Contrast-enhanced US of the prostate with time/intensity curves: Preliminary results

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KEYWORDS

Prostate;
Ultrasonography;
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Abstract *Purpose:* To evaluate the diagnostic performance of ultrasonography using second-generation contrast agent in the study of patients with focal prostate lesions and increased serum prostate-specific antigen (PSA) level.

Materials and methods: Six consecutive patients (age range: 72–87 years) with increased PSA (≥ 4 ng/ml) underwent transrectal ultrasonography (TRUS) followed by contrast-enhanced ultrasonography (CEUS) with injection of second-generation contrast agent. All patients showed areas of abnormal echostructure suspicious for neoplastic lesions. On the basis of CEUS, a time/intensity curve of the suspected area was compared to that of a normal-appearing distant area of the gland and to the results of biopsy of the hypoechoic area.

Results: At CEUS two different patterns of enhancement were identified and considered to be significant: pattern 1 characterized by a rapid rise in the time/intensity curve of the suspected area compared with the normal gland. Two out of six patients had this pattern and biopsy showed cancer in the biopsied area. Pattern 2 was characterized by a similar rise in the time/intensity curve of the suspected area compared with the normal gland. Four out of six patients had this pattern and biopsy showed prostatitis in the biopsied area.

Conclusions: CEUS using second-generation contrast agent can on the basis of time/intensity curves show differences in vascularization in normal and pathological tissue. Evaluation of the two patterns seems to be useful for identifying areas requiring biopsy, particularly when peripheral hypoechoic areas are observed at TRUS. Our data need to be confirmed in a larger patient population.

Sommario *Scopo:* Determinare la performance diagnostica dell'ecografia con mezzo di contrasto di seconda generazione nello studio delle lesioni focali della prostata nei pazienti con elevati valori sierologici di antigene prostatico specifico.

Materiali e metodi: Sei pazienti consecutivi (età 72–87 anni) con elevati valori di antigene prostatico specifico (≥ 4 ng/ml) sono stati sottoposti a ecografia transrettale tradizionale seguita da ecografia con mezzo di contrasto. In ogni paziente sono state identificate le aree periferiche di alterata ecostruttura sospette per lesione neoplastica. Queste aree sono state valutate con ecografia con mezzo di contrasto mediante curve di intensità/tempo. I dati ottenuti sono stati confrontati con la biopsia dell'area sospetta.

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Risultati: L'ecografia con mezzo di contrasto ha consentito di identificare due pattern distinti: pattern 1 caratterizzato da rapida elevazione della curva calcolata a livello della lesione rispetto all'intensità di impregnazione del parenchima adiacente. Due dei sei pazienti con questo pattern hanno dimostrato presenza di lesione neoplastica nell'area sottoposta a biopsia. Pattern 2 caratterizzato da scarsa elevazione della curva rispetto all'intensità dell'impregnazione del parenchima adiacente. I rimanenti 4 dei 6 pazienti esaminati avevano questo pattern e l'area biopsata ha dimostrato assenza di lesione neoplastica.

Conclusioni: L'ecografia con mezzo di contrasto di seconda generazione, attraverso le curve di intensità/tempo può identificare differenze di comportamento tra tessuto normale e patologico. Queste caratteristiche possono risultare utili soprattutto nel caso di aree ipocogene all'ecografia basale per identificare le aree da sottoporre a biopsia.

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Introduction

Prostate cancer is the most common cancer in men in their sixth to ninth decade of life in Europe and the United States [1]. Transrectal ultrasound (TRUS) guided biopsy, digital rectal examination (DRE) and prostate-specific antigen (PSA) serum assays are the standard methods for the diagnosis. Traditionally, a systematic sampling of the peripheral zone is obtained with a sensitivity of 70–80% in the detection of cancer [2]. However, the limitations of this method are well-known [3,4], and new imaging modalities have therefore been proposed as an alternative to identify and characterize tumors. Angiogenesis is one of the main characteristic processes of a tumor for the supply of required nutrients. Traditional color Doppler imaging is insufficient to detect this nutritive environment due to the small size of the new vessels and the reduced number of reflecting red cells [5]. Development of ultrasound contrast agents has increased the detectable ultrasound signal from the blood pool, thus improving cancer detection [6]. Improved cancer identification at contrast-enhanced ultrasound (CEUS) is related to the better detection of flow in the small tumor vessels. In this study we evaluated the vascularization of the prostate in patients with focal lesions in order to identify possible abnormalities permitting differentiation between benign and malignant lesions.

Materials and methods

Six consecutive patients (age range: 72–87 years) with increased PSA (≥ 4 ng/ml) underwent TRUS followed by CEUS. Table 1 lists study population characteristics. DRE was not considered in the decisional process, although it was included in the initial work up. All patients received antibiotic prophylaxis the day before the biopsy and for the following three days. A cleansing enema was administered on the morning of the examination. Diagnostic procedures were carried out by two radiologists. One investigator performed TRUS using IU22 Philips machine equipped with a c8-4v MHz end-fire transducer (8 to 4 MHz extended operating frequency) and contrast specific software operating at low mechanical

index. At color Doppler evaluation the focal lesions were identified and characterized for size, echogenicity and vascularization. CEUS was performed administering second-generation contrast medium (SonoVue™ Bracco, Milan, Italy). According to the protocol, 4.8 ml contrast agent was injected intravenously using a 20 gauge catheter placed in an antecubital vein and was immediately followed by a 10 ml flush of saline water (0.9% NaCl). The focal lesion identified at TRUS was then evaluated on the basis of contrast enhancement. A targeted biopsy of the lesion was performed in the area identified at CEUS. A second investigator blinded to the results of the previous procedure performed a sextant biopsy guided by TRUS. The samples were sent to a laboratory to be analyzed anonymously. At the end of the examination, time/intensity curves were calculated. Calculations were done on a region of interest (ROI) containing the nodule and on a second ROI in a distant portion of the prostate.

Ethical approval for this study was granted by the Medical Research Ethics Committee of our university, and informed consent was obtained from all patients.

Results

Biopsy showed that two out of six patients had prostate cancer and four out of six had prostatitis. At TRUS the six focal lesions appeared as hypoechoic nodules in the peripheral zone of the prostate. Mean size of the lesions was 9.4 mm (range 8–11 mm); vascularization at color Doppler was intense in four patients and poor in two patients. At CEUS, two patients had an early, intensive enhancement of the lesion as compared to the adjacent parenchyma; the time/intensity curves showed a rapid rise in the intensity line (Fig. 1). The remaining four patients had a mild enhancement of the lesions, and time/intensity curves in the focal lesion and in the adjacent parenchyma were similar (Fig. 2). Acceleration peak (AP) was 8 and 8.8 cm/s^2 in the two cases of prostate cancer and 0.1, 0.2, 2.5, and 4.2 cm/s^2 in the four cases of focal prostatitis. AP in the adjacent parenchyma was 1.95–9.1 cm/s^2 (Table 2).

Discussion

TRUS is the most widely used imaging method for detecting prostate cancer, and it is an essential tool for biopsy guidance [7,8]. However, TRUS has a limited role in identifying prostate cancer due to the variety of echopatterns observed in neoplastic lesions. It has a low sensitivity and poor specificity because of a high incidence of isoechoic

Table 1 Study population characteristics

Number of patients	6
PSA (ng/ml)	4–10
Nodule size (mm)	8–15

Fig. 1 Contrast-enhanced US with time/intensity curve. The study shows a rapid rise in the upper intensity line, measured in the suspected area. Biopsy confirmed prostate cancer.

Fig. 2 Contrast-enhanced US with time/intensity curve. In this patient the curves of the suspected area and adjacent parenchyma were similar. Biopsy demonstrated focal prostatitis.

Table 2 Acceleration peak (AP) in focal prostate lesions

Number of patients	Lesion AP	Parenchyma AP	Biopsy/ diagnosis
1	8.0	2.6	Cancer
2	8.8	1.95	Cancer
3	0.1	5.4	Prostatitis
4	0.2	4.9	Prostatitis
5	2.5	6.8	Prostatitis
6	4.2	9.1	Prostatitis

cancer and multifocality [9]. The most common ultrasonographic finding in prostate carcinoma is a hypoechoic focal area located in the peripheral zone, but it is observed in only 40–70% of cases [10]. The low specificity of TRUS is related to the same pattern of hypoechoic peripheral areas observed in prostatitis and particularly in granulomatous prostatitis [11]. A hypoechoic lesion detected in a patient with normal outcome of DRE is cancer in only 7–8% of cases, whereas random bilateral biopsies are more likely to detect cancer than directed biopsies of suspicious hypoechoic lesions [12,13]. To improve detection of prostate cancer and limit the number of biopsy cores, use of US contrast agents has been advocated by several authors [7,8,14]. Pelzer et al. have demonstrated that contrast-enhanced color Doppler sonography is able to detect lesions that cannot be detected using gray scale US or systematic biopsy [6]. In our preliminary experience, CEUS distinguished prostate cancer from areas of prostatitis on the basis of different vascular enhancements. The use of time/intensity curves allowed characterization of vascular alterations in the tumor area. Morphologic changes in the curves and the difference in AP values seem useful to distinguish neoplastic nodules from benign inflammatory nodules. The identification of suspected areas in patients with elevated PSA levels allowed guided biopsy, thus improving the probability of detecting a possible cancer.

The main limitation of this preliminary experience is the small number of patients involved. Another important limitation is that there were only hypervascularized nodules in our series, and no hypovascularized nodules. It is possible that also hypovascularized tumor lesions can show significant changes in time/intensity curves and AP values, but this is not included in our initial experience.

In conclusion, CEUS with time/intensity curves seems to be a promising modality for differentiating inflammatory from neoplastic areas. Characteristic vascular abnormalities were observed in tumor lesions, and the patterns that we described seem to be useful for differentiating peripheral

hypoechoic tumor areas from inflammatory areas observed at TRUS, before biopsy is performed. Time/intensity and AP values are more useful than standard ultrasound evaluation, because they offer quantitative measurements which are not operator dependent. This new technique may also reduce the number of core samples required for diagnosis of prostate cancer in patients with elevated PSA level. More extensive research is necessary to confirm these preliminary data.

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