The role of elastography in improving detection rates of prostate cancer

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Abstract

Objectives: In this study we sought to evaluate whether elastography targeted biopsy improves the detection rate of PCa (prostate cancer) compared to systematic biopsy guided by conventional grayscale ultrasound (GSU).

Materials and method: We conducted a prospective study and enrolled 240 patients on which we performed a 12 core prostate biopsy by conventional ultrasound guidance or elastography guided. The external prostate was divided into six sectors: base right, middle right, apex right, base left, middle left, apex left. These sectors were scanned for suspicious lesions by elastography – hard areas - and by gray scale ultrasound - hypoechogenic areas. If in a certain sector a suspicious area was found, regardless of the imaging method, a single biopsy from this area was performed, whilst considering it representative for that certain sector. Imaging results were correlated with the results received from the pathologist lab. The two tools used in prostate biopsy guidance were compared statistically in terms of the detection rate of prostate cancer. We did not find statistical differences between the two groups concerning age, PSA (prostatic specific antigen), prostate volume, the data obtained by digital rectal examination. Prostate cancer was detected in 42.5% of patients (102 of 240). PCa detection rate was significantly higher in those who used elastography 51.6% (62 of 120) compared to those that have used conventional ultrasound 38.3% (46 of 120). Elastography’s sensitivity was 56.8% compared to 17.5% for conventional ultrasound. Specificity was 70.7% compared to 92.8% for elastography to conventional ultrasound.

Conclusions: Using elastography in prostate biopsy has higher sensitivity than using conventional ultrasound. But the overall sensitivity obtained has not reached levels that allow omitting the randomized systematic biopsy.

Keywords: conventional ultrasound, elastography, prostate biopsy, prostate cancer (PCa)
Introduction

Ultrasound guided transrectal prostate biopsy is the standard method used in the diagnosis of prostate cancer. Conventional ultrasound has a low accuracy in the visualization and detection of lesions of PCa and therefore conventional ultrasound is recommended only to guide systematic randomized biopsy. Studies have shown that PCa was detected on initial biopsy in between 18% and 41% of cases [1,2]. Given this limitation, in order to reduce the rate of false-negative results, a series of models were used to calculate PSA and various protocols were devised for biopsy and imaging. MRI and the use of contrast enhancement with ultrasound, provided promising results but these involve a longer time and a much higher cost. There are several studies in the literature that have shown promising results regarding the use of elastography to guide prostate biopsy [3,4,5,6].

Ultrasound elastography is a relatively new method, whose principle is to differentiate tissue structures depending on their “hardness”, this concept being completely different from standard ultrasound which discriminates between tissues depending on the difference in acoustic impedance between them.

Palpation constituted, along the course of medical developments, one of the most important “weapons” used in the diagnosis of various diseases, being considered unequivocally a pivot in clinical semiology. Schematically, elastography is an “extension” of the clinician’s palpatory sense, creating a true deep tissue palpation impression. Today it is considered that nodules considered unequivocally a pivot in clinical semiology.

There are studies in groups led by Mitterberger and Junker showing that a 50% reduction in the number of biopsies taken using the randomized technique, by using the elastographically guided method provides the same detection rate of prostate cancer. There is insufficient evidence in the literature to exclude the randomized ultrasound guided prostate biopsy from the diagnostic protocol of Pca. The imaging results were correlated with the results received from the pathologist laboratory. The two tools used to guide the prostate biopsy were compared statistically in terms of the detection rate of prostate cancer.

Materials and Method

Between August 2012 and August 2013 we prospectively investigated 240 consecutive patients with a mean age of 62.7 years with increased PSA (above 4 ng/mL) or suspected PCa at the digital rectal examination. The characteristics of the population are presented below (Table 1). I have not included in this study patients who had a history of prostate biopsy, underwent surgery (TUR-P, TUIP, simple prostatectomy), those with a history of prostatitis during the last month. All patients signed an informed consent validated by the hospital ethics committee.

Patients in the study were randomized prospectively 120 in a lot and 120 in another lot. Patients received 24 hours preprocedural antibiotic - ciprofloxacin 500 mg BID, which continued five days after the procedure. The digital rectal examination was done by an experienced investigator who was not involved in performing the prostate biopsy.

Table 1. The characteristics of the populations included in the study

<table>
<thead>
<tr>
<th></th>
<th>RTE (real time elastography)</th>
<th>Conventional ultrasound</th>
<th>Total (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62.4 (44-84)</td>
<td>62.9 (41-87)</td>
<td>62.79 (41-87)</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td>10.3 (2.5-53)</td>
<td>12.8 (2.6-77)</td>
<td>11.5 (2.5-77)</td>
</tr>
<tr>
<td>Prostatic volume</td>
<td>43.1 (14-155)</td>
<td>37.5 (21-140)</td>
<td>40.7 (14-155)</td>
</tr>
</tbody>
</table>

For the ultrasound examination, I have used an Accusson Siemens S2000 with the guidance system attached to the EC9-4 transducer.

Local anesthesia was performed using instilagel administered rectally at the beginning of the procedure. We divided the external prostate in six sectors. We excluded the transitional area from the investigation (this is a limiting factor to the use of elastography in large prostates, when the depth exceeds 5cm). Each of these sectors was examined for suspected Pca. Among the first positive elastographic diagnostic criteria formulated for prostate cancer were described by Konig et al in 2005 [4,5]. The group described prostatic malignancy as the existence of a hard, reproducible and asymmetric –at least 5 mm in diameter- injury, being among the first to perform a prostate biopsy in those suspicious areas revealed by elastography. The results were superior to those of systematic prostate biopsies.

These criteria were slightly modified later by Pallwein et al [7]. The definition of prostate cancer using elastography, described by them, allowing more free-
dom, correlates the percentage of patients with a higher risk of prostate cancer with a particular aspect on elastography [8].

- Score 1 – normal appearance (homogeneous green)
- Score 2 – probably normal appearance (mosaic, striated)
- Score 3 – equivocal appearance (suspect lesion in the left lobe on RTE, without hypoechoic lesion on GSU)
- Score 4 – probable PCa (suspect lesion in the left lobe on RTE, with green peripheral halo, with associated hypoechoic lesion on GSU)
- Score 5 – obvious PCa (hard, assymetric, well circumscribed lesion in the right lobe)

The elastography procedure increased investigation time by 8-12 minutes.

At conventional ultrasound, hypoechoic lesions were considered suspicious for PCa. In the lateral sectors, six cores were prelevated on each side - 3 lateral and 3 in a more medial plane at the base, middle and apex of the prostate. If there was a suspicious area, a single core was prelevated from that sector, assuming that it was representative of that sector. If there were no suspicious areas, random biopsies were taken. The resulting cores were examined and the histopathological result was correlated with the imaging data. The Kolmogorov-Smirnov test was used for normality. Comparison of mean values was done using the Student-t test, if the values were normally distributed. \( P < 0.05 \) was considered statistically significant for this analysis.

**Results**

The distribution between the two groups regarding PSA, age and prostate volume was similar. Digital rectal examination raised malignity suspicions in 24% in the group with elastography and 30% in the group in which conventional ultrasound was used as a means of guiding prostate biopsies.

Overall cancer was diagnosed in 108 patients of 240 ie 45%. PCa was diagnosed in 62 patients in the group with elastography and 46 in the group with conventional ultrasound. Thus, the detection rate of PCa was higher for the group in which elastography was used than in that in which conventional ultrasound - 11.2% \( (p = 0.026) \).

In order to determine the accuracy of elastography compared to conventional ultrasound imaging, the imagistic characteristics were compared with pathological results for each of the six sectors defined (base, middle and apex on each side). In the 2 groups, 720 sectors were assessed. Using RTE in 75 sectors (10.4%) a PCa suspicion was raised and this was confirmed by histopathology.

The prediction of benignity was proven in 416 sectors (57.8%). Prostate cancer was diagnosed in 57 sectors (7.9%) considered „clean“ after elastographic examination. The false-positive rate was 23.88% for the RTE. For RTE, the sensitivity, specificity, PPV and VPN were calculated and these were 56.81%, 70.74%, 30.36% and 87.94% respectively. Hypoechoic areas were found to be PCa in 23 sectors out of the total 720 (3.19%). For the conventional ultrasound the sensitivity, specificity, PPV and VPN were 5%, 96.29%, 20% and 84.55%.
Fig. 4 RTE Image - soft tissue in the right lobe of prostate

Table 2. The results obtained in the group for which RTE was used

<table>
<thead>
<tr>
<th></th>
<th>No. RP</th>
<th>No. FP</th>
<th>No. FN</th>
<th>No. RN</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left basal</td>
<td>6 (0.8)</td>
<td>11 (1.5)</td>
<td>7 (0.9)</td>
<td>95 (13.2)</td>
<td>46.15</td>
<td>89.62</td>
<td>22.22</td>
<td>93.13</td>
</tr>
<tr>
<td>Left middle</td>
<td>23 (2.7)</td>
<td>36 (5)</td>
<td>14 (1.94)</td>
<td>60 (8.33)</td>
<td>58.82</td>
<td>62.5</td>
<td>35.71</td>
<td>81.06</td>
</tr>
<tr>
<td>Left apex</td>
<td>13 (1.8)</td>
<td>42 (5.8)</td>
<td>3 (0.4)</td>
<td>58 (8)</td>
<td>81.25</td>
<td>58</td>
<td>23.63</td>
<td>95.08</td>
</tr>
<tr>
<td>Right basal</td>
<td>8 (1.1)</td>
<td>13 (1.8)</td>
<td>16 (2.2)</td>
<td>83 (11.5)</td>
<td>33.33</td>
<td>86.45</td>
<td>38.09</td>
<td>8.83</td>
</tr>
<tr>
<td>Right middle</td>
<td>16 (2.2)</td>
<td>34 (4.7)</td>
<td>12 (1.6)</td>
<td>56 (7.7)</td>
<td>57.14</td>
<td>62.22</td>
<td>32</td>
<td>81.15</td>
</tr>
<tr>
<td>Right apex</td>
<td>12 (1.6)</td>
<td>36 (5)</td>
<td>5 (0.7)</td>
<td>64 (8.8)</td>
<td>70.58</td>
<td>64.1</td>
<td>25</td>
<td>92.75</td>
</tr>
<tr>
<td>Total</td>
<td>75 (10.7)</td>
<td>172 (23.8)</td>
<td>57 (7.9)</td>
<td>416</td>
<td>56.81</td>
<td>70.74</td>
<td>30.36</td>
<td>87.94</td>
</tr>
</tbody>
</table>

Table 3. The results obtained in the group for which GSU was used

<table>
<thead>
<tr>
<th></th>
<th>No. RP</th>
<th>No. FP</th>
<th>No. FN</th>
<th>No. RN</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left basal</td>
<td>5</td>
<td>6</td>
<td>19</td>
<td>110</td>
<td>20.83</td>
<td>94.82</td>
<td>45.45</td>
<td>85.27</td>
</tr>
<tr>
<td>Left middle</td>
<td>4</td>
<td>9</td>
<td>17</td>
<td>92</td>
<td>19.04</td>
<td>91.08</td>
<td>30.76</td>
<td>84.40</td>
</tr>
<tr>
<td>Left apex</td>
<td>4</td>
<td>6</td>
<td>20</td>
<td>85</td>
<td>16.66</td>
<td>93.4</td>
<td>40</td>
<td>80.95</td>
</tr>
<tr>
<td>Right basal</td>
<td>5</td>
<td>10</td>
<td>16</td>
<td>68</td>
<td>23.80</td>
<td>87.17</td>
<td>33.33</td>
<td>80.95</td>
</tr>
<tr>
<td>Right middle</td>
<td>4</td>
<td>7</td>
<td>17</td>
<td>88</td>
<td>19.04</td>
<td>92.63</td>
<td>36.36</td>
<td>83.80</td>
</tr>
<tr>
<td>Right apex</td>
<td>1</td>
<td>4</td>
<td>19</td>
<td>104</td>
<td>5</td>
<td>96.29</td>
<td>20</td>
<td>84.55</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>42</td>
<td>108</td>
<td>547</td>
<td>21.29</td>
<td>92.86</td>
<td>35.38</td>
<td>83.35</td>
</tr>
</tbody>
</table>

When using RTE, the highest sensitivity in the detection of PCA was at the apex, while using conventional ultrasound had the highest sensitivity at the base of the prostate.

The Gleason score distribution showed no difference between the 2 groups. Most cases showed an intermediate differentiation.

Table 4. The distribution of patients according to the Gleason score in the two groups

<table>
<thead>
<tr>
<th></th>
<th>Patients diagnosed by RTE</th>
<th>Patients diagnosed by GSU</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-6</td>
<td>48 (36.1)</td>
<td>31 (23.3)</td>
<td>79 (59.4)</td>
</tr>
<tr>
<td>7</td>
<td>23 (17.2)</td>
<td>15 (11.2)</td>
<td>38 (28.5)</td>
</tr>
<tr>
<td>8-10</td>
<td>6 (4.5)</td>
<td>10 (7.5)</td>
<td>16 (12.0)</td>
</tr>
</tbody>
</table>

Discussions

This is the first study to make a comparison between using elastography and conventional ultrasound in 12 core prostate biopsies.

In this prospective study we enrolled 240 patients with suspected biochemical or clinical examination (digital rectal examination) of PCA.

Thus, the detection rate of PCA was higher in the elastography group than in the conventional ultrasound one - 11.2% (p = 0.026).

The sensitivity for detecting PCA with RTE was 56.8% compared to 5% with the USG. Our data supports the idea that RTE improves the PCA detection rate when used for guided prostate biopsy.

So far, no imaging technique can accurately distinguish between cancerous lesions and benign prostatic tissue. In recent years, various ultrasound guided biopsy protocols have been presented increasing the number of biopsy cores collected, however the PCA detection rate remains low. To increase the accuracy of targeted prostate biopsies, a variety of imaging techniques have been developed. Elastography is a promising technique that evaluates the elasticity of structures/tissue. Data from the literature show that prostate cancer lesions have low elasticity. The Sommerfeld led group revealed that RTE increases the detection rate of PCA and also evaluates extracapsular extent [9]. Although it has been shown that elastography detects prostate cancer lesions, very few studies have analyzed its value in improving the rate of detection of PCA in prostate biopsy.

Several imaging techniques for identifying cancerous lesions and histological patterns of development that are under investigation are promising. Compared to benign prostate tissue, multifocal cancer development is associated with loss of histological benign glandular architecture, increased cellular density and modified microvasculature.
RTE visualizes the voltage differences in the prostatic tissue [10].

Aigner showed that RTE guided biopsy reveals almost the same proportion of PCa (19% vs 21%) compared with standard 10 core biopsy, but half the number of punctures required [11].

The integration of RTE to guide biopsies in a systematic protocol involves two advantages:

1) No specific additional biopsy has to be taken (reducing the risk of increased morbidity and reducing costs)

2) the potential benefits of an extra imaging instrument is used without the risk of not identifying prostate cancer, because of false negative results when using only oriented protocol. False negative rates on RTE targeted biopsy, in various prospective studies range from 5.6% to 53.8%. Therefore, Nelson et al concluded that RTE targeted approach was not able to replace systematic 12 core biopsy protocol.

In our study, consistent with the results of Nelson et al, histopathology revealed PCa in 108 areas (15%) classified as no lesion on RTE. The prospective study we conducted confirmed the results of Nelson et al that elastography can not replace systematic biopsy. RTE guided biopsy sensitivity was 56.8%. Low sensitivity of 5% for USG in viewing PCa is consistent with the results of other authors.

RTE sensitivity in detecting prostate cancer depends on other factors such as the location of PCa in the gland and different Gleason scores. For RTE we have noticed an increase in sensitivity on basal gland biopsies (33.3% to 46%) to the apex gland biopsies (70% to 81%). Obviously, the compression and decompression of lower volumes at the apex of the gland could be more efficient. Salomon et al described the same phenomenon in a study of patient-staging before radical prostatectomy.

RTE showed a correlation between PCa detection and increased Gleason score. Accuracy for Gleason score 7 or higher was 66.1% and 70.8%, respectively. This may be the result of a greater cell density in tumor cells of high grade tumors, resulting in a more rigid tissue. Other studies have indicated the same trend, although the accuracy was significantly higher. The detection rate of Gleason score greater than 7 was between 93% and 100%, in the Salomon and Pallwein studies. The sensitivity of conventional ultrasound in prostate cancer was not influenced by the Gleason score or by the prostatic region (base/ apex).

If the B-mode is used at the same time, errors may be encountered for hipoechoic lesions. However, half of prostate cancer lesions are not detected by conventional sonography. On the other hand, there are two benign conditions mimicking ultrasonographic appearance of prostate cancer: BPH (benign prostatic hyperplasia) and prostatitis.

RTE can determine and assess tissue elasticity to a depth of 5 cm, but in large BPH with increased ultrasound depth many „tough“ artifacts appear. The tilting of the transducer can discriminate between these „tough lateral artifacts“ but „tough“ artifacts which are deeply situated remain a major problem for ultrasound. Therefore RTE does not detect cancer in the transitional zone. Another limitation of this method is the altering in the structure and elasticity of chronic inflammatory tissue, with stromal hyperplasia and fibrosis.

In conclusion, RTE would have limitations [12]:

- small tumors (probably the development of new technical solutions will enable the detection of tumors below 5 mm)
- increasing hardness of fibrous tissue in chronic prostatitis.
- BPH
- elasticity can not be objectively determined.

We noted some limitations in our study. From any suspect sector there was only one targeted biopsy core performed. As the number of cores was limited to 12, the PCa detection rate could have been higher if more targeted biopsies per prostate sector were performed. We used a systematic 12-core biopsy in our study as gold standard to assess the sensitivity and specificity of RTE and GSU. A systematic 12-core biopsy is the standard method of detecting PCa.

Conclusions

In this study, RTE guided biopsy had a higher sensitivity in detecting PCa compared to conventional techniques. In general, the sensitivity in detecting PCa remains low. Therefore, a systematic approach to prostate biopsy remains mandatory. Continuous improvement of current imaging techniques is required, and other techniques to increase the sensitivity and specificity of detection of PCa should be further studied.

Starting from the low sensitivity of gray scale ultrasound in detecting prostate cancer, various imaging techniques have been introduced in order to optimize the detection of the PCa. Since its introduction in 1991
by Ophir et al, RTE has been used in various urological centers as an additional tool for detecting PCa [13]. Many research groups have investigated the accuracy of RTE in correlation with biopsy results for the detection of PCa. Despite promising results in terms of this imaging technique, sensitivity and specificity have not yet reached levels that allow it to safely visualize glandular lesions. In order to determine the true sensitivity and specificity, correlation with histopathological sections of prostatectomy specimens is required.

We take into consideration that operator subjectivity in detecting prostate areas with high rigidity is the first cause for obtaining discordant results. In this matter, it is important to reduce the subjective interpretation and to standardize the used method as much as possible. Kapoor et al suggested that RTE association with TRUS (transrectal ultrasound) significantly improves sensitivity for detecting prostate carcinoma in patients with high PSA. Ultrasonic elastography of the prostate does not seem to have an obvious contribution to the early detection of prostate cancer, but rather useful in malignant lesions clearly outlined.

False positive prostate cancer aspects in elastography may occur in the following situations: chronic prostatitis lesions, intraprostatic calcifications, “distance” effect, “attenuation” effect, adenomatous nodules, “striated” appearance of the base, often difficult to recognize.

False-negative prostate cancer aspects in elastography can be caused by any event generating false-positive images by “hiding” information, the absence of sound information postobstacle (high intraprostatic calcifications) or small tumors, soft or some infiltrative forms.

Prostate elastography is a relatively new and available ultrasound diagnostic tool, whose skill correctly and efficiently inevitably involve learning curve appropriate.

References