ORIGINAL ARTICLE

Transrectal doppler ultrasound during prostate biopsy: Clinical utility and limitations


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KEYWORDS
Prostate neoplasms; Doppler; Transrectal ultrasound

Abstract
Objective: To determine the clinical utility and limitations of guided prostate biopsy power Doppler in patients with elevated serum PSA levels.

Materials and methods: Prospective study. From April 2012 to May 2013, 111 men over 45 years of age with serum PSA level greater than 4.0 ng/dl who underwent a transrectal prostate biopsy were included. The hypoechoic nodules in the peripheral region were considered positive on the gray scale. Subsequently, the study was conducted with the power Doppler, where the vasculization of suspicious images was analyzed for sampling. In addition, samples were taken from the suspected areas when performing the digital rectal examination. We calculated sensitivity, specificity, positive predictive value and negative predictive value of the three tests (digital rectal examination, standard gray scale ultrasound and power Doppler).

Results: Prostate cancer was diagnosed in 48 of the 111 patients (43%). Fifty-nine cases (53%) were defined as positive with the power Doppler. Of these, 39 (66%) corresponded to a diagnosis of prostate adenocarcinoma. The power Doppler was positive in 39 cases of the 48 patients diagnosed with cancer and the gray scale ultrasound was positive in 31 cases. Overall sensitivity of the power Doppler was 81%, specificity 68%, PPV 66% and NPV 82%, which was higher compared to the other methods (p < .05).

Conclusion: Currently, prostate biopsy using power Doppler does not seem to identify prostate cancer with sufficient accuracy to omit the guided systematic biopsy gray scale, the combined use of these methods.

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PALABRAS CLAVE
Neoplasias de próstata; Doppler; Ecografía transrectal

Ecografía doppler transrectal durante la biopsia prostática: utilidad clínica y limitaciones

Resumen
Objetivo: Determinar la utilidad clínica y limitaciones de la biopsia de próstata guiada por power doppler en pacientes con elevación de los niveles séricos de PSA.

Materiales y método: Estudio prospectivo. Desde abril del 2012 a mayo del 2013 se incluyeron un total de 111 hombres mayores de 45 años con un nivel de PSA sérico mayor a 4,0 ng/dl, los cuales fueron sometidos a una biopsia prostática transrectal. Los nódulos hipoecogénicos en la zona periférica fueron considerados positivos en la escala de grises. Posteriormente se efectuó el estudio con el power doppler, donde la vascularización de las imágenes sospechosas fue analizada para tomar las muestras. Además se tomó muestra de las zonas sospechosas al examen digitorrectal. Se calculó la sensibilidad, especificidad, valor predictivo positivo y valor predictivo negativo de las 3 pruebas (examen digitorrectal, ecografía estándar con escala de grises, y power doppler).

Resultados: El diagnóstico de cáncer de próstata fue hallado en 48 pacientes (43%) del total de 111. Cincuenta y nueve casos (53%) fueron definidos como positivo al power doppler, y de estos 39 (66%) correspondieron a un diagnóstico de adenocarcinoma de próstata. Del total de los 48 pacientes con diagnóstico de cáncer el power doppler fue positivo en 39 casos y la ecografía en escala de grises fue positiva en 31 casos. La sensibilidad global del power doppler fue del 81%, especificidad del 68%, VPP 66% y VPN 82%, lo cual resultó superior en comparación con los otros métodos (p < 0,05).

Conclusión: En la actualidad la biopsia prostática utilizando power doppler no parece identificar el cáncer de próstata con una precisión suficiente para omitir la biopsia sistemática guiada por escala de grises, siendo preferible el uso combinado de estos métodos siendo preferable.

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Introduction

The diagnosis of prostate cancer is currently based on the combination of different procedures. In general, the most commonly used ones in routine urological practice are prostate-specific antigen (PSA) determination, digital rectal examination (DRE) and, depending on the results and findings obtained, an ultrason-guided transrectal prostate biopsy (TPB). However, the frequency of positive biopsies for prostate cancer remains low. Although TPB is widely used to guide the needle, its clinical utility is compromised by an unsatisfactory positive predictive value (PPV). In this context, a limitation of the technique is reflected on the relatively low specificity for the detection of hypoechoic nodules in the peripheral area (PA). Hence, different authors have suggested the need not only for biopsies of possible nodules, but also a randomized sextant system. Systematic sextant biopsy under ultrasound control generally shows prostate cancer in 20–30% of men with serum PSA levels from 4.1 to 10 ng/ml and in 50–67% of those with PSA levels higher than 10 ng/ml.

In an attempt to overcome the constraints of standard diagnostic methods, new techniques have been developed. Among these, color Doppler ultrasound (CDU) has been described as being more sensitive than grayscale imaging in traditional ultrasound. Rifkin et al. were the first to suggest that most of the cancers detected in the PA and visible on transrectal ultrasound showed hypervascularization when analyzed by CDU. Thereafter, the distribution of signals as shown by CDU on a normal prostate gland has also contributed to clarify the changes in that pattern in relation to malignancy. Nonetheless, its use could be limited in the clinical setting since there is evidence that the addition of CDU increases PPV, but decreases sensitivity for the detection of prostate cancer. Furthermore, blood flows in small cancerous lesions are difficult to identify. Pelzer et al. studied a total of 380 patients with PSA levels between 4 and 10 ng/ml, assessing the results obtained when using Doppler ultrasound plus an intravenous contrast substance compared to traditional grayscale ultrasound. The cancer detection rate with the method using the combination of Doppler plus contrast was significantly higher than that obtained with grayscale ultrasound (32.6 versus 17.9% p < 0.01). In the same way, in the study conducted by Halpern et al. on a total of 301 patients, it was concluded that prostate cancer detection was 1.5 times more likely when using Doppler ultrasound in suspected areas, when compared to randomized grayscale systematic biopsy.

The power Doppler (PD) technique has a theoretical advantage over CDU, enabling a better detection of slow blood flows. Several investigations have suggested that PD can better characterize anechoic lesions in the peripheral area and help identify appropriate sites for biopsy. In a recently published study, it was estimated that the areas with abnormal blood flow accumulation that can be detected with PD may be present in 96% of the spots with prostate adenocarcinoma in patients with elevated PSA and a suspicious DRE.

While the advances in Doppler imaging techniques provide advantages, randomized grayscale systematic biopsy is still widely used, which suggests that a larger number of studies is necessary in order to register new
methodologies. Currently, a valid option would be the use of both methods in a complementary manner.21

On the basis of that cited above, the aim of this study was to: determine the clinical utility and limitations of prostate biopsy guided by PD in patients with elevated serum PSA levels.

Materials and methods

From April 2012 to May 2013, we included a total of 111 men over age 45 with a serum PSA level higher than 4.0 ng/dl. These patients underwent TPB using CHISON-Q6 portable ultrasound equipment with color Doppler system and a 6.0 MHz Electronic Micro-Convex transducer, using grayscale features for the systematic biopsy and then using PD.

Prior to the procedure, each patient underwent preparation, consisting of previous fasting for 8h, an evacuating enema 4h before the study, urine culture, updated prothrombin time and activated partial thromboplastin time to evaluate the antibiotic therapy to be used. Hypoechogenic nodules on the PA were considered positive in the grayscale mode. The PD study was subsequently carried out, where the vascularization of suspicious images was analyzed according to the following system19: 0 with no abnormal accumulation; 1 mild focal accumulation; 2 high focal accumulation; and 3 diffuse accumulation. Grades from 1 to 3 were considered positive and grade 0 was considered negative.

Prostate tissue sample collection was performed using an 18G-caliber HISTO Biocore II MG needle, of 25 cm in length, and using an automatic gun for TRU-CUT needles with a 2.2-cm penetration (HISTO DANA 2.2 MG). 2 samples were taken from each hypoechogenic area and/or positive PD, followed by a randomized systematic biopsy, in accordance with the protocol proposed by Vashi et al.22 (Fig. 1), which determines the number of samples to be taken depending on prostate volume. When PD showed a diffuse accumulation pattern in terms of vascularization (grade 3), the sample was collected from the area with the highest signal strength. Besides, in those cases with clearly suspicious DRE, the sample was directly taken from that area with manual guidance. Those patients with neither suspicious DRE found, nor with hypoechogenic areas and with a negative PD, only underwent a systematic biopsy. Tissue samples taken from each region were separately submitted for pathologic analysis.

We calculated the validity (sensitivity, specificity, positive predictive value and negative predictive value [NPV]) of the 3 tests (DRE, standard grayscale ultrasound and PD) and compared whether their validity differed by using the Chi-square test and the ROC curve diagram. p values below 0.05 were considered statistically significant. We used IBM SPSS Statistics 15 and Stata 11 software for calculations.

Results

A diagnosis of prostate cancer was found in 48 patients (43%) of the total of the 111 patients included in this study. The relationship between what was found by biopsy and the PD findings is shown in Table 1. Out of the 111 patients analyzed in this study, 59 cases (53%) were defined as positive at PD, whereas the remaining 52 (47%) were defined as negative by that test. Out of the total of patients with a PD with positive characteristics, 39 (66%) of them corresponded to a diagnosis of prostate adenocarcinoma and 20 (34%) had benign findings (BPH and/or an inflammatory process). 100% of the patients with a Gleason score ≥7 (22) showed a vascularization grade 3 (diffuse accumulation) at the time of PD.

There was a total of 20 cases of false positives at PD, which corresponded to 13 cases with inflammatory changes and 7 with characteristics of benign prostatic hyperplasia. It is also important to highlight that 9 cases of false negatives were found at PD, which could be due to the existence, at least in some of them, of an acoustic shadow caused by the presence of prostate calcifications in the peripheral area. Comparatively speaking, out of the total of 48 patients with a diagnosis of cancer, the PD was positive in 39 cases and grayscale ultrasound imaging was positive in 31 cases. Table 2 shows a summary of the existing relationship between the results of both PD and grayscale TPB among those patients with a positive biopsy result, as well as among all patients. Of 36 cases with hypoechogenicity characteristics plus hypervascularization, 23 (63%) were positive at biopsy (Fig. 2). When contrasting the results, cancer was found in only 8 (26%) patients out of the 30 who showed hypoechogenicity with normal vascularization, whereas the diagnosis of cancer was positive in 16 (70%) cases

Table 1 Relationship between PD and biopsy results.

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>PD Positive</th>
<th>PD Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6</td>
<td>17</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>≥ 7</td>
<td>22</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>Subtotal</td>
<td>39</td>
<td>9</td>
<td>48</td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory changes</td>
<td>13</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>BPH/normal</td>
<td>7</td>
<td>31</td>
<td>38</td>
</tr>
<tr>
<td>Subtotal</td>
<td>20</td>
<td>43</td>
<td>63</td>
</tr>
<tr>
<td>Total</td>
<td>59</td>
<td>52</td>
<td>111</td>
</tr>
</tbody>
</table>

Figure 1 Randomized biopsy protocol according to the glandular volume.
Figure 2 70-year-old patient with PSA = 12 ng/ml. (A) Transrectal ultrasound is observed grayscale showing a hypoechoic nodule in the peripheral zone. (B) That nodule clearly shows hypervascularization at PD (focus of prostate adenocarcinoma).

Figure 3 62-year-old patient with PSA = 6.1 ng/ml. (A) Transrectal ultrasound is observed grayscale without a suspected focus. (B) A focal area with hypervascularization at PD (focus of prostate adenocarcinoma) is observed.

out of the 23 who showed normal echogenicity with hypervascularization (Fig. 3).

Table 3 comparatively shows the values corresponding to the sensitivity, specificity, positive predictive value (PPV) and the negative predictive value (NPV) of the 3 diagnostic methods used.

The overall sensitivity of PD (n = 111) was 81%, its specificity 68%, PPV 66% and its NPV 82%. When comparing the results with those obtained for DRE and grayscale TPB, we observed that the parameters assessed (sensitivity, specificity, PPV and NPV) were higher for PD, this difference being statistically significant (p < 0.05). Fig. 4 graphically represents by using ROC curves the results achieved for the 3 methods, and one can observe that PD showed greater diagnostic accuracy (PD curve).

Table 2  Relationship between PD and TPB grayscale with the results of the biopsy (n = 111).

<table>
<thead>
<tr>
<th>Hypervascularized zone at PD</th>
<th>Hypoechoic area by TPB</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Positive</td>
<td>23/36</td>
<td>16/23</td>
</tr>
<tr>
<td>Negative</td>
<td>8/30</td>
<td>1/22</td>
</tr>
<tr>
<td>Total</td>
<td>31/67</td>
<td>17/44</td>
</tr>
</tbody>
</table>

Data: number of patients with positive/negative biopsy, with the PD and TPB findings grayscale.

Of the 42 patients with PSA values between 4 and 10 ng/ml, the biopsy was positive for cancer in 11 cases (45%), and PD found 25 cases positive (26%). PD and grayscale TPB independently detected neoplastic foci in 10 and 4 patients, respectively. Besides, within the group with PSA values between 4 and 10 ng/ml, PD also appeared to be superior as a diagnostic method versus grayscale TPB (Table 3). Fig. 5 shows the graph of the ROC curves for this group of patients.

Figure 4 ROC curves for all patients (n = 111). The area under the PD curve is higher compared to the others (p < 0.05).
Table 3  Comparison of the results of the tests for the detection of prostate cancer.

<table>
<thead>
<tr>
<th>Diagnostic method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n = 111)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRE</td>
<td>66%</td>
<td>62%</td>
<td>57%</td>
<td>70%</td>
</tr>
<tr>
<td>TPB grayscale</td>
<td>65%</td>
<td>44%</td>
<td>47%</td>
<td>62%</td>
</tr>
<tr>
<td>PD</td>
<td>81%</td>
<td>68%</td>
<td>66%</td>
<td>82%</td>
</tr>
<tr>
<td>p value</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>PSA 4-10ng/ml (n = 42)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRE</td>
<td>9%</td>
<td>65%</td>
<td>8%</td>
<td>66%</td>
</tr>
<tr>
<td>TPB grayscale</td>
<td>36%</td>
<td>52%</td>
<td>21%</td>
<td>69%</td>
</tr>
<tr>
<td>PD</td>
<td>91%</td>
<td>68%</td>
<td>50%</td>
<td>95%</td>
</tr>
<tr>
<td>p value</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

Discussion

A review of the evidence available suggests that a single taking of a sextant biopsy is associated with a significant rate of false negatives. However, it is still difficult to find the ideal methodology to perform this procedure. Several schemes have been developed to improve the diagnostic yield of prostate biopsies, which aim at increasing the number of samples, until a saturation biopsy with 45 cores is achieved. For some authors, the combination of sextant and guided methods maximizes the sensitivity of the biopsy, detects cancers in early stages and does not increase the detection of potentially insignificant tumors. It is clear that a huge effort has been focused on the early detection of the disease. In the last decade, serum PSA measurement as a screening test has played a central role in this strategy. However, the frequency of positive biopsies for prostate cancer is still low among men, with serum PSA levels between 4.1 and 10 ng/ml, and many of them undergo unnecessary procedures. There are publications demonstrating that CDU has a higher sensitivity than grayscale TPB for the detection of prostate tumors. However, CDU cannot identify small and weak blood flows in tumor vessels. PD has a theoretical advantage over CDU since it can distinguish slow-flow vessels irrespective of flow direction. Sakarya et al. evaluated the usefulness of PD in 36 patients with possible prostate cancer and found that its sensitivity, specificity and PPV were 90, 75 and 82%, respectively. According to this, PD would increase sensitivity and would help identify the appropriate sites for biopsy. Okihara et al. reported a high performance of PD in the detection of prostate cancer, with a sensitivity of 98% and a NPV of 99%. These results suggest that PD could reduce the number of unnecessary biopsies in patients with abnormally elevated PSA levels in the blood. In more recent years, the combination of the Doppler procedure with the use of intravenous contrast has provided satisfactory results, increasing cancer detection rates with elevated Gleason scores and decreasing the number of samples, both in patients undergoing first-time prostate biopsy and in those with a previous diagnosis of high-grade intraepithelial neoplasia. In the present work, the diagnosis of prostate cancer was found in 48 patients (43%) out of the total of 111 patients included in this study. The rate of false negatives was significantly lower in the case of PD (19%) when compared to grayscale TPB (35%) and DRE (33%). According to our results, among the total of patients evaluated, there were 36 with hypoechoigenicity characteristics plus hypervascularization, 23 (63%) of whom were positive at biopsy, suggesting that those sites with alterations on the gray scale (hypoechoigenic) associated with hypervascularization at PD should be firmly considered for biopsy taking. When carrying out the same analysis, it caught our attention that cancer was only found in 8 (26%) patients out of the 30 who showed hypoechoigenicity with normal vascularization, whereas the diagnosis of cancer was positive in 16 (70%) cases of the 23 who showed normal echogenicity with hypervascularization. The findings shown herein would indicate that PD could provide more useful information for the selection of the sites considered to be biopsied. In the study carried out by Ho et al., they determined that the sensitivity, specificity, PPV and NPV for PD were 66.7, 24.4, 19.4 and 73% respectively; more recently, Sauvain et al. used PD for the detection of low-risk prostate cancer (PSA <10ng/ml) in a total of 243 patients, finding sensitivity, specificity and PPV values of 87, 71 and 85% respectively. Consistently with what other authors have published, this study demonstrates a superiority of the results of prostate cancer detection tests in favor of PD, basically due to the fact that its sensitivity,
specificity, PPV and NPV were higher than those of the other 2 methods taken into consideration (DRE and grayscale TPB). For a PSA range between 4 and 10 ng/ml, PD would show greater usefulness, although it is clear that the number of patients studied within this range of values was small.

It is important to bear in mind that for some authors it is relevant to consider the existence or not of palpable nodules when choosing an interventionist practice pattern,\textsuperscript{11,12} which is in concordance with our results, since there were only 3 patients where the biopsy was positive while having normal DRE and PD.

On some occasions, it is hard to differentiate between cancerous lesions and inflammatory areas by using PD, since both can show hypervascularization areas. Numerous attempts have been made in the search for specific findings enabling better differentiation between malignant and benign lesions.\textsuperscript{19,31} Okihara et al.\textsuperscript{19} concluded that prostate volume was significantly greater in the positive PD cases without cancer than in the negative PD cases of a similar group. It is speculated that enlarged prostate tissue requires greater vascular flow. Prostate calculi would seem to be a cause of confusion which may hide a cancerous lesion in the transition area. Since prostate calculi are generally located in the border between peripheral and transition areas, their acoustic shadow can interfere with ultrasound observation in the transition area.\textsuperscript{32} The results found in the present work showed a total of 9 patients with a positive biopsy and PD with normal flow, which shows similarity with what has been expressed by other authors regarding the restrictions of this method.

It is worth mentioning that nowadays new imaging methods are gaining in importance regarding the diagnosis of prostate cancer, as in the case of magnetic resonance imaging (MRI). Even though in our environment there is still little experience with the use of MRI for prostate disease, important series have already been published on the international stage demonstrating that multiparametric MRI provides a good detection rate of prostate cancer,\textsuperscript{34,35} and even evaluates the existence of extracapsular disease.\textsuperscript{36} While these results are better than those achieved by biopsy under transrectal ultrasound guidance, we believe that its implementation is more difficult due to the costs involved.

We should not fail to mention some limitations in this study. All the procedures were carried out using CHISON Q6 equipment with color Doppler system and a 6.0-MHz Electronic Micro-Convex transducer, so our results may be different to those obtained with other tools. As shown by Halpern et al.\textsuperscript{37} the lateral decubitus position may cause increased Doppler flow on the dependent’s side. However, the results of his study also revealed an asymmetry in blood flow, despite the lithotomy position. On the other hand, a 60-MHz transrectal transducer was used. The use of more modern technology is likely to enable improved sensitivity of the method.\textsuperscript{37,38}

Conclusions

PD can identify appropriate sites for biopsy as hypervascularized ones and improve the cancer detection rate when compared to grayscale transrectal ultrasound and systematic biopsies. However, inflammatory reactions and prostate calculi would represent the main causes of results with false positives and false negatives, respectively, thus compromising the usefulness of the method. Therefore, we conclude that, at present, the use of PD does not appear to identify prostate cancer with a sufficient degree of accuracy to omit grayscale guided systematic biopsy, the combined use of these methods being preferable.

Conflict of interest

The authors declare that they have no conflict of interest.

References

15. Halpern EJ, Ramey JR, Strup SE, Frauscher F, McCue P, Gomes LG. Detection of prostate carcinoma with
Transrectal doppler ultrasound during prostate biopsy