Value of transrectal power Doppler sonography in the detection of low-risk prostate cancers

J.-L. Sauvain\textsuperscript{a,}\textsuperscript{*}, E. Sauvain\textsuperscript{b}, P. Rohmer\textsuperscript{a}, D. Louis\textsuperscript{c}, N. Nader\textsuperscript{d}, R. Papavero\textsuperscript{a}, J.-M. Bremon\textsuperscript{a}, J. Jehl\textsuperscript{b}

\textsuperscript{a} Centre d’Imagerie Médicale, 6, passage Jules-Didier, 70000 Vesoul, France
\textsuperscript{b} CHU Hôpital Jean-Minjoz, 2, boulevard Fleming, 25030 Besançon cedex, France
\textsuperscript{c} Unité d’urologie, Clinique Saint-Martin, les Haberges, 70000 Vesoul, France
\textsuperscript{d} Service d’Urologie, CHI Hôpital Paul-Morel, 41, avenue Aristide-Briand, 70000 Vesoul, France

**KEYWORDS**
Prostate; Cancer; Sonography; Doppler

**Abstract**

**Purpose:** To evaluate the risk of low-risk prostate cancer or prostate cancer that may benefit from surveillance in patients with a PSA level less than 10 ng/ml, a normal digital rectal examination (DRE) and a transrectal power Doppler sonography (PDS) without anomaly.

**Patients and methods:** Two hundred and forty-three consecutive patients with a PSA level less than 10 ng/ml and a DRE without anomaly had PDS-guided biopsies: 12 to 15 samples were systematically taken and echo-guided in the suspect areas. The PDS results were rated from 1 to 4: 1: normal, 2: slightly hypoechoic avascular area in which the hypo-echogenicity disappears after compression by probe, 3: hypoechoic avascular area, 4: hypoechoic vascularised area with power Doppler sonography. Patients rated 3 or 4 were considered to be pathological. D’Amico’s criteria were used to assess the risk of a biological recurrence after treatment and those of Dall’Era were used to select the patients that could benefit from active surveillance (AS). The PDS was considered to be a true positive if at least one biopsy was positive in the same sextant as the suspect image.

**Results:** In a prospective manner, 106 cancers were diagnosed that could be qualified as low-risk in 84% of the cases (89% with a normal PDS and 79% with an abnormal PDS). Sixty-nine percent of the cases could be subject to AS (86% of the normal PDS cases and 47% of the abnormal PDS cases; \( P < 0.001 \)). The PDS was normal in 159 of the 243 patients (65%). With a normal PDS, there was a 96% probability of not having a high-risk cancer. With an abnormal PDS, at least one biopsy was positive in 57% of the cases and the probability of having a significant cancer was 30% according to the Dall’Era criteria. A significant reduction was noted with a normal PDS, to 36% and 5%, respectively (VPN = 95%) \( P = 0.015 \).

**Conclusion:** A normal PDS in patients presenting a PSA level less than 10 ng/ml and a DRE without anomaly may be used to put off the indication for a biopsy in order to reduce their number as well as the risks of overtreatment for a latent cancer.

© 2012 Éditions françaises de radiologie. Published by Elsevier Masson SAS. All rights reserved.

\* Corresponding author.
E-mail address: jlsauvain@aol.com (J.-L. Sauvain).

http://dx.doi.org/10.1016/j.diii.2012.09.003
The limited benefits-risk ratio and the overtreatment induced by the screening of prostate cancer make it necessary to better select candidate patients for a prostate biopsy with the search for more individual characteristics that help differentiate patients with aggressive lesions from those with indolent lesions [1].

The screening is currently based on a consensus including the age of the patient (50 years), a clinical examination and an assay of the PSA level for which the upper limit is set at 4 ng/ml [2]. However, some aggressive cancers are below this level [3].

Imaging may provide a more personalised approach to the risk of having an aggressive tumour [4–7].

The value of sonography combined with color Doppler sonography (CDS) and power Doppler sonography (PDS) in the detection of prostate cancer has given rise to a great many evaluations. Cornud et al. calculated that the risk of a positive biopsy was 11% with a normal digital rectal examination (DRE), a PSA level less than 10 ng/ml and a normal CDS and that the CDS may be of use to distinguish avascular low-risk tumours from hypervascular high-risk tumours [8,9]. The increasing use of individual screening and the increased number of biopsies has led to the early detection of increasingly small lesions. In view of these small lesions, the value of the PDS was low since a significant number of sometimes little differentiated cancers were non-palpable and not visible [10,11].

Sometimes large, anterior cancers as well as those of the transition area were not detectable in the sonography examination. The only known value of the PDS was that of directing the biopsies when a suspect area was detected.

Among the small lesions thereby detected, some well-differentiated lesions may be qualified as latent, painless or non-significant. They are at the origin of an overdiagnosis involving 40% of the patients treated [12]. The risk of an overdiagnosis and overtreatment of a lesion has until now been underestimated and the active surveillance protocols proposed are probably not adapted to the psychological profile of each patient.

Technical progress in Doppler sonography and a better understanding of its value and limits may help better integrate them in a diagnostic approach [13,14].

The purpose of this paper is to assess the probability of not having an evolving high-risk lesion in prostate biopsies in patients with a normal DRE, a PSA level between 4 and 10 ng/ml and a prostatic transrectal sonography with a normal PDS examination.

### Materials and methods

#### The patients

Four hundred and thirteen patients (49 to 87 years, mean age: 64 years and median age: 66 years), between September 2009 and December 2011 underwent a series of biopsies. Two hundred and ninety-nine presented a PSA level between 4 ng/ml and 10 ng/ml. The digital rectal examination was normal in 243 of them. Hundred and six non-palpable cancers were diagnosed in the biopsies and classified as cT1c in the cTNM classification for prostate cancer (mean PSA: 6.2 ng/ml, median: 7 ng/ml, from 4.01 to 10 ng/ml) (Table 1).

#### Sonography technique and power Doppler mode

This study was carried out with Philips HDI 5000 power Doppler sonography instruments (Philips Ultrasound, Bothell, WA, USA) coupled with a C 9-5 ICT endocavity probe and Toshiba Aplio MX (Toshiba M5, Nasu, Japan) coupled with a Biplane PVT-770RT endocavity probe (5–10 mhz). As a complement to the endorectal sonography, an exploration with a power Doppler was carried out in all patients. The Doppler increase was optimised in each patient so that there was no background noise at about 80%. We privileged a low PRF that was adjusted to 500 Hz in standard value: the filtration and persistence were pre-set at their maximum level in order to limit the movement artefacts.

A weak compression with the end of the probe was systematically carried out in case of a hypoechogenic area in the search for a modification of its echostructure. The mean time for a Doppler sonography of the prostate was about 15 minutes.

#### Ultrasound semiology and power Doppler [13]

In B mode, the peripheral area was in the normal state homogenous and more echogenic than the transition area. The suspect echostructure anomalies in the peripheral prostate area may be qualified as hypoechogenic, weakly hypoechogenic or subtle, heterogenic. The power Doppler mode searched for the presence of intraregional vessels in a suspect lesion in the mode B sonography. A visible lesion in B mode was said to be hypervascularised if it included one or several vessels. The lesion was qualified as focal if it was under 5 mm. However, this lesion was qualified as nodular.

<table>
<thead>
<tr>
<th>Patients biopsied</th>
<th>Positive patients after biopsies</th>
<th>Positive patients after EDP</th>
<th>Low-risk CaP according to d’Amico</th>
<th>CaP that may benefit from SA (Dall’Era)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA &gt; 10 ng/ml</td>
<td>114 62 (54%)</td>
<td>43</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PSA &lt; 10 ng/ml</td>
<td>299 139 (46%)</td>
<td>79</td>
<td>94</td>
<td>82</td>
</tr>
<tr>
<td>PSA &lt; 10 ng/ml T1c</td>
<td>243 106 (43%)</td>
<td>48</td>
<td>90 (84%)</td>
<td>73 (69%)</td>
</tr>
<tr>
<td>Total</td>
<td>413 201 (48%)</td>
<td>122</td>
<td>94</td>
<td>82</td>
</tr>
</tbody>
</table>

Table 1 Study on 413 consecutive patients undergoing biopsy after power Doppler sonography (PDS) and classified according to their PSA level, PDS results and the risks of biological recurrence (D’Amico) or the possible indication for active surveillance (Dall’Era) [16,18].
if it was over 5 mm and confined to a single sextant, comprising vessels remaining strictly intralésional. If the zone hypoechogenic area involved three sextants or more and/or if the vessels extended beyond the hypoechogenic area, the lesion was qualified as infiltrating. If the lesion was nodular or focal and associated with outer seats without real contiguity, the lesion was qualified as multifocal. The PDS results were rated from 1 to 4: 1: normal, 2: slightly hypoechogenic avascular lesion in which the hypoechogenicity disappears after slight compression with the probe (Fig. 1), 3: hypoechogenic avascular lesion (Fig. 2), 4: weakly hypoechogenic hypervascularised lesion (Fig. 3) and hypervascularised heterogenous or hypervascularised hypoechogenic lesion (Fig. 4). Classes 3 and 4 were considered to be pathological.

Biopsies

This study was prospective and was declared to the CNIL. Each patient included in the series received an information form that was drawn up by the French Association of Urology (AFU) [15]. Each patient benefited from a Doppler sonography examination before the biopsies. In case of a visible lesion, the location was determined by sextant and indicated in the information sheet appended to the samples sent to the anatomopathologist. The radiologist carried out the echo-guidance and oriented the biopsies performed by the urologist surgeon. Two urologist surgeons and four experienced radiologists participated in this study. Twelve samples were systematically taken, according to the recommendations for good biopsy practices proposed by the AFU [15]. One to three additional samples were sometimes added in case of suspect lesions in the PDS located outside of the path of the systematic biopsies.

All non-palpable cancers (clinical stage: cT1c) with a PSA level less than 10 ng/ml were classified according to D’Amico’s classification that introduced three levels of risk of biological recurrence after treatment (low, intermediate and high) and Dall’Era’s criteria [18] to assess the possibility of active surveillance (Table 2) [16,17]. These criteria were considered as the best evaluated and appear to be the most consensual in the European community [19].

Statistical analysis

The imaging results were correlated with the anatomopathological examinations of the biopsies. A result was declared to be a true positive if at least one biopsy was positive in the

![Figure 1](image1.png)

**Figure 1.** Class 2: weakly hypoechogenic peripheral prostate without vascular anomaly, the hypoechogenic appearance disappears under compression: PSA 6.2 ng/ml, negative biopsies.

![Figure 2](image2.png)

**Figure 2.** Class 3: weakly hypoechogenic and avascular peripheral prostate, the hypoechogenic appearance continues after compression: Prostate 45 g, clinical examination normal, PSA 7 ng/ml, Gleason score 6 (3 + 3).
same sextant as a class 3 or 4 image. A result was declared to be a true negative if no biopsy was found to be positive during an examination without a visible lesion (class 1 and 2). The sensitivity, specificity, positive and negative predictive values (NPV), as well as the accuracy of the diagnosis of cancer were calculated and the significance assessed with the Chi² test ($P < 0.05$). Mac Nemar’s test was used when both methods were compared (threshold of significance: $< 0.05$).

EPI info 6 programmes were used for the statistical calculations.

**Results**

Two hundred and forty-three (59%) of all patients screened in our study had a PSA level less than 10 ng/ml without palpable
lesion: 106 patients presented a cancer (43% of the cases), including 58 with a normal PDS (Table 1).

These 106 diagnosed cT1c cancers may be qualified as low-risk in 84% of the cases (89% with a normal PDS and 79% with an abnormal PDS). Sixty-nine percent of the cases may benefit from AS (86% of the normal PDS cases and 47% of the abnormal PDS cases; $P < 0.001$).

The diagnostic accuracy of the PDS was 65% when it consisted of the diagnosis of all of the T1c cancers. It was 83% in the cancers with an intermediate or high risk according to D’Amico and 82% in the diagnosis of significant cancers that may not benefit from AS according to Dall’Era ($P < 0.01$) (Table 3, Fig. 5).

The 58 negative PDS cancers account for 55% of all of the cT1c cancers and 42% of all of the cancers where the PSA level did not exceed 10 ng/ml.

Among the 243 patients tested, the PDS was normal in 159 (65%) of them. With a normal PDS, the probability of not having a cancer with a high risk is 96% (NPV). With an abnormal PDS, the probability of having a positive biopsy was 57% and the probability of having a significant cancer was 30% according to the Dall’Era criteria. With a normal PDS, these probabilities decrease in a significant manner to 36% and 5% respectively (NPV = 95%) ($P = 0.015$) (Table 4).

Discussion

The negative predictive value of the PDS can differentiate most low-risk lesions from intermediate and high-risk lesions.

Several studies have already found high VPN values (between 73 and 80%) and higher than those observed in our population (63%) (Table 3). This involves all patients with a cT1c cancer, independent of the criteria for risk of evolution [6,10].

The statistical criteria to judge the gravity of a prostate cancer are multiple but difficult to apply individually.

The screening of prostate cancer by the assay of the PSA level is the cause of an overdiagnosis [20,21]. The randomised European study [22] notes that, to avoid one case of death due to prostate cancer, it is necessary to screen almost 1410 men considering themselves to be healthy and treat 48 patients with prostate cancer. The annual rate of mortality of low-risk cancers of the prostate seems to remain stable 15 years after their diagnosis [23] and Sandblom [24] demonstrated that, after a survival of 20 years, the difference in the mortality due to prostate cancer does not differ between the screened group and the reference group.

The overdiagnosis concerns 40% of the screened patients [21] (82 of the 201 cancers or 40.7% of the patients in our series after the biopsies would have benefited from active surveillance) (Table 1). Without a non-invasive diagnostic tool, the risk of an overdiagnosis cannot be evaluated before.
the biopsies are carried out. Our study shows that the PDS can assess part of this risk: when the PDS is normal in the 243 patients in our study in which the clinical examination is normal and the PSA level does not exceed 10 ng/ml, the probability of detecting a high-risk lesion in the biopsies is only 5%. In addition, consideration of the results of the PDS in this group of patients may put off or even cancel a great many useless biopsies.

The cT1c cancers associate low-risk lesions with other higher-risk lesions. By selecting the patients without palpable lesion and in whom the PSA level does not exceed 10 ng/ml, we have two of the three conditions included in D'Amico's group of low-risk cancers. Certain studies have shown a correlation between the grade of tumour and the Doppler sonography imaging [4–7], although this correlation has never been validated.

In our study, patients with a PSA level ranging from 4 to 10 ng/ml and a normal DRE had a 46% risk of having a cancer and a 36% risk of having a cancer that could not benefit from AS: with a normal PDS, these risks decrease to 36% and 5% respectively in this same population. Thompson [3] observed that 10 to 25% of the cancers associated with a PSA level ranging from 0.6 to 4 ng/ml had a Gleason score equal to or higher than 7. This risk is usually accepted in the individual screening strategy.

The negative predictive value of the PDS may significantly modify the risk of having or not having an aggressive lesion and may weigh the statistical risk of the PSA level.

The negative predictive value of the MRI exceeds 90% with an accuracy of 98% in the diagnosis of significant cancers [25]. Independent of the fact that its high sensitivity also favours the overdiagnosis of a great many lesions under 0.5 cc, its negative predictive value in the diagnosis of high-risk cancers is not much higher than that of the PDS and the technique is much more complicated. The low availability of the machines and the high cost of the examination do not allow for its systematic use before the biopsies. The MRI may play a role when the kinetics of the PSA level is suspect and when no target is visible in the PDS examination.

Is it legitimate to delay biopsies when an indolent lesion is suspected? The existence of latent or non-significant cancers has been suspected since the results of the first series were published after autopsies [26–28]. After radical prostatectomy, Epstein [29] and Mc Neal [30] considered lesions as probably indolent when the volume was less than 0.5 cc and accompanied by a Gleason score less than 7.

The idea of non-significant lesions based on the results of biopsies is less consensual since the biopsies underestimate the volume of the tumour and cell differentiation.

D'Amico's criteria to assess the risks of biological recurrence after treatment have gained a wide consensus [16, 17]. The criteria proposed by Dall'Era (Table 2) [18] are most often used in Europe [19] and have been validated over long periods of time. Studies on cohorts of patients with clinically localised and non-treated prostate cancer have shown that the overall survival of patients with a Gleason score less than 7 is excellent [17]. Therefore, after 20 years, the specific survival of the patients ranges from 70 to 90% [23, 31, 32]. The data from the ERSPC group was presented in 2005 [22] with even less constraining criteria (PSA < 15 ng/ml and Gleason score < 8): 66% of the patients did not need treatment after a follow-up of 6 years. According to Dall'Era, there is no significant prognostic difference between the low-risk patients immediately treated and those that benefited from active surveillance before surgery [33].

Certain authors question the use of systematic biopsies: William [1], in cases where the PSA greater than 4 ng/ml proposes reducing the biopsy indications to only patients with a PSAD greater than 0.1 ng/ml/cc or with an abnormal DRE and in case of a PSAD less than 0.1 ng/ml/cc to patients with family antecedents or obesity.

The stability of the PSA level is an element that is rarely taken into account for the indication of a first series of biopsies. It is one of the criteria for active surveillance. This criterion is not evaluated in our study. Depending on whether the PSA level is stable or decreasing or, on the contrary, increasing significantly, the risk with this diagnosis probably differs. This parameter may have a statistical impact with a correlation between increasing and less than 10 ng/ml PSA and abnormal PDS and stable PSA and normal PDS. In this case, the variable PDS would not be independent. If demonstrated, in patients with a PSA level not exceeding 10 ng/ml, a normal clinical examination and a normal PDS, study of the PSA kinetics is probably justified before raising the indication of biopsies.

Our study presents several limits: the biopsies underestimate the volume and the grade of the lesions. Twenty-three to 35% of the cancers qualified as low-risk present an extraprostatic extension or impairment of the seminal vesicles after radical prostatectomy [34]. The grade of tumour is an important predictive factor in the recurrence of cancer after treatment. The absence of biopsy with a negative PDS risks underestimating small lesions with a high grade or certain infiltrating lesions that are difficult to identify by sonography. However, this risk is present in patients with a PSA level under 4 ng/ml although it is consensually accepted, as we reported above, since Thompson's work [3].

The PDS does not diagnose transitional or anterior lesions of the prostate. The latter are usually less aggressive, their diagnostic later and they accompany a PSA level often exceeding 10 ng/ml [35].

Compression with the end of the probe of weakly hypoechoic and avascular lesions may be replaced by elastography. This is currently being evaluated and may help improve the specificity and negative predictive value [36] of the DRE-PDS pair. Sonography is an operator-dependent and material-dependent examination and the clinical examination is subjective.

Sonography coupled with the Doppler examination remains an examination that is easily accessible and cheap. Its performance may be improved by the rules of good practice that still have to be determined.

**Conclusion**

Twenty-eight percent of all cancers diagnosed in our series were T1c cancers where the PSA level did not exceed 10 ng/ml and were not visible in the PDS. Eighty-nine percent of these cancers involved a low-risk of biological recurrence and 86% of the cases could benefit from active surveillance according to the Dall’Era criteria after the biopsies. Patients with a PSA level not exceeding 10 ng/ml without a DRE anomaly and with a negative PDS (35% of the
subjects tested) had less than a 5% risk of having a high-risk cancer. In these patients, the biopsies probably could be differed and carried out on the basis of arguments other than only the initial assay of the PSA level in order to limit the number of useless biopsies and reduce the risks of overdiagnosis.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


