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Diagnostic performance of power doppler and ultrasound contrast agents in early imaging-based diagnosis of organ-confined prostate cancer: Is it possible to spare cores with contrast-guided biopsy?

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ABSTRACT

Objectives: To evaluate the diagnostic performance of gray scale transrectal ultrasound-B-mode US (BMUS), power Doppler (PDUS), and sonographic contrast (CEUS) in early imaging-based diagnosis of localized prostate cancer (PCa) and to compare the diagnostic profitability of randomized biopsy (RB), US-targeted prostate biopsy by means of PDUS and CEUS.

Material and methods: A single-center, prospective, transversal, epidemiological study was conducted from January 2010 to January 2014. We consecutively included patients who an imaging study of the prostate with BMUS, PDUS, and CEUS was performed, followed by prostate biopsy due to clinical suspicion of prostate cancer (PSA 4–20 ng/mL and/or rectal exam suggestive of malignancy). The diagnostic performance of BMUS, PDUS, and CEUS was determined by calculating the Sensitivity (S), Specificity (Sp), Predictive values (PV), and diagnostic odds ratio (OR) of the diagnosis tests and, for these variables, in the population general and based on their clinical stage according to rectal exam (cT1 and cT2). PCa detection rates determined by means of a randomized 10-core biopsy scheme were compared with detection rates of CEUS-targeted (SonoVue) 2-core biopsies.

Results: Of the initial 984 patients, US contrast SonoVue was administered to 179 (18.2%). The PCa detection rate by organ of BMUS/PDUS in the global population was 38% versus 43% in the subpopulation with CEUS. The mean age of the patients was 64.3 ± 7.01 years (95% CI, 63.75–64.70); mean total PSA was 8.9 ± 3.61 ng/mL (95% CI, 8.67–9.13) and the mean prostate volume was 56.2 ± 29 cc (95% CI, 54.2–58.1). The detection rate by organ of targeted biopsy with BMUS, PDUS, and CEUS were as follows: Global population (10.6, 8.2, 24.5%), stage cT1 (5.6, 4.2, 16.4%), and stage cT2 (32.4, 22.3, 43.5%). Comparing the detection rates of the CEUS-targeted biopsy and randomized biopsy, the following results were obtained: Global population (24.5% vs. 41.8%), stage cT1 (16% vs. 35%), and stage cT2 (43.5% vs. 66.6%), with a p value < 0.05. Following the "core-by-core" analysis, the detection rates by core of CEUS-targeted biopsy versus randomized biopsy were: Global population (16% vs. 13%), stage cT1 (30.3% vs. 28%), and stage cT2 (48% vs. 37%), with a p value > 0.05. The NNT for CEUS-targeted biopsy was 83.3.

Conclusions: The low sensitivity, specificity, positive predictive and negative predictive values of gray scale-B-mode, PDUS and CEUS represent scant diagnostic performance of these variables in prostate cancer detection. Prostate cancer detection rates yielded by randomized biopsy were superior than the detection rate of targeted biopsy using B-mode, PDUS and CEUS; as a result, randomized biopsy versus CEUS-targeted biopsies cannot be excluded from biopsy strategy plans for the diagnosis of prostate cancer.

1. Introduction

Prostate cancer (PCa) is the fourth most common neoplasm in men worldwide and is probably the most prevalent oncological disease [1,2]. In Spain, some 13,300 cases of prostate cancer are diagnosed annually, accounting for 13.6% of all tumors in men. Although the incidence in Spain can be considered low in com-

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parison with the rest of developed countries, the trend is toward a sharp rise since the beginning of the 1990s [3,4].

Several different diagnostic strategies have been developed over the course of the last decade aimed at enhancing prostate cancer detection rates. These strategies focus on three main assumptions: an attempt to increase PSA diagnostic profitability of PSA (with the determination of PSA density and free versus total PSA, PSA velocity, PSA density of the transition zone, etc.); improve prostate biopsy schemes (including selective biopsies of the suspicious areas in gray scale, increasing the number of biopsies of specific areas of the prostate (such as the lateral lobes) or by means of saturation biopsies with 20–45 cores), and developing new imaging-based diagnostic elements, such as color Doppler (CDUS), power Doppler (PDUS) and US contrast (CEUS), that enable better morphological analyses of the prostate gland to be performed and increase our diagnostic capacity to discriminate benign from malignant lesions [5,6,7,8,9,10].

Power Doppler (PDUS) studies make it possible to detect hypervascular areas inside the prostate that are suggestive of malignancy and to conduct biopsies targeting these areas, thereby increasing the diagnostic performance of gray scale ultrasound-B-mode (BMUS) on its own [11,12]. However, it is difficult for PDUS to detect small, low-flow vessels (<40 μm) [13,14]. For this reason, ultrasound contrast has been developed that amplifies the hypervascular signal provided by PDUS and helps to define and characterize neoplastic areas within the periphery of the prostate for subsequent biopsy [15].

Many studies have revealed that it is possible to establish a biopsy scheme comprised of contrast-targeted cores, increasing PCa detection rates and decreasing the number of unnecessary randomized biopsies [13,14,16,17].

The aims of our study were to evaluate the diagnostic performance of gray scale, transrectal ultrasound B-mode, power Doppler, and US contrast in the early imaging-based diagnosis of localized prostate cancer and to compare the diagnostic profitability of randomized prostate biopsy to US-targeted biopsy by means of power Doppler and CEUS.

We pretend evaluate the diagnostic accuracy of parameters TRUS in cases with clinically suspected PCa localized (PSA < 10 ng/mL and normal DRE) and assess the possibility of reducing unnecessary cylinders in prostate biopsy randomized, trying to reduce the biopsy procedure only to targeted TRUS biopsies.

2. Material and methods

A prospective, transversal, epidemiological study was conducted from January 2010 to January 2014 of patients ascribed to the Hospital Universitari i Politécnic La Fe de Valencia catchment area with a clinical suspicion of PCa based on digital rectal examination and elevated PSA values. Patients aged 40–80 years, with a rectal examination suggestive of malignance, a total PSA level of between 4 and 20 ng/mL, and a total PSA of 4–10 ng/mL plus a free/total PSA ratio of less than 0.2 were included in the study. Patients were excluded from the study if they presented a total PSA greater than 20 ng/mL, clinical evidence or imaging tests (CT and bone scan) of disseminated disease and local relapse following radical prostatectomy.

Nine hundred and eighty-four (984) patients were admitted into the study and underwent a transrectal ultrasound, power Doppler imaging study of the prostate. US contrast *SonoVue*® by *Rovi*® Laboratories was administered to a 179 of them. The population was then subdivided by clinical stages according to the rectal exam into stage cT1 (with a normal or adenomatous rectal exam) and stage cT2 (with palpable nodule).

The diagnostic performance of US-imaging in BMUS, PDUS, and CEUS was initially evaluated in both the global population, as well as in the population subdivided on the basis of clinical stages, by determining the diagnostic tests of sensitivity (S), specificity (Sp), predictive values (PV), diagnostic odds ratio (OR).

Subsequently, detection and/or prevalence rates of PCa were determined for each of the imaging-based diagnostic variables (BMUS, PDUS, and CEUS) in the general study population and by clinical stages. PCa detection rates were determined by means of selective biopsy with BMUS, PDUS, and CEUS and the McNemar test was used to compare the detection rate of the selective biopsy with contrast and randomized biopsy. The detection rates of CEUS-targeted biopsy and randomized biopsy were also compared following the "core-by-core" analysis of the samples sent to Pathology.

All of the procedures were performed with the patient placed in left lateral decubitus. Thirty minutes prior to examination, a dose of 240 mg of tobramycin in 100 cc of physiological saline was administered and prophylaxis was completed with 3 days of 500 mg ciprofloxacin every 12 h. Additionally, 100 mg of meperidine in 100 cc of physiological saline, together with a 10-mg ampule of metoclopramide for analgesia prior to the examination were administered.

The following study variables were ascertained: *clinical* (age, rectal exam, total PSA (ng/mL), and free/total PSA ratio (%); sonogram and post PDUS (prostate volume, transition zone volume (cc), echographic appearance of the seminal vesicles ("thickened", "suspected infiltration", "infiltrated"), prostate capsule ("intact", "suspected rupture", "rupture"), and prostate-seminal angle ("conserved", "not conserved")), presence and location of hypoechoic nodules, presence/absence of vascular flow with PDUS in the PZ and the vascular resistance indices); *Following the study with contrast* (presence of vascular enhancement in the PZ over the suspicious areas revealed on BMUS and on PDUS and selective vascular enhancement in the peripheral zone of the prostate following infusion of contrast).

2.1. US image technical parameters

The US system used was a *Siemens*® *Sonoline Antares* with a multi-frequency, EC9-4 endorectal transducer with frequencies ranging from 3.6 and 9 MHz. The *US-technical parameters* of the study were the same in all patients, so as to achieve maximum uniformity of the images obtained. In order to avoid errors, the US system was preconfigured with these parameters, saving them on the system's hard disc, selecting this configuration prior to beginning each study. The parameters were 9 MHz frequency, 30–45 dB gain, and mechanical index of 0.4. In order to conduct the examination in the very best conditions in gray scale, on the study with Doppler, and following the infusion of contrast, the parameters were set in accordance with similar studies already published, with the recommendations of the US system's technical service, and with instructions from *Rovi*® Laboratory, who provided us with the US contrast.

*"BM*US positive" (Fig. 1) was defined as the presence of a hypoechoic nodule in the peripheral zone (PZ) of the prostate and "BMUS negative" as the absence of said nodule. Thus, *"PDUS positive"* (Fig. 2) was defined as the presence of delimited signal enhancement on power Doppler in the peripheral zone and "PDUS negative" as the absence of signal in the PZ on power Doppler. We define *"CEUS positive"* (Fig. 3) as selective vascular enhancement in PZ with power Doppler following the administration of contrast and "*CEUS negative*" as the absence of vascular enhancement in PZ following administration of contrast.