Imaging Assessment Of The New Vasculature Of The Prostate Cancer – A Non-Invasive Tool Of Diagnostic And Prognostic

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ABSTRACT More than 46% of men older than 50 years could have at least microscopic cancer in their prostate glands. Because the morbidity of treatment may outweigh its benefits, in Europe it is common not to treat for prostate cancer (CaP) asymptomatic men older than 70 years. CaP screening is based on the serum concentration of prostate specific antigen (PSA) and digital rectal examination, which have a low sensibility and are followed by “blind” systematic biopsy with negative results in the most cases. Purpose: To illustrate and present an analysis of the new vasculature features of CaP on Doppler Ultrasound, multidetector enhanced CT and MRI. Materials and methods: We performed a prospective study between June 2008 and July 2010 of the prostate vasculature demonstrated on Doppler US in 53 consecutive patients (range 28-77 years); among them 21 performed MRI exam and/or multislice CT. Results: 21/53 patients presented clinical, biological and/or US abnormal findings and underwent further imaging exams; among them 18 were finally diagnosed with CaP. Another 3 patients with abnormal Doppler US were directly biopsied with malignancy proved in 2 cases. The PPV of Doppler US was 83%. The MRI findings in 19 patients confirmed the abnormal vasculature and further targeted/ surgical biopsies proved malignancy in 17 cases (PPV 89%). Conclusion: CaP presented more vasculature as compared with the non-cancer areas in Doppler US, spiral CT and MRI on the same patient. Even in early stages, when no evident tumor mass was present on the imaging exams, we suspected cancer when the pericapsular vessels were enlarged or presented high flow (Doppler, MRI). MRI had better sensibility, but we agree the Full Prostate Ultrasonography, including Doppler exam and Sono-Elastography, will be soon the best non-invasive, available and low cost imaging method of detection, follow-up and guided targeted biopsy of the CaP.

KEY WORDS Imagery, Prostate cancer, New vasculature

Introduction
It is estimated approximately 20% of USA men will have clinical prostate cancer (CaP) during their lives, yet as many as 46% of men older than 50 years have at least microscopic cancer in their prostate glands. Because the morbidity of treatment may outweigh its benefits, in Europe it is common not to treat asymptomatic men for CaP if they are older than 70 years.

In contrast to breast cancer, the present consensus is that imaging has no role in screening for CaP. However, there are important applications of Ultrasonography (US) and, increasingly, Magnetic Resonance Imaging (MRI) and multidetector computed tomography (CT) in the prostate.

The chief tool for CaP screening is the serum concentration of prostate specific antigen (PSA). However, PSA is not specific for cancer: as many as 80% of the men with an elevated serum PSA concentration do not have CaP.

A lesser role is played by digital rectal examination, which has a low sensibility (40% of the CaP arise in the anterior peripheral zone, 20% in the transitional zone and 10% in the central prostate zone, which can not be examined by the urologist finger).

To integrate multiple factors for the prediction of an initial biopsy outcome, image-based clinical support models were implemented, and the performance of a support vector machine (SVM) was considered superior to the performance of an artificial neural network (ANN) or a multiple logistic model [1].

When these examinations present important abnormalities, the next step is usually represented by the “blind” biopsy with a systematic 10 core samples for the detection of the CaP. However, there are cases with not proved cancer (in 70%-75% cases), and so how many biopsies should we perform to a patient and what frequency/what interval should they be performed? There is not a reasonable consensus.

The goal of the management of CaP is the diagnostic as earlier as possible, with a non-invasive technique, repeatable, available for all and with a low cost.

As one might intuitively expect, it has been shown histo-pathologically that neovascularity/
microvessel density in prostate carcinoma is an independent predictor of pathologic stage and presumably malignant potential [2]. Some recent observations suggest that the vasculature could play a more central role in the regulation of the normal prostate and prostate tumors; therefore, the factors controlling blood flow, endothelial cell proliferation, and other aspects of angiogenesis in the normal prostate and in prostate cancers are almost unknown. In addition, the growth of a human prostate cancer cell line (PC3) in nude mice is clearly inhibited after treatment with the angiogenesis inhibitor angiostatin [3].

Vascular density and vascular invasion correlates significantly with capsular perforation, seminal vesicle invasion, positive margins of resection, perineural invasion, high grade, and pathologic stage, as demonstrated a study of van den Ouden and col [4]. In their experience, multivariate analysis showed that vascular invasion was associated with a 2.5-fold increased risk for clinical progression, 2.3 for biochemical progression, and 2.7 for cancer-specific survival.

Moreover, many studies indicate that the vasculature could be regulated, directly or indirectly, by androgens, and castration-induced involution is a therapeutical method of choice for CaP.

Anatomically, the prostate is supplied from the internal iliac arteries by the prostatico-vesical arteries [5; 6]. The prostatico-vesical artery gives rise to two terminal branches, the prostate artery and the inferior vesical artery. The prostate artery then divides into urethral and capsular arteries. The latter divides into two sets on the surface of the gland, one located anteriorly and the other posterolaterally. Centripetal branches from these vessels perforate the capsule to supply the prostatic parenchyma as they course towards the periurethral zone.

**Purpose**

Imaging flow assessment may become even more important in the diagnostic and treatment of CaP, and our purpose is to illustrate and present an analysis of the new vasculature features of CaP on Doppler US, multidetector enhanced CT and MRI of these patients, and to compare the results with non-malignant prostate pathology.

**Materials and methods**

We performed a prospective study between June 2008 and July 2010 of the prostate vasculature as it is demonstrated on Doppler US in 53 consecutive patients (range 28-77 years), among them 21 performed MRI exam and/or multislice CT. The inclusion criteria for the US as first imaging exam were relevant clinical symptoms and abnormal findings on digital rectal examination (DRE). Patients with increased level of the PSA over 4ng/ml, proven CaP or with suspect lesion on US were included in the sublot that underwent further imaging exams. The local ethics committee approved the study protocol and an informed consent of the all patients was provided.

**The protocol of US examination included:**

- Detection of a suspect prostatic mass: a hypoechoic mass with/without calcifications, usually localized in the outer area of the prostate (peripheral zone and central zone), with/without capsular invasion and with salient new vasculature;

- Determination of the gland volume with TRUS/transabdomino- pelvic measurements:

\[
\text{Gland Volume} = (\text{width (w)} \times \text{height (h)} \times \text{length (l)} \times 0.5)
\]

- Determination of the expected tumor volume:

\[
\text{Predicted PSA} = \text{gland volume} \times 0.12
\]

This is useful to calculate the

\[
\text{Excess PSA} = \text{serum PSA} – \text{predicted PSA}
\]

and then to evaluate the

\[
\text{Expected tumor volume} = \frac{\text{excess PSA}}{2}
\]

based on the formula: 1 cm³ of cancer produces near 2 ng/ml of PSA.

- Determination the average tumor dimension:

\[
\text{Tumor volume} = \frac{(w + h + l)}{3}
\]

In the cases we used Aloka US equipments the prostate volume, the tumor volume, and the predicted PSA were automatically calculated.

- Determination the abnormal prostate vasculature on color/power Doppler and spectral Doppler. The cases were classified upon a qualitative characterization: low-symmetrical vasculature for normal prostate, abnormal asymmetrical increased vasculature, abnormal diffuse hyper vasculature. Spectral Doppler confirmed the arterial and venous flow-type and allowed the differential diagnosis with the twinkling artifacts that may be present in prostate calcifications. We calculated the mean pulsatility index and the mean resistance index values for the capsular artery when it was detectable.

**The standard protocol of MRI exam (1.5-T MRI system) included:** axial and coronal T1 and T2WI, axial/coronal acquisitions with fat
saturation and 3D reconstructions for the estimation of the symmetry and volume of the prostate and of the seminal vesicles, axial and coronal T1WI with contrast agents (Gadovist from Bayer Schering Pharma, MultiHance® from Bracco Diagnostics, Inc.) (Fig. 1).

**Fig. 1** Normal prostate on MRI exam in T2WI, T1WI native and postcontrast: the peripheral prostatic area in hyper signal T2, izosignal T1, enhances much more than the periurethral zone.

The multidetector CT exam included native abdominal-pelvic scan and post contrast acquisitions in the arterial and venous phase, 2.5mm slice thickness, with multi planar reconstructions; CT was used in the evaluation of the bony density, of the pelvic and abdominal lymph nodes, of the kidneys, and in the pelvis for the estimation of the prostate vasculature, of the periprostate fatty tissues, of the vesical wall and of seminal vesicles appearance.

**Results**

Among all 53 patients examined on US, 21 presented clinical, biological and/or US abnormal findings and underwent further imaging exams; among them 18 were finally diagnosed with prostate cancer. Another 3 patients with abnormal Doppler US findings were biopsied without other imaging examination and malignancy was proved in 2 cases. The PPV of Doppler US was 83%.

The most important findings for CaP on US were considered the asymmetrical increasing vascularity in number and velocity (Fig. 2), the low velocity indices of the prostate capsular arteries (Fig. 3), the asymmetrical prostate enlargement, the unequal enlargement of the seminal vesicles, and the predicted value of PSA over 4 ng/ml (Fig. 4).

Less specificity resulted for the echogeneity of the prostatic structure and for the prostatic volume, which is more important in the periurethral hyperplasia (adenoma).

The transrectal US was not always possible, conditioned by the patient, local conditions or recent previous biopsies, but the most recent US machines are able to detect and calculate the precised parameters.

**Fig. 2** NG, 65-year-old with over 4ng/ml level of the PSA: Color Doppler US presents left anterior pericapsular enlarged salient vascular pedicle, with apparently right lobe suspect hypo echoic area. DRE presented indurations of the right posterior lobe, but the biopsies were negative.

**Fig. 3** The same case: the low PI of 0.62 and low RI of 0.46 are high suspicious of malignancy for the left lobe of the prostate.

**Fig. 4** The same case: the determination of the prostate volume and of the predicted PSA of 4.7ng/ml is concordant with high malignancy risk.

**Fig. 5** The same case: MRI exam with T1WI before and post intravenous contrast presents left pericapsular increasing number of vessels, and high flow-velocity with the void-signal sign of the peripheral and intraprostatic vessels in the imaging suspect area.
Fig. 6 MRI T1 and T2WI is very useful in the characterization of the seminal vesicles, which present an asymmetrical enlargement without any signal changes in the early stages of the CaP.

Fig. 7 3D MRI reconstructions allows better analyze of the anatomic unity: bladder, prostate and seminal vesicles.

Fig. 8 Dynamic enhanced CT presents increased vasculature in the left periprostatic area (a, b, d), associated with the enlargement of the homonymous seminal vesicle (c).

The 18th case of cancer confirmed by imaging exam was examined only by CT because of the suspicion of the bony metastases. CT was not used for the early stages/detection of the CaP, except 4 cases with post-intravenous contrast dynamic acquisitions for scientific reason, as comparison with the US and MRI acquisition (Fig. 8). The detection of the prostate new vascularity was depending of the type of the multidetector CT, which allows fine slides and better reconstructions and was not significantly influenced by the iodinated contrast agent type.

In follow-up exams, CT was useful in the detection of local recurrence, capsular perforation, seminal vesicle invasion, vesical wall invasion, pelvic lymph nodes involvement and bony metastases (Fig. 9).

Fig. 9 Dynamic enhanced CT in a case of CaP after incomplete transurethral resection, presents new periprostatic vessels and prostate enhancement (a, b), vesical invasion, seminal vesicle enlargement and pelvic lymph nodes metastases (c, d), and bony metastases (not shown).

Discussion

The imaging techniques of diagnosis have improved their performances, so there are already a lot of papers presenting the achievements of the US, MRI and spiral CT.

Prostate Ultrasound

The combination of prostate specific antigen (PSA) testing with transrectal ultrasound (TRUS) with subsequent ultrasound guided biopsies (random biopsy) and digital rectal examination (DRE) has been responsible for diagnosing most prostate cancers (PC) in the USA last years. It is agreed early detection and early intervention of progressive CaP may help to reduce the 30,000 prostate cancer-related deaths each year [7]. Therefore not all CaP need treatment, some men may have so-called “latent” or “insignificant” tumors, thus precise ultrasound evaluation with proper biopsy will provide us with valuable information to make a decision between watchful waiting and appropriate early intervention. In
practice, a serum PSA > 3ng/ml, a PSA increase of 1ng/ml in a year, or abnormal DRE are the indications for TRUS [8]. Unfortunately, TRUS has several deficiencies. Only tumors in the peripheral zone can be detected reliably. Although 60% to 70% of CaP lesions are hypoechoic, most of the remainder are isoechoic and thus invisible by TRUS.

**Doppler and tissue harmonic imaging US**

Doppler characterization with/without contrast agents and Tissue Harmonic Imaging (THI) seems to improve the specificity and sensitivity of US. The utility of the sonographic evaluation of the prostate is more complex than DRE, and the results are improved when using Doppler and THI.

Usually, cancer tissue shows a higher blood flow (tumor neovascularity) than that of normal tissue, so Doppler characterization improves detection and actual tumor size measurement. Harmonic technology improves spatial resolution and contrast resolution to discern very subtle differences in grayscale, so the detection of the small hypoechoic masses is easier. Because the hypoechoic texture is not specific for prostate cancer, the Doppler signal is an alarm that indicates the biopsy or the Sono-elastography. The mean pulsatility index value for the capsular artery of group with CaP (1.49 ± 0.57) was significantly lower than that of benign control group (1.71 ± 0.52; \( P = .048 \)) according to a study published in 2007 [9].

Some authors consider pathologic categories were not separable by apparent vascular measurement, because all pathologic categories showed low, moderate, or high vascularity; thus focal hyper vascular hypoechoic areas did not increase the likelihood of cancer in their study [10]. However, Mitterberger et al. have reported comparative data on the effectiveness of biopsies guided by transrectal, contrast-enhanced, color Doppler ultrasound (CECD-US) as compared to a systematic biopsy in 1,776 men between 2002 and 2006. They concluded the 5-core CECD-US-guided biopsy identified prostate cancer in 476/1,776 patients (27 percent), while the 10-core systematic biopsy identified prostate cancer in 410/1,776 patients (23 percent). The reducing on half of the biopsies samples with better accuracy is significant for the vascular characterization of the prostate cancer, with double detection rate using CECD-US targeted biopsy (10.8%) against systematic biopsy (5.1%) [11].

A prospective study published in 2008 presented improved statistical parameters of color Doppler versus grayscale sonography: sensitivity 88.23 vs. 73.52, specificity 66.66 vs. 33.33, positive predictive value 93.75 vs. 85.18, and negative predictive value 50 vs. 22.22, respectively [12].

**The Full Prostate Ultrasonography concept**

The future prostate US will add the Sono-Elastography or Real-Time Elastography (RTE) as a more sensitive method to detect the stiffness abnormalities, and combined with Doppler characterization we will realize the Full Ultrasonography (FU) for the prostate, a new concept already in use for the breast examination [13]. In addition, Doppler and RTE are able to detect the extracapsular spread, thus the tumor staging is improved. The aim of the FU is to use good ultrasound evaluation with guided staging (strategic) biopsy and eliminate the “guesstimations” from random biopsies [7]. In a study of Aigner and col, RTE targeted biopsy allows prostate cancer detection in men with prostate specific antigen 1.25 ng/ml or greater and 4 ng/ml or less with a decreased number of cores compared with that of systematic biopsy, with positive cancer cores of 24% in RTE targeted cores as compared with 5.1% in systematic cores [14]. It would be wrong practice if we will expect some amazing results from the RTE as a unique examination, because this technique is just complementary to the Doppler US. We should avoid the overestimation of any method, thus the score 4 or 5 Ueno/Tsukuba on RTE [15; 16], suggesting malignancy, must be correlated with the presence of a new vasculature on Doppler for a positive diagnosis, otherwise a hard tissue with benign calcification could be misdiagnosed for malignancy on RTE, while the low vasculature suggests chronic prostatitis.

**The sites of the anatomical weakness of the prostate cancer**

Localization of the tumour in the outer gland in over 60-80% cases is suspected when there is an excess PSA greater 2 ng/ml and it is easily to visualize on US because this region is more homogeneous; the cancer is present usually in the areas of anatomic weakness (entry of neurovascular bundle branches, seminal vesicles, and apex), with high risk for extracapsular spreading.

The anatomic weakness of the inner gland, the anterior apex and the bladder neck, are suspected when the excess PSA is 4 to 6 ng/ml and no lesion is found in the outer gland. TRUS sensitivity is
less for the inner gland, but Doppler may be useful and FU is expected to be more accurate.

**Prostate MRI**

A wide range of accuracy figures can be found in the literature, from 54% to 90%. With the use of appropriate parameters, however, MRI can be expected to be superior to digital rectal examination in detecting extracapsular extension. CaP enhances more rapidly and to a greater degree than normal tissue during the first pass on fast dynamic imaging. Moreover, poorly differentiated tumors show the fastest enhancement.

MR spectroscopy may be helpful both for local staging and for noninvasive determination of the aggressiveness of a CaP. Typically, stimulated echo acquisition mode (STEAM) or point-resolved spatial selection (PRESS) is used with three-dimensional phase encoding (chemical shift imaging). The data can be fused with anatomic images. Because of their higher rate of cell proliferation and their greater cellular density, CaPs have higher than normal concentrations of choline. Also, the amount of citrate is lower than in normal tissue [17].

The latest approach to local staging is fusion of images from MRI, SPECT, and Computed Tomography (CT) into a three-dimensional image that can be rotated to view the prostate from all angles. However, we think this is an excellent engineering achievement, but too expensive for the most countries and less available than FU, while RTE is more spread and adapted to various types of US devices from different manufacturers.

**Prostate Computed Tomography**

Despite the low accuracy of the CT in the early diagnosis of the CaP, we observed that the arterial phase is useful in the visualization of the vescico-prostatic artery and its branches that are enlarged as compared with the opposite side and of the asymmetrical high enhancement of the malignant area. The multiplanar reconstructions are useful for the estimation of the prostate volume, and allow better visualization of the periprostatic invasion of the fatty tissue, seminal vesicles, bladder or rectum. MIP and VR (volume rendering) techniques are very useful tools in the discrimination of the abnormalities and in the automatic volume estimation.

**Lymph Node Metastases**

Spiral multislice CT is helpful in looking for metastases to the pelvic lymph nodes. Typically, a dynamic scan with a bolus injection of iodated contrast medium is used, and nodes 1 cm or larger are considered suspect. Under these conditions, the accuracy of CT is between 70% and 94%. If the tumor is stage T1 or T2 with a low Gleason score and the serum PSA concentration is <20 ng/mL, the probability of metastases is less than 1%.

**Distant Metastases**

An almost universal site of CaP spread in advanced disease is the pelvis and lumbar spine. A common rule is to perform a skeletal survey in a patient with a serum PSA concentration >20 ng/mL and in any patient with a stage T3 or T4 primary tumor or a tumor with a Gleason score of 8 to 10.

Radionuclide scintigraphy with 99mTc diphosphonate is the method of choice, with whole-body planar imaging as initial exam, but because of the low specificity, SPECT or MRI may be added to characterize lesions. When performing CT, the bone spreading of the tumor is well demonstrated, but a plain film is more accessible, repeatable and cheaper than the other methods and it is useful as a routine exam, the most CaP metastases presenting a bony sclerosing aspect.

**Conclusion**

Although imaging offers much that can assist urologists in managing men with suspected or known prostate cancer, much more is needed. Current methods for determining confined PC for the individual patient are only “guesstimations” [7]. The pathological outcomes for clinically confined CaP have only a 50% probability of being correct.

In Europe, where older patients do not receive treatment for asymptomatic prostate cancer, 85% of them are alive at 5 years, so it is very important to minimize the toxicity of any treatment for PC.

As tumor angiogenesis factors potentially play a more important role in the understanding and treatment of prostate cancer [18], imaging flow assessment may become even more important in the diagnosis and the treatment of these patients.

In our experience, the prostate cancer has more vasculature as compared with the non-cancer areas, and that was proved in Doppler US, spiral CT and MRI on the same patient. Even in early stages, when no evident tumor mass was present on the imaging exams, we suspected cancer when the pericapsular vessels were enlarged or presented high flow (Doppler, MRI). As differential diagnosis, acute prostatitis has more homogeneous increased vasculature and the clinical diagnosis is conclusive, while chronic prostatitis is sometimes similar with the cancer on the clinical exam and native imaging diagnosis but has no vascular changes. Similarly, with acute
prostatitis, markedly increased color flow reflects the severity of inflammatory cellular reaction, but in case there is usually a diffuse, homogeneous hyper vasculature, as it is seen 24 hours after ejaculation in normal subjects, too [19].

Our study has inherent limitations, among them the small number of patients or the technological level of the imagery; however, the utility of the vasculature assessment was demonstrable, even in the cases with DRE discordance, or post surgical incomplete lesion removal.

MRI had the best sensibility, but we agree Full Prostate Ultrasonography, including Doppler exam in 2D and 3D/4D acquisitions and Sonographic Elastography will be soon the best non-invasive, available and low cost imaging method of detection, follow-up and guided target biopsy of the prostate cancer.

References

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