec, resulting no statistical difference compared to mean ADC of abnormal prostate tissue (PCa, HG-PIN or ASAP). By contrast, although there was a statistically

significant difference compared to mean value of ADC calculated in healthy prostate tissue ($p<.05$), we noticed that there were too many overlapping values. Based on this result, in the present study ADC values are not very reliable in distinguishing residual tumor or recurrence from histologic changes due to radiotherapy, especially, as in the present study, without knowing the correct site of the neoplastic and normal prostate tissue ADC values before RT. Anyway, our results are consistent with previous reports [93] concluding that on DWI the ADC values alone are not sufficient in discriminate recurrence or residual PCa. In this regard, Sciarra et al [94] has shown that the addition of proton 1H-spectroscopic imaging and DCE-MRI could represent a powerful tool for the definition of a biochemical progression after radiotherapy, distinguishing between fibrotic reaction and local recurrence [95].

V.4.e. Study limitations

We are aware that our study has a limitation on the number of patients, specially in order to the reduct number of patient. ASAP and HG PIN probably frequently misdiagnosed on pathology so the main difficult have been specially referred to the recruitment of patients with precancerous condition.

VI. CONCLUSION AND STUDY PERSPECTIVES

The present research work first of all shows that in mp-MRI evaluation of the prostate pathologies, the apparent diffusion coefficient (ADC) value analisys represent a valuable tool in discriminating between normal prostatic tissue and intrapathologic group conditions (PCa, HG-PIN, ASAP) and to post RT changes of the gland.

Referring to the intrapathologic group significant differences in ADC values have been identified between PCa and precancerous condition, even if the presence of too many overlaps beteween ADC values in different groups does not allow, actually, to consider the ADC analysis as an affordable parameter if considered alone, but the association with other functional imaging technique is actually mandatory. To overrun this limitation in order to definite confirm the ability of ADC analysis in discriminating between intrapathologic group, it is being done the increasing of intraphologic group number in order to dispose of more data and be able to perform a robust evaluation of the ADC analysis results.

Referring to the study of the effects of the RT treatment on prostate, the ADC analysis allows an affordable tool in discriminating normal prostatic tissue to post RT, mainly, fibrotic changes of the gland. Contrariwise non statistically significant data have been found in order to discriminate post RT prostatic changes by the intrapathologic groups, that includes PCa, HG-PIN, ASAP, and fibrosis.

Over the increase of patient numbers, in perspectives there are two others interesting field of application of the research, and in particular first of we are now working on the exploration of intravoxel incoherent motion (IVIM) imaging, that is part of DW-MRI, and which is focused on fast water molecules fraction of tissutal diffusion, and depends mainly on the microvascular system variations. The IVIM imaging, acquired by applying of low multi-b values represent the first component of the bi-exponential decay of MR signal, and his conditioning by microvascular

changes allows the study of the tumoral neoangiogenesis on DWI technique. Another interesting field of research in DWI applicated to prostate is the evaluation of impact of ultra-high (1000-2000 mm/sec2) on the cancer detection. The application of higher bvalue, in fact, have been reported essentially provides a greater contrast between cancer and non cancer tissue. We are now applying to each patient referred to our institutions diffusion sequences with b value of 2000 sec/mm2, observing an higher rate in cancer detection, on qualitative methods. Hopefully the ultrahigh b value will represent a signfiicant field of develop of our research.

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VIII. TABLES

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Table 1: MR Image Acquisition Parameters (morphological images and DWI).

Table 2: Patient and Biopsy Characteristics

Table 3: ADC values and p-values

Table 1: MR Image Acquisition Parameters (morphological images and DWI).

Sequence and Imaging Plane	Sequence Type	Freq FOV	Slice Thickness (mm)	Spacing (mm)	TR (msec)	TE (msec)	NEX
Sagittal T2w	Fast spin echo	22	3	0.8	3725	120	4
Axial T2w	Fast spin echo	14	4	0	3250	120	4
Coronal T2w	Fast spin echo	14	3	0.4	3000	120	4
Axial T1w	Fast spin echo	14	4	0.0	600	Min full (10.6-21.2)	4
DWI	Single-shot echoplanar imaging	14	4	0.0	1800	Min full (102.3-295)	NA

*FOV: field of view, TR:repetition rime; TE: echo time; NEX: number of excitations; DWI: diffusion weighted imaging.

Table 2: Patient and Biopsy Characteristics

Characteristic	All Patients	Normal tissue	PCa	HGPIN	ASAP	Post-RT histologic alterations
N° of included patients	123					
N° of excluded patients	30[1]					
N° of included biopsy specimens	177	81	58	16	10	12
Location of suspicious areas						
PZ			52	16	10	
TZ			6			

[1]No suspicious regions were detected in 18 patients. 12 patients underwent radical prostatectomy before MRI examination.

*PCa: prostate cancer; HGPIN: high-grade prostatic intraepithelial neoplasia; ASAP: atypical small acinar proliferation; Post-RT: post radiation therapy; PZ: peripheral zone; TZ: transition zone.

Table 3: ADC values and p-values

Histopathologic Groups	*Mean ADC values ± Standard Deviation*	*p-value vs Normal tissue*	*p-value vs PCa*	*p-value vs HG-PIN*	*p-value vs ASAP*	*p-value vs Post-RT alterations*
Normal tissue	1.50 ± 0.26		<0.01	<0.01	<0.05	<0.05
PCa	0.74 ± 0.24	<0.01		<0.05	<0.01	=0.24
HGPIN	0.91 ± 0.12	<0.01	<0.05		=0.17	=0.76
ASAP	1.04 ± 0.1	<0.05	<0.01	=0.17		=0.69
Post-RT fibrosis	0.96 ± 0.31	<0.05	=0.24	=0.76	=0.69	

*ADC: Apparent diffusion coefficient; PCa: prostate cancer; HGPIN: high-grade prostatic intraepithelial neoplasia; ASAP: atypical small acinar proliferation; Post-RT: post radiation therapy.