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Doppler Ultrasound in Prostate Cancer: It's Utility for the Diagnosis of High-Grade Tumors

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Abstract

Purpose: The aim of the present study was to evaluate the association between prostate vascularization seen in Doppler ultrasound and histopathological grade (Gleason score) in patients with a diagnosis of prostate cancer.

Methods: A Gleason score >7 was the dependent variable and Doppler ultrasound findings (vascular analysis, presence of nodule and prostate weight) were the independent variables. Univariate analysis was performed considering advanced tumors (Gleason >7) as the dependent variable and area of hypervascularization, age and PSA as the independent variables. Multivariate analysis was performed using a binary regression model with the occurrence of advanced tumors (Gleason >7) as the dependent variable.

Results: In the univariate analysis, samples with Gleason ≤7 had a lower chance of being hypervascularized (OR: 0.44, 95% CI: 0.29-0.69), whereas those with Gleason scores >7 had a fourfold greater chance of being hypervascularized (OR: 4.136, 95% CI: 2.598-6.554, p<0.001). Moreover, hypervascularized tumors had a 7.4-fold greater chance of having a score >7.

Conclusion: The present study reveals an association between tumor hypervascularization detected using Doppler ultrasound and higher Gleason scores (more aggressive tumors), enabling an indirect inference of a worse prognosis for hypervascularized prostatic tumors. These findings should be confirmed in longitudinal studies.

Keywords: Prostate cancer; Gleason Hypervascularization; Doppler; Prostate carcinoma; Ultrasonography; Biopsy

Abbreviations: PSA: Postate Secific Antigen; MRI: Multiparametric Magnetic Resonance Imaging; ISUP: International Society of Urological Pathology; TNM: Tumor Node Metastasis; TRUS: Transrectal Ultrasound.

Introduction

Prostate cancer is the most common noncutaneous cancer among males [1]. Most cases are found in patients

older than 75 years of age, with only 1% of cases found in men younger than 50 years of age [2]. The main methods for investigating and detecting prostate cancer are a digital rectal exam, the serum concentration of prostate specific antigen (PSA) and transrectal ultrasound biopsy followed by histopathological analysis [3]. Among the diagnostic tools used today to date for prostate cancer, multiparametric magnetic resonance imaging (mpMRI) has demonstrated an improvement in detection and characterization of prostate cancer [4]. Although well validated in terms of diagnostic accuracy, mpMRI requires technical rigour, patient's tolerability and safety, expertise in interpretation, and high costs [5]. Conventional imaging techniques, as conventional ultrasound, that are optimized for well-defined, round tumor masses may be less effective for the prostate considering that 85% of prostate cancer cases is multifocal [6]. Due to the varied prognosis, knowledge of prognostic markers is useful for better counseling and the definition of the course to be taken. Since there is a correlation between early detection of tumors and improved prognosis, enhancing current tumor imaging approaches is critical.

The increased of vessel density has a predictive value in the identification of high-risk patients with a poor prognosis [7]. Considering that have been demonstrated the role of angiogenesis in solid neoplasia which correlates with rapid tumor growth and potential for metastasis [8] ultrasound Doppler techniques can be used. This technique offers a low-cost and noninvasive approach with which to measure changes in vascular and bloody features [9].

Studies describe the prognostic importance of angiogenic factors in different types of cancer (lung, ovarian, stomach cancer and squamous cell carcinoma of the head and neck) [10-13]. As with other tumors, an angiogenesis is found in prostate cancer [14-16] and this characteristic can be evaluated using Doppler, although the efficiency of this technique is debated [16]. Although Doppler techniques may provide some improvement in the imaging detection of prostate cancer, targeted biopsy based on conventional ultrasound with Doppler is not sufficient to replace systematic biopsy [17]. Gleason grading system is a histopathological grade in diagnosis of prostatic neoplasm [18]. Khanduri, et al. Reported that transrectal ultrasound with color Doppler flowmetry can play an important role in the detection of prostate cancer, with high sensitivity as well as specificity, comparing with histopathological data [18]. Up to now, it is worth mentioning that the most important prognostic parameters to consider are the PSA level, the International Society of Urological Pathology (ISUP) graduation and the Tumor, Node, Metastasis (TNM) staging system [19].

Based on this context, the aim of the present study was to evaluate the association between prostate vascularization, with color Doppler fluxometry and histopathological grade (Gleason score) in patients with a diagnosis of prostate cancer.

Methods

Sample

The retrospective cross-sectional observational study received approval from the Human Research Ethics Committee of our service. The study involved 188 patients with prostate cancer confirmed by anatomopathological analysis that underwent a Doppler ultrasound exam by a single specialist with more than 20 years of experience with this type of exam. It was conducted at the Radiology service of the authors' Hospital. Patient age and serum prostate-specific antigen (PSA) level were also recorded.

Ultrasound Analysis

All patients who fulfilled the inclusion criteria were examined by trans rectal ultrasound (TRUS) with a color Doppler for the detection of prostatic lesion using Toshiba Xario Istyle (Toshiba Corporation, Tokyo, Japan) ultrasonography color Doppler machine, with a TRUS probe (6 MHz). After the analysis of the exams, the sample was divided into two groups based on the presence or absence of hypervascularization areas (dominant increase in the number of vessels) in prostate (Figure 1).

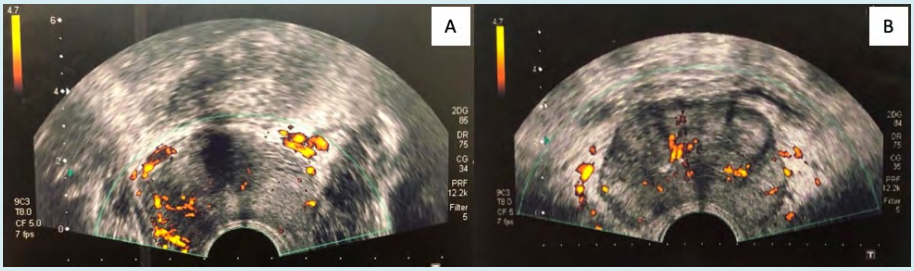

Figure 1: Representative images of doppler ultrasound findings. (A) Hyper vascularized area in peripheral prostatic zone. (B) Area with normal vascularization in peripheral prostatic zone.

Hypervascularization was defined as the presence of a high color code found using power Doppler ultrasound [20] which was based on the association between the increase in the color code and an increase in blood flow.

Histopathological Analysis

The samples included in the present study were classified using the Gleason score described on the individual histopathological files. This grading system categorizes the two largest biopsy fragments on a scale of 1 to 5 based on the similarity of the neoplastic tissue to healthy tissue, according to International Society of Urological Pathology [21].

Data Analysis

The two groups were compared in terms of age, PSA, ultrasound findings and Gleason score. A regression model was created to evaluate the capacity of hypervascularization to predict tumor aggressivity. For such, the dependent variable was a Gleason score >7. The independent variables were the presence of a hypervascularized area and variables known to be associated with a worse prognosis: PSA (≥20 ng/ml) and (>65 y.o.) [22,23]. The categorical variables were described in absolute number and percentage values and compared using either the chi-squared test or Fisher's exact test. Continuous variables were expressed as median and interquartile range (IQR) and compared using the Wilcoxon test. For the evaluation of predictive factors of advanced tumors, the Gleason score was dichotomized as ≤7 (low grade) and >7 (intermediate and high grade). This cutoff point was based on the definition of the American Cancer Society [24].

Univariate analysis was performed considering advanced tumors (Gleason >7) as the dependent variable and area of hypervascularization, age and PSA as the independent variables. Multivariate analysis was performed using a binary regression model with the occurrence of advanced tumors (Gleason >7) as the dependent variable. Covariates with a p-value <0.10 were incorporated into the multivariate model using a backward stepwise procedure. The final model included the most restricted subset of variables with statistical significance. Associations were expressed by odds ratios and respective 95% confidence intervals. The goodness of fit of the model was evaluated using the Hosmer-Lemeshow test. A p-value ≤0.05 in the final model was considered indicative of statistical significance.

Results

188 patients were included in the study. All participants were treated at the radiology sector of our Hospital between February 5th and December 17th, 2018. Median age was 67 y.o. (IQR: 62-72 y.o.). Median prostate weight was 43.55g (IQR: 33.63-59.88g). The Gleason score ranged from 6 to 10 (Table 1).

Feature	Hypervascularization (n=34)	Normal vascularization (n=154)	p-value
Age (y.o.)[1]	67 (61-72)	67 (63-73)	0.314
Prostate weight (grams) [1]	52.55 (38.50-96.60)	41.15 (33.00-58.30)	0.013
Serum concentration of PSA (ng/ml)[1]	8.84 (5.18-49.68)	7.89 (5.18-17.22)	0.185
Presence of nodules[2]	11 (17.74)	51 (82.26)	<0.001
Gleason 2[2]	0 (0)	0 (0)	<0.001
Gleason 3[2]	0 (0)	0 (0)	
Gleason 4[2]	0 (0)	0 (0)	
Gleason 5[2]	0 (0)	0 (0)	
Gleason 6[2]	9 (20.93)	34 (79.07)	
Gleason 8[2]	7 (43.75)	9 (56.25)	
Gleason 9[2]	13 (48.15)	14 (51.85)	
Gleason 10[2]	1 (100)	0 (0)	
Gleason >7[2]	21 (47.73)	23 (52.27)	<0.001
Gleason ≤7[2]	13 (9.03)	131 (90.97)	

Table 1: Characterization of the dichotomization sample (hypervascularization *versus* normal vascularization).
y.o.= years old.
[1]data were presented as median and interquartile interval
[2]data were expressed as absolute and percentage values.
PSA level ranged from 0.67 to 3332.60 ng/ml.

A total of 33.88% of the samples had prostatic tumors with nodules and 66.12% did not have nodules. In the comparison of prostate weight, presence/absence of nodules and the Gleason score (dichotomized or not), significant differences were found between the group with hypervascularization and the group with normal vascularization (Table 1).

In the univariate analysis, hypervascularization and PSA ≥20 ng/ml were individually associated with a poorer prognosis (Table 2).

Feature	OR	95% CI	p-value*
Hypervascularization	4.1	2.598-6.554	<0.001
PSA ≥20 ng/ml	5.3	2.335-12.086	<0.001
Age >65y.o.	0.9	0.525-1.544	0.738

Table 2: Univariate analysis.
OR = odds ratio; CI = confidence interval.
*Multivariate analysis.

These two variables remained independent prognostic factors in the multivariate analysis (Table 3).

Feature	OR	95% CI	p-value*
Hypervascularization	7.4	2.841-19.449	<0.001
PSA ≥20 ng/ml	4.7	1.928-11.483	0.001

Table 3: Multivariate analysis (Binary Logistic Regression).

Discussion

The present study demonstrated that an increase in vascularization in cases of prostate cancer is associated with a worse Gleason score and, indirectly, a worse prognosis. Khanduri, et al. (2017), previously reported a study involving color Doppler flowmetry in the detection of prostate malignancy. It was found that moderate vascularization and focal vascular asymmetry were significantly associated with malignancy.[16] In the multivariate analysis, the group with hypervascularization had a 7.4-fold greater chance of having a Gleason score >7. Moreover, patients with a Gleason score >7 had a 4.1-fold greater chance of exhibiting hypervascularization. Malignant areas of the prostate tend to have more vessels per mm^2 than benign fragments and, consequently, greater blood flow evidenced by color Doppler ultrasound. This finding tends to direct biopsies to regions related to a higher Gleason score [25].

The diagnosis of prostate cancer is currently performed using clinical and laboratory exams, such as the digital rectal exam, the serum concentration of PSA and a histopathological analysis of an ultrasound-guided biopsy fragment graded using the Gleason score that is based on the degree of glandular differentiation and, consequently, tumor aggressivity [26]. Thus, the Gleason score has considerable prognostic power in cases of prostate cancer and continues to be an important factor to consider in the decision-making process for the most indicated form of treatment [27]. In a study, prognostic groups were formed considering both the probability of recurrence in the next five years and the Gleason score determined during the histopathological exam. The prognostic groups were classified from 1 to 5. Group 1 corresponded to Gleason score ≤ 6 in patients with well-formed glands and a 96% probability of being free of reoccurrence in the five years following prostatic resection, whereas prognostic Group 5 (Gleason score of 9 or 10) has a 26% probability of being free of recurrence in five years [28]. Then, inverse and significant correlation was demonstrated between increasing group grading and recurrence-free progression following prostatectomy or radiotherapy. Some studies disagreed with the use of transrectal ultrasound with a color Doppler, demonstrating the absence of benefit [29,30]. But the detection of abnormal blood flow patterns within prostatic tumors is the main application of Doppler ultrasound in prostate cancer imaging. In addition, color Doppler is an alternative to more-invasive procedures which can show an increased vascularization from hypo echoic nodules which is similar to benign hyperplastic nodules. Few cases of prostatic lesion had abnormal flow on color Doppler scanning which was no obviously identifiable abnormality on ultrasound scanning [31]. Our study revealed an association between hyper vascularization and a worse prognosis of prostate cancer based on the Gleason score. However, studies involving the analysis of tumoral vascularization, survival, quality of life and/or cure rates should be conducted to confirm this inference.

Like other tumors, increased angiogenesis is found in prostate cancer, resulting in an increase in the density of vessels [16]. Tumoral blood vessels also have random paths and increased tortuosity that can assist in the detection of tumors or the guiding of the biopsy using a color Doppler exam [16-25]. Louvar, et al. Evaluated prostate cancer biopsies using Doppler ultrasound and found no significant differences in vasculature variables between high-flow and normal-flow color Doppler findings but biopsies with high-flow color Doppler had a mean Gleason score of 6.7, whereas those with normal-flow color Doppler had a mean score of 5.9 ($p < 0.025$) [25].

PSA is routinely one of the first tests performed in men with symptoms that may be caused by prostate cancer. The concentration of this marker is directly related to the presence of prostate cancer, with an increase in PSA increasing the chance of having cancer [32]. It has prognostic power and enables the evaluation of the staging of the tumor, which exerts an influence on the treatment options as well as the

monitoring of prostate cancer during and after treatment. The results of the present investigation and previous studies demonstrate an association between increased PSA and more aggressive tumors as well as an association with a higher Gleason score and a greater risk of recurrence [32,33].

The use of color (Power) Doppler assesses vascular permeability, providing more hemodynamic information. However, the detection of hyper vascularized tumors may not increase because angiogenesis of most small tumors is below the flow range of the Doppler. Despite the promising findings, questions remain regarding the efficiency of color Doppler ultrasound due to the resolution of the images. Some researchers strongly defend the systematic use of this technology during guided biopsies due to the ability to diagnose advanced tumors [34]. High-resolution color Doppler ultrasound and tissue harmonic imaging have improved the capacity for detecting cancer [34]. Moreover, a biopsy guided to the tumor together with a biopsy of the potential pathway of tumor escape (such as a neurovascular bundle or nearby seminal vesicles) improves the determination of the staging of the cancer and the Gleason classification [34]. With these advantages, color Doppler ultrasound gained popularity over conventional transrectal ultrasound used as a diagnostic modality, as Doppler ultrasound offers benefits in the differentiation of cancer among other prostatic lesions [34]. While Doppler imaging may be effective in detecting increased blood density, it is only possible if is in larger macro vessels that may be found in late-stage higher Gleason-grade tumors [35]. In this study, we qualitatively evaluated the hyper vascularization (yes or no) and Gleason score. And, considering our findings, in the next time, a quantitative analysis of the hyper vascularization can also predict whether it is a moderately differentiated carcinoma or poorly differentiated carcinoma, clinically.

The diagnosis and treatment of prostate cancer remain challenging. Current screening methods include the determination of serum PSA levels, the digital rectal exam and transrectal ultrasound. Color Doppler ultrasound has better diagnostic and prognostic value due to its capacity to visualize vascular changes [16] but is not sufficient to replace systematic biopsy [17].

This study showed an association between tumoral hyper vascularization and higher Gleason scores (more aggressive tumors). Tumors with a Gleason score >7 had a 4.1-fold greater chance of having a Doppler ultrasound finding of hyper vascularization. Moreover, hyper vascularized tumors had a 7.4-fold greater chance of having a Gleason score >7 in the histopathological analysis. These findings suggest an indirect association between hyper vascularization and a poorer prognosis, considering the previously described association between the Gleason score and prognosis of patients with prostate cancer. Thus, the use of Doppler ultrasound for prostate analysis can assist in the location of prostatic tumors in more advanced stages.

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Conflicts of Interest/Competing Interests: None

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