Transrectal Colour Doppler Contrast Sonography in the Diagnosis of Local Recurrence after Radical Prostatectomy – Comparison with MRI

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Transrektale Farbdoppler-Kontrastmittel-Sonographie bei der Diagnose von Lokalrezidiven nach radikaler Prostatektomie – Vergleich mit MRT

Zusammenfassung

Ziel: Die Bestimmung der Wertigkeit der transrektalen Farb-Power-Doppler-Sonographie bei der Diagnose von Lokalrezidiven vor/nach der Anwendung von Kontrastmitteln bei Patienten mit ansteigenden PSA-Werten nach radikaler Prostatektomie sowie der Vergleich mit der MRT-Darstellung. **Material und Methoden:** 18 Patienten mit ansteigenden PSA-Werten nach Prostatektomie wurden untersucht mittels digitaler rektaler Palpation, Knochenszintigraphie, MRT, transrektaler Farb-Power-Doppler-Sonographie vor/nach Kontrastmittelapplikation und transrektaler ultraschallgezielter Biopsie. Sensitivität, Spezifität, Genauigkeit, positive und negative Vorhersagewerte wurden bestimmt. Die Ergebnisse wurden mittels des McNemar-2-stufigen Binominal-P-Tests korreliert. **Ergebnisse:** Die transrektale Farb-Power-Doppler-Sonographie mit und ohne Kontrastmittel und das Kontrastmittel-MRT ergaben Rezidive bei jeweils 6, 10 und 10 Patienten. Die Biopsie bestätigte ein Rezidiv bei 10 Patienten, erbrachte aber auch positive Ergebnisse bei 2 Patienten, die bei der rektalen Farb-Power-Doppler-Sonographie und im Kontrastmittel-MRT unauffällig waren. Die übrigen 6 Patienten waren sowohl bei den bildgebenden Verfahren als auch bei der Biopsie nach 30 Tagen weiterhin negativ. Die Werte der transrektalen B-Bild-Sonographie waren: Sensitivität 91,7%, Spezifität 66%, PPV 91,6%, NPV 40%. Die Werte der transrektalen Farb-Power-Doppler waren: Sensitivität 38,5%, Spezifität 85%, diagnostische Genauigkeit 50%, PPV 83,3%, NPV 33,3%. Die transrektale kontrastmittelgestützte Farb-Power-

Abstract

Objective: To assess the usefulness of colour power-Doppler transrectal sonography before/after contrast agent in the detection of local recurrence in patients with rising prostate-specific antigen values after radical prostatectomy and to compare with magnetic resonance imaging. **Materials and Methods:** 18 patients with rising prostate-specific antigen values after prostatectomy underwent digital rectal examination, bone scintigraphy, magnetic resonance imaging, transrectal colour power-Doppler sonography before/after contrast agent, and transrectal sonography-guided biopsy. Sensitivity, specificity, accuracy, positive and negative predictive values were calculated. Results were correlated using McNemar binomial 2-tailed P-test. **Results:** Baseline and contrast-enhanced transrectal colour power-Doppler sonography and contrast-enhanced magnetic resonance imaging identified recurrent disease in 6, 10 and 10 patients, respectively. Biopsy confirmed recurrence in 10 patients, but was positive also in 2 additional patients who were negative at contrast-enhanced transrectal colour power-Doppler sonography and contrast-enhanced magnetic resonance imaging. The remaining 6 patients were negative also at diagnostic imaging and biopsy after 30 days. Grey-scale transrectal sonography values were: sensitivity 91.7%, specificity 66%, PPV 91.6%, NPV 40%. Baseline colour power-Doppler transrectal sonography values were: sensitivity 38.5%, specificity 85%, diagnostic accuracy 50%, PPV 83.3%, NPV 33.3%. Contrast enhanced colour power-

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received: 16.8.2005 · **accepted:** 13.12.2005

bibliography
Ultraschall in Med 2006; 27: 146 – 151 © Georg Thieme Verlag KG Stuttgart · New York
DOI 10.1055/s-2006-926583 · Published online 2006
ISSN 0172-4614

Doppler-Sonographie und das MRT ergaben folgende Werte: Sensitivität 76,9%, Spezifität 100%, diagnostische Genauigkeit 83,3%, PPV 100%, NPV 62,5%. **Schlussfolgerung:** Die kontrastmittelgestützte transrektale Farb-Power-Doppler-Sonographie erhöht die Spezifität bei der Diagnose von Lokalrezidiven nach radikaler Prostatektomie. Das MRT erreicht eine entsprechende Genauigkeit. Die Biopsie bleibt der diagnostische Goldstandard. Die Anwendung bildgebender Verfahren könnte jedoch die Zahl der notwendigen Biopsien verringern.

Schlüsselwörter
Prostatakarzinom · Lokalrezidiv · transrektale Sonographie · MRT · Kontrastmittel · Biopsie

Doppler transrectal sonography and magnetic resonance imaging values were: sensitivity 76.9%, specificity 100%, diagnostic accuracy 83.3%, PPV 100%, NPV 62.5%. **Conclusion:** Contrast-enhanced transrectal colour power-Doppler sonography increases specificity in the detection of local recurrence after prostatectomy. Magnetic resonance imaging yields equivalent accuracy. Biopsy remains the diagnostic gold standard, but the use of imaging methods may reduce the number of biopsies.

Key words
Prostatic cancer · local recurrence · transrectal sonography · MR · contrast agent · biopsy

Introduction

Radical prostatectomy has become the most common surgical procedure for organ-confined prostate cancer [1, 2]. Some patients, however, still develop local or distant recurrence after surgery, in most cases heralded months to years before other evidence by rising prostate-specific antigen (PSA) values [3–5]. After radical prostatectomy, if all malignant and benign prostatic tissue has been removed, the serum concentration of PSA should become undetectable [3, 5, 6]. PSA measured after radical prostatectomy is therefore the most sensitive and specific tumour marker to monitor patients after surgery [6, 7]. Any level of detectable PSA after radical prostatectomy means tumour persistence, but this parameter provides no information concerning tumour site [3, 7, 8]. Probability of 10-year biochemical recurrence in patients who undergo surgery for prostate cancer stage T1 and T2 ranges from 27 to 53% [9, 10].

Early detection of persistent local or distant disease is important in order to choose the most adequate therapy [11]. Digital rectal examination (DRE) has proved to be inadequate in the evaluation of local tumour recurrence, and digitally guided biopsy of the vesico-urethral anastomosis (VUA) is not reliable, as post-operative fibrosis often mimics local recurrence [7]. Non-invasive imaging in men who have undergone radical prostatectomy and have rising PSA levels is therefore needed to determine the presence of local recurrence or systemic disease, as this affects treatment.

Sensitivity of traditional grey-scale transrectal (TR) sonography is high (95%) in the detection of small tumours, but specificity is poor [12–14]. Colour power-Doppler (CD-PD) used during TR sonographic examination increases specificity of grey-scale sonography [12, 15]. The use of microbubble ultrasound contrast agents (CA) enhances the CD signal and thereby the tumour vascularity [16], but so far there are no guidelines in the literature for the use of CA in prostatic pathologies [17]. Magnetic resonance (MR) imaging is also useful in the pre-operative detection and staging of lesions as well as for the detection of recurrent prostate carcinoma after radical prostatectomy [18–21].

The aim of this prospective study was to assess the role of CD-PD TR sonography before and after CA injection in the detection of local recurrence in patients who had undergone radical prostatectomy. The outcome was compared with results of contrast-enhanced MR imaging to establish if the combination of these two methods reached a higher accuracy. TR sonography-guided biopsy was considered as the gold standard.

Materials and methods

From January 2000 to April 2003, 80 patients underwent radical prostatectomy. Eighteen with altered PSA values were selected for this study (mean age 64 years/range 56–73). Selection criteria: first increase in PSA value after 1 year (cut-off 0.5 ng/ml Tandem R), postoperative PSA doubling time > 6 months, surgical specimen staged pT1-pT2, Gleason score 5 or 6, negative preoperative bone scintigraphy. All patients underwent digital rectal examination (DRE), bone scintigraphy, contrast-enhanced MR imaging, grey-scale TR sonography, baseline and contrast enhanced CD-PD TR sonography and TR sonography-guided biopsy. CD-PD TR sonographic examinations were performed on Esaote Biomedica AU 4/5 and Technos (Genoa, Italy), using a biplane, convex and linear transrectal 7.5 MHz probe. Intravenous ultrasound CA was injected as a bolus (Levovist-SHU-508, Schering), concentration 300 mg/ml, 10 cc. Grey-scale ultrasound examination was performed mainly to detect and map existing hypoechoic masses in pre-established sextants: 3 to the right and 3 to the left of the VUA. The dimension of the masses was measured and volume was calculated. CD-PD examination before and after injection of CA was performed to identify possible colour signals at the level of the targets identified at grey-scale sonography. Sensitivity scales were set to their greatest levels (lowest frame rate), and wall filters were adjusted to their lowest settings to maximise detection of low-velocity flow states. A colour signal was interpreted as a sign of recurrent disease, and absence of a colour signal as a sign of fibrosis.

MR examination was performed using a 1.5-T scanner (Magnetom Vision Plus, Siemens, Erlangen, Germany), a phased array coil and intravenous infusion of CA Gadolinium DTPA (Magnevist) at an infusion rate of 2 ml/sec to a total dose of 20 ml. Sagittal and axial T1 weighted spin-echo images (repetition time msec/echo time msec = 400–600/8–11) were obtained. Fat-saturated T2 weighted fast spin echo images were acquired; gadolinium-enhanced MR images of the prostatic bed were obtained. MR images of the prostatic bed and the adjacent muscles were analysed extending the study to the entire pelvis. Signal intensity relative to the levator

ani and internal obturator muscles was determined on the T1-weighted, T2-weighted, and gadolinium-enhanced sequence. Post-operative fibrosis or scar was presumed to have no enhancement and to be hypointense relative to the muscles on both T1- and T2-weighted images [17]. Focal pathology was considered if the lesion was isointense in T1-weighted images relative to the muscles, hyperintense on T2-weighted images and enhanced with gadolinium administration.

MR imaging was performed in consensus by two expert radiologists who analysed the images before and after bolus injection of CA. If a suspicious lesion was detected, the site was indicated according to the pre-established sextants: 3 to the right and 3 to the left of the VUA. Sonographic examination before and after CA injection was performed by a third radiologist who was blinded to the result of MR imaging. Before biopsy was performed, the results of all diagnostic procedures were compared.

Trans-perineal US-guided biopsy was performed using a 16-gauge needle and an automated biopsy device. A specimen was taken from the target identified by colour signal, and random specimens were taken from the peri-anastomotic tissues surrounding the VUA with a total of 6 or more specimens. If the result of the biopsy was negative, contrast-enhanced CD-PD TR sonography and biopsy (targeted and random) were repeated after 30 days.

Written informed consent was obtained from all patients, and the procedures followed were in accordance with the ethical standards of the Committee on Human Experimentation of this institution.

Statistical analysis: sensitivity, specificity and diagnostic accuracy of TR sonography and CD-PD TR sonography before and after CA injection were calculated. Results were correlated using McNemar binomial 2-tailed P test. Diagnostic accuracy of positive predictive value (PPV) and negative predictive value (NPV) were evaluated. The same analysis was performed on the results of MR imaging.

Results

The 18 selected patients presented a first increase in PSA value > 0.5 ng/ml after an average of 30 months from surgery (range 9 – 46 months) and post-operative doubling time of PSA > 6 months. In 4 patients, outcome of DRE was suspicious. In 13 patients out of 18 (72 %), grey-scale TR sonography detected 14 suspicious lesions: 6 on the right peri-anastomotic side (R 1 – 2); 4 on the left peri-anastomotic side (L 1 – 2); 1 on the right side (R 2 – 3); 1 on the left side (L 2 – 3); 1 patient presented 2 hypoechoic lesions in R 1 – 2. Mean volume was 8.54 cm^3 (range 2.88 cm^3 to 10.8 cm^3). CD-PD TR sonography showed colour signals in 6 patients. Contrast-enhanced CD-PD TR sonography displayed colour signals in 10 patients: the 6 patients positive at CD-PD, and 4 patients who were negative before CA. Of these 10 patients, 8 showed colour signals in the peri-anastomotic tissues surrounding the VUA, and 2 presented colour signals outside this area. The remaining 8 patients were negative at CD-PD TR sonography before and after CA injection as no colour signal was detected. Contrast-enhanced MR imaging confirmed the 10 cases of recurrence as shown by contrast-enhanced CD-PD TR sonography. In these patients, MR imaging detected hyperintense T2-weighted focal masses which were enhanced after gadolinium injection. In the 8 negative patients, MR imaging showed no distinct soft-tissue nodule or area of enhancement in the prostatic bed.

In the 10 positive patients, biopsy specimens confirmed recurrent disease at the level of the targets identified at contrast enhanced CD-PD TR sonography. Biopsy was also positive in 2 patients who were negative at CD-PD after CA injection and at contrast-enhanced MR imaging. Random biopsy specimens were positive in one patient whose targeted biopsy was positive (target identified at contrast-enhanced CD-PD TR sonography). Biopsy was negative in the 6 patients who presented no colour signal. They underwent further contrast-enhanced CD-PD TR sonography and biopsy after 30 days with a negative outcome.

Statistical analysis was carried out on the results of grey-scale TR sonography, CD-PD TR sonography before and after CA. Grey-scale TR sonography values were: sensitivity 91.7 %, specificity 66 %, PPV 91.6 %, NPV 40 %. Baseline CD-PD TR sonography values were: sensitivity 38.5 %, specificity 80 %, diagnostic accuracy 50 %, PPV 83.3 %, NPV 33.3 %. Contrast-enhanced CD-PD TR sonography values were: sensitivity 76.9 %, specificity 100 %, diagnostic accuracy 83.3 %, PPV 100 %, NPV 62.5 %. McNemar binomial 2-tailed P test showed $P = 0.039$ in the correlation between biopsy and baseline CD; $P = 0.250$ in the correlation between biopsy and contrast-enhanced CD; $P = 0.218$ in the correlation between CD before and after CA. Statistical analysis carried out on results of MR imaging findings yielded the same values.

Discussion

Radical prostatectomy currently represents the mainstay treatment for organ-confined prostate cancer, but some patients still develop recurrent disease months to years after surgery [3]. The first sign of recurrence is often a rising PSA value, which does not differentiate between local recurrence and systemic disease, although the likelihood of recurrence being local increases as the time interval to detection of PSA increases after the first year [20, 21]. Local recurrence and systemic disease require different treatment approaches: local radiotherapy and/or hormone therapy. It is therefore important to establish if the recurrent tumour is arising within the prostatic fossa [22].

In the present study, we investigated the role of grey-scale TR sonography and CD-PD TR sonography before and after CA administration in comparison with contrast-enhanced MR imaging in the detection of local recurrence. As our aim was to study cases of local recurrence, patients previously operated for prostate cancer and whose values indicated the presence of possible local recurrence were carefully selected according to criteria listed in the literature [20, 21].

PSA evaluation and TR sonography are essential in the early diagnosis of tumour recurrence as sensitivity and specificity of DRE are low [7, 11]. Sensitivity of grey-scale TR sonography is higher in the detection of "suspicious" areas, but specificity is low. Recurrent tumour and fibrosis present similar echogenicity; both are hypoechoic and therefore difficult to differentiate [7, 9]. Fibrosis is hypocellular, it contains collagen and has few acoustic interfaces and

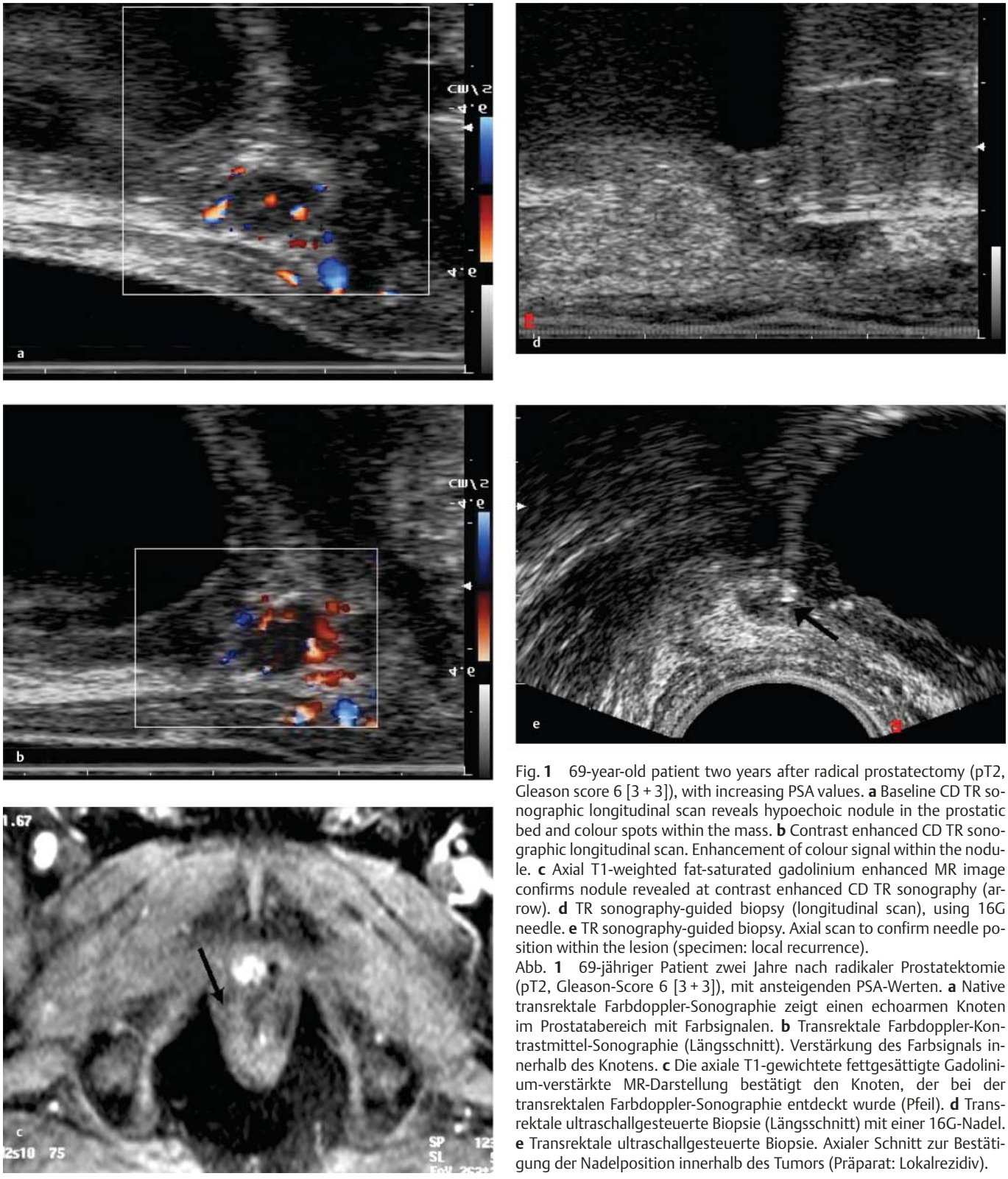
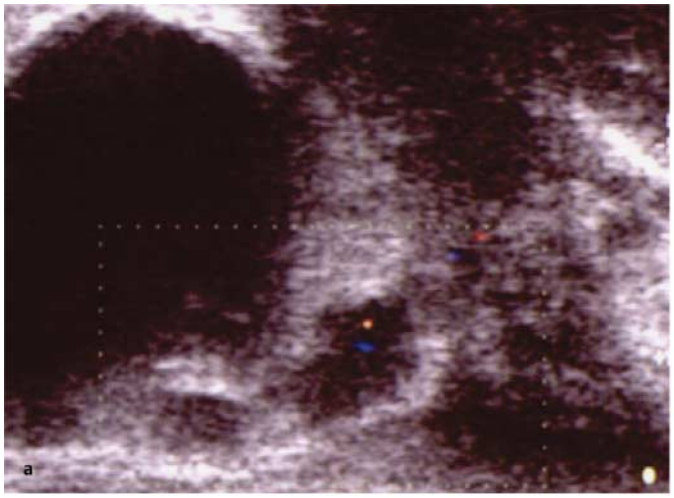
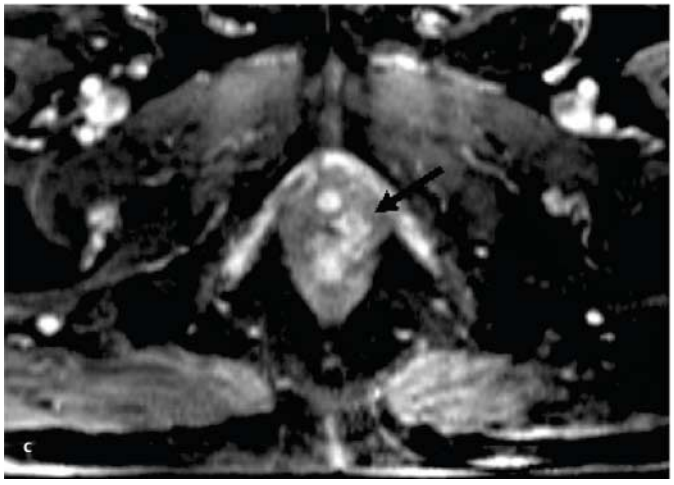


Fig. **1** 69-year-old patient two years after radical prostatectomy (pT2, Gleason score 6 [3 + 3]), with increasing PSA values. **a** Baseline CD TR sonographic longitudinal scan reveals hypoechoic nodule in the prostatic bed and colour spots within the mass. **b** Contrast enhanced CD TR sonographic longitudinal scan. Enhancement of colour signal within the nodule. **c** Axial T1-weighted fat-saturated gadolinium enhanced MR image confirms nodule revealed at contrast enhanced CD TR sonography (arrow). **d** TR sonography-guided biopsy (longitudinal scan), using 16G needle. **e** TR sonography-guided biopsy. Axial scan to confirm needle position within the lesion (specimen: local recurrence).
Abb. **1** 69-jähriger Patient zwei Jahre nach radikaler Prostatektomie (pT2, Gleason-Score 6 [3 + 3]), mit ansteigenden PSA-Werten. **a** Native transrektale Farbdoppler-Sonographie zeigt einen echoarmen Knoten im Prostatabereich mit Farbsignalen. **b** Transrektale Farbdoppler-Kontrastmittel-Sonographie (Längsschnitt). Verstärkung des Farbsignals innerhalb des Knotens. **c** Die axiale T1-gewichtete fettgesättigte Gadolinium-verstärkte MR-Darstellung bestätigt den Knoten, der bei der transrektalen Farbdoppler-Sonographie entdeckt wurde (Pfeil). **d** Transrektale ultraschallgesteuerte Biopsie (Längsschnitt) mit einer 16G-Nadel. **e** Transrektale ultraschallgesteuerte Biopsie. Axialer Schnitt zur Bestätigung der Nadelposition innerhalb des Tumors (Präparat: Lokalrezidiv).

is therefore hypoechoic like tumour tissue, which rarely appears isoechoic [9]. Vascularisation is therefore a differential diagnostic sign, since fibrous tissue has only minimal vascularity, thus showing an absent colour signal, whereas malignant recurrence is characterised by vascularisation within the mass.

In our study, grey-scale TR sonography identified solid hypoechoic areas suggesting possible neoplastic recurrence of various dimensions in 13 patients out of 18 showing an elevated sensitivity (91.7%), but a low specificity (66%). It should be pointed out that the present patient population was carefully selected with the aim to study local recurrence, thus resulting in a high concentration of lesions. In a larger, randomised patient population, both sensitivity and specificity of TRUS could be substantially reduced compared to the values achieved in this study. Baseline CD-PD TR sonography showed a rather poor sensitivity of 50% but a specificity





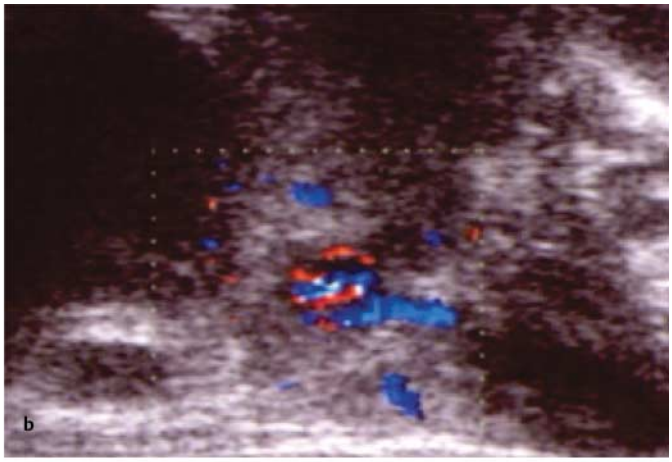


Fig. **2** 65-year-old patient, three years after radical prostatectomy (pT2, Gleason score 5 [3 + 2]) with rising PSA values: **a** Baseline CD TR sonographic longitudinal scan reveals 2 hypoechoic lesions. Small colour spot signals are present within the largest nodule. **b** Contrast enhanced CD TR sonographic longitudinal scan. Colour signal enhancement in the largest lesion. Note the absence of colour signals before and after contrast application in the smallest lesion. **c** Axial T1-weighted fat-saturated gadolinium enhanced MR image confirms nodule revealed at contrast enhanced CD TR sonography (arrow). Histological analysis showed local recurrence in the largest lesion; fibrosis in the smallest lesion.
Abb. **2** 65-jähriger Patient drei Jahre nach radikaler Prostatektomie (pT2, Gleason score 5 [3 + 2]) mit ansteigenden PSA –Werten. **a** Die native transrektale Farbdoppler-Sonographie(Längsschnitt) zeigt zwei echoarme Knoten. Im größeren Knoten sieht man kleine Farbsignale. **b** Transrektale Farbdoppler-Kontrastmittel-Sonographie (Längsschnitt). Verstärkung des Farbsignals innerhalb des größeren Knotens. Bemerkenswert ist die Abwesenheit von Farbsignalen im kleineren Knoten vor und nach Kontrastmittelapplikation. **c** Die axiale T1-gewichtete fettgesättigte Gadolinium-verstärkte MR-Darstellung bestätigt den Knoten, der bei der transrektalen Farbdoppler-Sonographie entdeckt wurde (Pfeil). Die Histologie ergab ein Lokalrezidiv im größeren Knoten sowie eine Fibrose im kleineren Knoten.

of 100%, as local tumour recurrence was correctly identified in 6 patients out of 18 (34%). The administration of CA increased CD-PD specificity in the differentiation between malignant and fibrous tissue. Contrast-enhanced CD-PD TR sonography thus confirmed colour signals in the 6 patients positive at baseline CD-PD TR sonography, and also identified colour signals in 4 patients whose baseline CD-PD was negative. Contrast-enhanced TR sonography thus increased sensitivity to 83%, achieving identification of recurrent tumours in 10 patients whose biopsy was positive. This shows that grey-scale TR sonography can detect the lesion, baseline CD-PD TR sonography can provide colour signals, if any, and CA can confirm or detect vascularity within the lesion (Fig. **1a–e**; Fig. **2a–c**). An ultrasound contrast agent of the first generation was used, essentially because the study started in 2000. However, this did not affect the outcome, as no quantitative evaluations or calculations of perfusion or transit time were performed, and only the presence or absence of enhancement was observed. The combination of these diagnostic methods increased PPV to 100%. NPV was poor (62.5%), because it is difficult to distinguish healthy from false negative patients as neither group presents colour signals. Biopsy, however, identified recurrence in 2 patients who were negative at all diagnostic procedures.

McNemar test was carried out and showed that contrast-enhanced CD-PD TR sonography is more accurate than baseline CD-PD TR sonography.

The 6 patients whose outcome was negative at all initial diagnostic procedures including biopsy, underwent further investigation after 30 days. This second series of examinations did not reveal suspicious lesions, and also biopsy was negative. The lack of bioptic proof of locally recurrent prostatic cancer, however, does not imply that no locally recurrent prostatic cancer is present. A false negative result may be caused by sampling error, and serial biopsies can be taken to reduce the error percentage [10]. In one of these 6 patients, distant metastases were in fact identified at a subsequent scintigraphic examination. In the remaining 5 patients, distant metastases cannot be excluded in spite of negative outcome also of the second scintigraphy, as most patients whose PSA values remain elevated over a long period eventually present positive scintigraphic results. These patients were considered as cases of persistent disease without evidence of tumour. They received hormonal therapy, which prevented further diagnostic verification [23].

In this study, MR imaging revealed soft tissue nodules in the prostatic bed in 10 patients; enhancement characteristics and signal intensity on T2-weighted images were distinct compared with the surrounding soft tissue and muscles. Contrast-enhanced MR imaging yielded results identical to those obtained with contrast-enhanced CD-PD TR sonography.

To date, management of patients with rising PSA values in spite of radical prostatectomy includes grey-scale TR sonography with the addition of CD-PD TR sonography to increase specificity. If CD-PD TR sonography outcome is negative, the examination should be continued using CA in order to increase the accuracy. MR imaging permits a more adequate visualisation of the entire pelvis and may be able to detect possible suspicious non-peri-anastomotic masses missed at sonography whose field of view is 6 – 8 cm. However, this issue has not been addressed in this study.

Contrast-enhanced CD-PD TR sonography seems to be a promising tool in the detection of local recurrence after radical prostatectomy, thus increasing sensitivity and specificity of CD-PD TR sonography. However, further studies on larger series are mandatory to confirm these encouraging results, possibly using second generation contrast media. Interestingly, contrast-enhanced MR imaging achieved the same results. To date, biopsy remains the diagnostic gold standard, but a correct use of imaging methods may reduce the number of biopsies, thus reserving them for particular cases.

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