Objective To report on the use of automated image analysis in the interpretation of transrectal ultrasonographic images of the prostate.

Patients and methods During transrectal ultrasonography, images were recorded from biopsies performed in 127 patients. Subsequently in the image, the puncture place was marked and analysed. Analysis of the images was performed with the Automated Urologic Diagnostic Expert (AUDEX) system, consisting of a personal computer connected to the ultrasound machine. From the images collected, parameters can be calculated for image classification. The parameters obtained with this procedure were correlated with the histological result.

Results Evaluation showed a sensitivity of 84.8% and specificity of 87.5%. The positive and negative predictive values, to predict prostate carcinoma, were 84.8% and 87.5%, respectively.

Conclusion Automated image analysis can help in the diagnosis of prostate carcinoma. In patients with non-palpable lesions or with poorly visualized tumours, image analysis is superior to the standard current diagnostic techniques.

Keywords Prostate cancer, diagnosis, ultrasound, computer, image analysis

Introduction

The prostate has become the main site of cancer in men, with prostate cancer the second leading cause of death from cancer in men in the United States [1]. Many investigators have attempted to lower the mortality rate from this disease. In the absence of a cure for advanced prostate cancer, the most feasible approach may be to improve early diagnosis. If the percentage of men whose tumours are localized at an early stage could be increased, the mortality rate might be lowered [2].

The early detection of prostate cancer in (asymptomatic) men depends not only on digital rectal examination (DRE) but also on prostate-specific antigen (PSA) and transrectal ultrasound (TRUS). The overall results for prostate examinations (DRE, PSA and/or TRUS) have a predictive value of between 29.2% and 42% [3,4]. These results seem disappointing and may, in addition to the difficulty of palpation of the tumour, be explained by the poor detection by TRUS caused by iso- or poor hypo-echogeneity. Up to 35% of clinically detected early-stage prostate cancer cannot be distinguished by TRUS from the normal surrounding prostatic tissue [3]. Several other features may contribute to cancer being undetectable by ultrasonography, e.g. tumour size, grade, location, stage and pattern of growth. Because of these limitations, the malignancy of 'suspicious prostates' can only be determined if biopsies are taken for histological analysis of the tissue. This procedure, however, carries the risk of severe bleeding, infection or even urosepsis and may be very uncomfortable for the patient. Furthermore, accurate location of suspicious areas of the prostate may be difficult. To overcome the problem of detection of prostate carcinoma caused by the poor hypoechogeneity of some carcinomas during TRUS investigations we looked for other tools and techniques. Image analysis techniques are already being used on a regular basis to interpret satellite photography or light microscopy [5–7]. Similar techniques have been applied in the field of medical imaging to diagnose liver, female breast, thyroid or prostate pathology [8–14]. Early results from these studies are promising. We therefore initiated research to determine the possibilities and additional value of automated analysis and interpretation of TRUS images [15]. This report describes the initial results of the use of automated image analysis techniques for the detection of prostate cancer.
Patients and methods
To exclude the presence of cancer of the prostate in 127 patients, one or more transrectal ultrasound-guided prostate biopsies were taken. Reasons for biopsy were: abnormal DRE (n = 64), elevated PSA (PSA > 10 ng/mL, Hybritech) (n = 77), and/or suspicious TRUS (n = 60). The images of 60 patients were used because the histology of the corresponding tissue was unambiguously benign (n = 32) or malignant (n = 28). For analysis, only the images collected in these patients were used. This resulted in 102 images of which 56 were of benign histology and 46 of malignant histology. Two-thirds of the samples (n = 69) were used for the learning phase while all of the samples were used for testing the system (n = 102). Histologies that were found, but not used in this study, were prostatitis and severe atypia without proof of malignancy. Five images could not be used because of poor quality. In patients with a PSA of 4–10 ng/mL, biopsies were performed if the rectal examination and/or ultrasound scan was abnormal, as isolated minor elevations of PSA are almost invariably innocent and may be caused by benign prostatic hyperplasia (BPH).

Using a Kretz Combison 330 ultrasound scanner (Multiplane 3D rectal transducer 7 MHz VRW 774AK), longitudinal and transverse images were recorded. All investigations were performed by two urologists experienced in using TRUS. A personal computer (486 DX2, 66 MHz) with additional framegrabber (Pc Vision Plus framegrabber by Difa Measurement Systems), was connected to the ultrasound machine, and a system was developed for the classification of prostate tissue; the Automated Urologic Diagnostic Expert (AUDEX) system.

The function of this system depends upon (i) the parameters for image classification; (ii) the histology of the biopsies; and (iii) the algorithm used for correlating the parameter values with corresponding histology.

Before such a system can classify images, it has to be programmed to distinguish images from benign and malignant tissue. Therefore images from tissue with known histology must be recorded. For this, two consecutive sagittal images were stored from prostate biopsies that were taken just before the biopsy and after the biopsy (both with the biopsy needle in situ) (Fig. 1). Thus the exact position of the removed tissue was determined and correlated with the final histological examination (Fig. 2). For transrectal punctures of the prostate the biopsy gun was used (18 gauge needle). In patients without abnormalities on TRUS, sextant biopsies were taken in the midline from apex to base. These biopsies were randomly marked. If a hypoechoic lesion was detected, guided punctures were taken from this lesion.

In the present study, the parameters for image classification were calculated from the co-occurrence matrix which is a representation of the grey tone transitions in the image. From this matrix, five parameters were derived for the classification of prostate tissue: uniformity, contrast, inverse difference moment, entropy and correlation [16,17]. Uniformity was a measure of the homogeneity of the texture, the contrast measured the changes in grey level in the texture, the correlation responded to highly ordered structures within the texture, inverse difference moment represented the variation in grey tone and the entropy a measure of randomness.

Once the histology of the biopsies was known, the
parameter values of all biopsies were correlated to the histology of the tissue [18]. The correlation was determined using binary decision trees, which are hierarchical representations of the decisions made to obtain a classification [19,20]. A more technical description of this automated analysis system has been published [18].

Once a decision tree has been constructed, the system can be used in a predictive way: structures in ultrasound images of the prostate are labelled benign or malignant and are presented in colour. Each colour code represents the estimated probability of the presence of malignant tissue (red = 100% chance, blue = 0% chance).

The aim of the present study was to investigate whether or not this image analysis technique distinguished images of benign tissue from those of malignant prostate tissue. Therefore, to obtain unambiguous results only those patients with a clear malignant or benign histology in the biopsies were included in this study. Patients with prostatitis and atypia were excluded.

Results

For the detection of carcinoma the technique had a sensitivity of 84.8%, a specificity of 87.5%, a positive predictive value of 84.8% and a negative predictive value of 87.5% (Tables 1, 2 and 3).

A total of 54.9% of the punctures were taken at random, where there were no suspicious lesions on the ultrasound image. In this group the sensitivity was 84.6% and the specificity 86.0%. In three patients with a malignancy, the lesions were isoechogenic on TRUS, and in two of these patients a tumour was detected on DRE. In all three patients the automated analysis predicted malignancy. In only one patient was a tumour found on TRUS but not detected by DRE. In this patient, the system also predicted malignancy. However, in three patients the system did not diagnose an existing malignancy (see Discussion), and identified a malignancy in seven patients without malignancy.
Table 1 Results of retrospective analysis of 69 images (67.6%) for specificity, sensitivity, predictive negative value, predictive positive value of the automated system (AUDEX), TRUS, DRE and PSA

<table>
<thead>
<tr>
<th></th>
<th>AUDEX</th>
<th>TRUS</th>
<th>DRE</th>
<th>PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>33</td>
<td>34</td>
<td>31</td>
<td>14</td>
</tr>
<tr>
<td>Malignant</td>
<td>27</td>
<td>23</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.868</td>
<td>0.895</td>
<td>0.816</td>
<td>0.368</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.871</td>
<td>0.742</td>
<td>0.645</td>
<td>0.839</td>
</tr>
<tr>
<td>Predictive negative</td>
<td>0.892</td>
<td>0.810</td>
<td>0.771</td>
<td>0.737</td>
</tr>
<tr>
<td>Predictive positive</td>
<td>0.844</td>
<td>0.852</td>
<td>0.741</td>
<td>0.510</td>
</tr>
</tbody>
</table>

Table 2 Results of prospective analysis of 33 images (32.4%) for specificity, sensitivity, predictive negative value, predictive positive value of the automated system (AUDEX), TRUS, DRE and PSA

<table>
<thead>
<tr>
<th></th>
<th>AUDEX</th>
<th>TRUS</th>
<th>DRE</th>
<th>PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>16</td>
<td>17</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Malignant</td>
<td>12</td>
<td>9</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.889</td>
<td>0.944</td>
<td>0.833</td>
<td>0.556</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.800</td>
<td>0.600</td>
<td>0.667</td>
<td>0.800</td>
</tr>
<tr>
<td>Predictive negative</td>
<td>0.842</td>
<td>0.739</td>
<td>0.750</td>
<td>0.714</td>
</tr>
<tr>
<td>Predictive positive</td>
<td>0.857</td>
<td>0.900</td>
<td>0.769</td>
<td>0.543</td>
</tr>
</tbody>
</table>

Table 3 Result of analysis of all images \( n = 102 \) for specificity, sensitivity, predictive negative value, predictive positive value of the automated system (AUDEX), TRUS, DRE and PSA

<table>
<thead>
<tr>
<th></th>
<th>AUDEX</th>
<th>TRUS</th>
<th>DRE</th>
<th>PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>49</td>
<td>51</td>
<td>46</td>
<td>24</td>
</tr>
<tr>
<td>Malignant</td>
<td>39</td>
<td>32</td>
<td>30</td>
<td>18</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.875</td>
<td>0.911</td>
<td>0.821</td>
<td>0.429</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.848</td>
<td>0.696</td>
<td>0.652</td>
<td>0.826</td>
</tr>
<tr>
<td>Predictive negative</td>
<td>0.875</td>
<td>0.785</td>
<td>0.742</td>
<td>0.750</td>
</tr>
<tr>
<td>Predictive positive</td>
<td>0.848</td>
<td>0.865</td>
<td>0.750</td>
<td>0.543</td>
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</tbody>
</table>

Discussion and conclusions

Digital rectal examination remains the basis for clinical staging of prostate cancer. The results of palpation correlate significantly with the pathological extent of the tumour and the prognosis of the patient. However, many prostate cancers are not palpable (stage A), and those that are palpable are frequently understaged [21]. Thus palpation does not adequately predict tumour volume or location.

TRUS, computed tomography (CT) and, in recent years, magnetic resonance imaging (MRI) and colour Doppler ultrasound have been increasingly used to image the prostate [22-26]. The driving force behind this development has been the ability to provide an image of prostate cancer [27,28].

CT is approximately 60% accurate in the detection of prostate cancer [22], while MRI has an advantage over CT in that the tumour involvement within the gland as well as outside the gland can be assessed [23]. Over the past few years, much interest has been directed towards defining both the value and the limitations of TRUS in evaluating patients with prostatic disease. TRUS offers a detailed view of the prostate, adding important information to that available from palpation alone [28,29]. Its ready availability and safety, its lack of radiation exposure, relative inexpensiveness, ease of repeated application and its capacity for guiding biopsy sites make it the imaging technique of choice.

The rapid evolution of TRUS has resulted in the widespread use of this diagnostic test to improve early detection. In the past few years, screening studies showed that TRUS detected approximately twice as many prostate cancers as DRE [29,30]. Simultaneously, new techniques for radical surgery and a better understanding of the biology of early prostate cancer have increased this interest in early diagnosis. Intense study of the echo characteristics of cancer has been fostered by the belief that ultrasonography may be able to detect cancer at an earlier and perhaps more curable stage (A and B).

Initially, many investigators believed that prostate cancer was typically hyperechoic [24,31]. The first recognition of the hypoechoic nature of prostate cancer came in 1983, when Frentzel-Beyne et al. reported that hypoechoic or heterogeneous areas near the prostatic capsule were suspicious for cancer [32]. Dihnhert et al. presented the results of scans of radical prostatectomy specimens in vitro and reported that 54% of the tumours were hypoechoic, 22% slightly hypoechoic and 24% isoechoic [33]. Rifkin et al. and Kelly et al. presented their experience with colour Doppler ultrasound scanning [25,26]. They concluded that colour Doppler ultrasound improves the positive predictive value of TRUS but appears to have little additional value over TRUS alone in the diagnosis of prostate cancer. Similar results were obtained in this department using colour Doppler ultrasound investigations.

The results of earlier studies of automated image analysis are promising [9-14]. For example, image analysis of liver tissue was used to emphasize texture changes and to measure, quantify and visualize non-visible parameters. These computer analyses are used to discriminate normal, fatty and cirrhotic liver tissue [34].

The results of this study are better than results reported before [3,4]. Standard investigations (DRE, PSA and TRUS) have a positive predictive value of approximately 40%, while computerized analysis alone had a positive predictive value of 84.8%. Three patients with
The detection of a part of a lesion is critical in establishing the presence of cancer.

In the study, the sensitivity and specificity reached 99.6% for the lesion detection in 12.6% of the patients. The lesion of the lesion was not detected in 10.7% and 0.9% of the patients.

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group, the results of the image analysis have a good specificity (87.5%) and sensitivity (84.8%) and these values have not been reached by any other means of diagnosis. The good results obtained by TRUS and DRE in the present study may be explained by the selection of patients. Moreover, the urologist involved in the TRUS examinations included the knowledge of the result of the DRE before TRUS in the interpretation of the TRUS image. The results of the computerized analysis system may be further improved by adding other data. At this stage of the project, only image analysis parameters were used for the characterization of tissue. No clinical data, such as DRE or PSA, were used. In future, these data will be included in an artificial intelligence system and combined with the image analysis results. This may lead to an improvement of the computerized analysis system. When we tested this system inflammatory histology was excluded. This may lead to a number of focal changes in the tissue and may be detected by the system as malignancy. Another study showed unequivocally that a difference can be made between benign and inflammatory histology [36]. A similar analysis needs to be performed for malignant and inflammatory histology.

Finally, the system was used only for the classification of the tissue in one particular place, namely the puncture location but may also be used for the classification of larger parts of an image. A small window can be placed over the image and the histology of the tissue, visible in this window, can be predicted. The image is then coloured according to the prediction of the system. An example of such an analysis of a part of the image is shown in Fig. 3. As this system is likely to prove reliable in tumour detection in the near future, the next stage will be for real time image analysis which will guide the biopsy needle exactly to the suspected lesion. Furthermore, small clinically undetectable prostate cancers might be diagnosed and changes in the size of these tumours followed more accurately.

In conclusion, the technical developments that have ensued from the earliest attempts at prostatic ultrasonography can now produce reliable, high definition ultrasonograms of the prostate. New areas of technical research such as computer analysis should further increase the scope of applications for transrectal ultrasonography. The first results of such an application are very promising. Computer analysis can support the urologist in the interpretation of ultrasonographic images, resulting in good specificity and sensitivity for malignancy. Moreover, this system seems capable of detecting prostate cancers that are not palpable and/or cannot be visualized.

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