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Computerized contrast angiosonography: a new diagnostic tool for the urologist?

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Objectives To evaluate the diagnostic potential of echo-enhanced ultrasonography (US) for depicting the vascularization pattern of renal cell carcinoma (RCC), and calculating the first-pass effect using harmonic imaging, against that obtained by triphasic helical computed tomography (CT).

Patients and methods Sixty patients with surgically confirmed RCC underwent US using B-mode and power Doppler methods with or without an intravenous microbubble echo-enhancing agent. After depicting and defining the tumour extent by B-mode US, the first-pass effect/enhancement by the echo-enhancing agent within the lesion, and that of a reference area of unaffected renal cortex, were recorded on-line by calculating the mean pixel intensity. Time-intensity curves, i.e. the rise time and gradient of both the suspected tumour and reference areas, were constructed.

Results Using B-mode US, the extent of all tumours was delineated (mean tumour size 3.8 cm, SD 0.6). After applying the microbubble agent all tumours were enhanced, whereas the perfusion was decreased (in 48%), increased (in 16%) or similar (in 36%) compared with the cortical reference area. Using the Hounsfield classification, these results correlated well with the hypo/hypervascularity shown on CT.

Conclusion Ultrasonography has considerable potential in diagnosing RCC, if combined with echo-enhancing methods, harmonic imaging and computer-based calculation of tumour vascularization. Dynamic US studies should provide a diagnostic yield similar to that of CT.

Keywords Ultrasonography, microbubble enhancement, vascularity, renal cell carcinoma, diagnosis

Introduction

Imaging techniques commonly used for diagnosing RCC include CT, MRI and ultrasonography (US). To date, CT has been the investigation of choice for staging patients with RCC, despite limitations in determining the extracapsular tumour extent (T2a–T3) and regional lymphadenopathy [1].

US is a widely used first-line modality for evaluating the kidney; it is noninvasive, portable and requires minimal patient preparation. Renal US can be used to estimate kidney size, determine the presence or absence of hydronephrosis and the presence and characteristics of any renal mass or cyst. The addition of colour-, and more recently, power-Doppler US methods has enhanced the diagnostic capability of renal US. Colour and power Doppler US have distinct but complementary uses, and knowledge of the advantages and limitations of each are essential for the proper application of these powerful methods.

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If a renal mass requires further evaluation, CT has two major advantages over US. First, by using contrast media, CT can be used to visualize tumour vascularity; a renal tumour is basically diagnosed by determining the presence or absence of contrast enhancement. Second, CT uses well-defined scanning variables to determine whether or not a lesion enhances; this can be objectively estimated using Hounsfield units (HU). US lacks such objective measures to define the type of echo structure and tissue density. Such quantitative or semi-quantitative variables would be useful (in addition to qualitative factors) but current ultrasound equipment does not provide them.

However, substantial progress in both echo-enhancing agents and computer technology has dramatically improved the diagnostic capabilities of US [2]. The use of echo-enhancers provides new avenues and these agents are expected to improve the conspicuity of lesions, resulting in an easier diagnosis [3]. Other potential features of these contrast agents are the possibility of evaluating their transit time through vessels, the speed of uptake and vascular ‘washout’.

Thus, using echo-enhancers could provide contrast enhancement to match that obtained with CT.

To match the second advantage of CT, i.e. objective scanning variables, a computer program was used to interpret the Doppler images, allowing a dynamic analysis like that used in angiography. This established the inflow and outflow curves, interpreting and quantifying the enhanced Doppler images within a defined region of interest (ROI).

Thus the purpose of the present pilot study was to develop a diagnostic tool for quantitatively analysing abnormal blood flow within various kidney lesions, compared with corresponding areas of normal renal parenchyma, using both echo-enhancing agents and advanced computer analysis.

Patients and methods

Between February 1998 and June 1999, 60 patients with a renal mass confirmed on CT underwent US, in a prospective study. The postoperative pathological findings showed RCC; 18 additional patients had renal cysts (mean diameter 3.5 cm, SD 0.5). The enhancement pattern in these benign lesions was also assessed. Using computerized analysis techniques, time-intensity curves were constructed after injecting the patient with an echo-enhancing agent (a suspension of semi-free microbubbles stabilized by palmitic acid in a galactose-water solution, Levovist or SHU 508 A, Schering AG, Berlin, Germany) [4]. The agent was delivered as an intravenous bolus of 7.5 mL (right antebrachial vein, injection time 7 s, 16 G plastic cannula) at a concentration of 300 mg/mL.

The patients were examined using an ultrasound scanner (HDI 5000, ATL, Bothwell, WA). To improve the signal/noise ratio for backscattered signals from microbubble material, second harmonic imaging was assessed by transmitting at 2.5 MHz and filtering the received signal at 5.0 MHz. All patients were examined by one physician experienced in renal US. The complete US study included a first scan with conventional B-mode US followed by a power Doppler evaluation of the suspicious region. The US probe was then placed to acquire an image plane containing a cross-section of the tumour at its maximum diameter, including previously identified vessels and areas of normal renal parenchyma. Holding the probe in that position, Levovist was administered after reducing the gain; power Doppler images were recorded on videotape, and analysed and interpreted off-line. The video data were digitized and transformed to individual frames at 3–6 Hz over 60–80 s. These frames were analysed with dedicated software (Quanticon, 3-D Echotech, Hallbergmoos, Germany and HDILab, ATL) by counting pixel intensity within a particular ROI (the renal lesion) compared with a reference area of unaffected renal cortex. The sum of these pixels was defined as a perfused area at that time in the sequence, allowing the construction of time-intensity curves for contrast enhancement after the application of the echo-enhancer. The enhancement plateau was determined at 25–45 s after injection; three different perfusion patterns could be defined. Compared with the enhancement plateau of the curve of the unaffected cortex, a plateau of $>20\%$ corresponded to a hypervascularized renal mass, one of $\pm 20\%$ defined similar vascularization, whereas one of $<20\%$ was defined as hypovascularization.

Results

Using B-mode US, the extent of all RCCs was delineated (mean tumour size 3.8 cm, SD 0.6). After applying Levovist all tumours enhanced, whereas the perfusion decreased (in 48%), increased (in 16%) or was similar (in 36%), compared with the cortical reference area (Table 1). Typical examples of time-intensity curves and the corresponding ROI and US images are shown in Figs 1–4. All figures show pixel intensity values that correlated well with the vascularization patterns determined using contrast-enhanced US. After a lag phase of 10–20 s there was an increase in the colour Doppler signals in all patients, reaching a plateau of enhancement. High and low amplitudes were caused by the heart beat; these could be modulated using an average filter (curves not shown). Movement artefacts are possible,

Table 1 Vascularization patterns on US compared with adjacent unaffected cortex in 78 patients (60 with RCC, 18 with renal cysts)

Variable	*Hypervascular*	*Similar*	*Hypovascular*	*Cyst*
No. of patients	10	17	33	18
% of 60 RCC	16	36	48	–
Mean (SD) lesion size, cm	2.8 (0.3)	4.2 (0.4)	4.1 (0.6)	3.1 (0.5)
Enhancement on CT mean (SD) HU	61.2 (11)	35.3 (8)	26.3 (9)	7.2 (2)

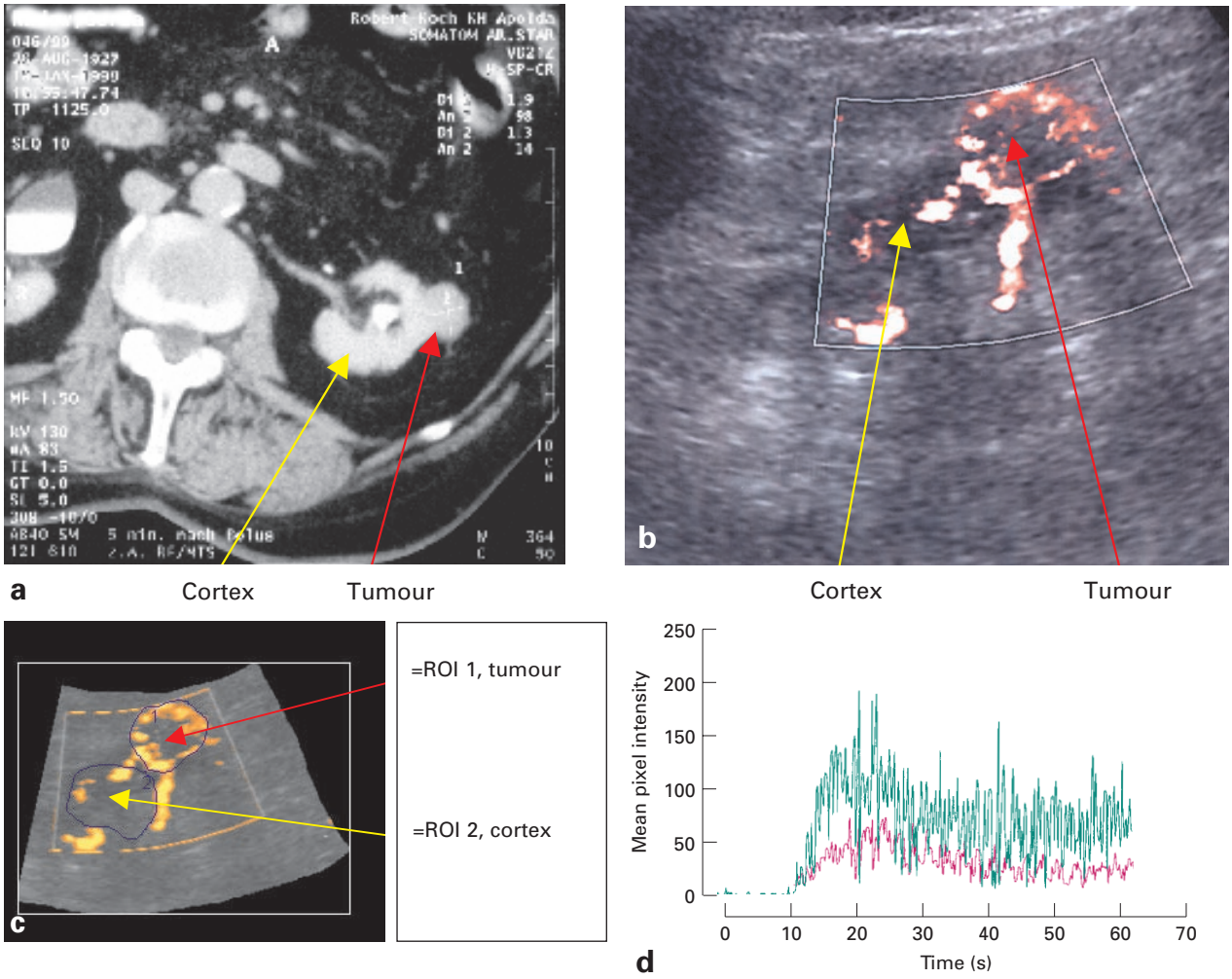

Fig. 1. A 72-year-old patient presenting with a hypervascularized left-sided renal tumour. There is visibly higher perfusion within the tumour than in the healthy renal cortex on contrast power Doppler US. **a,** CT of this patient also showed homogeneous high vascularization within the tumour. **b,** Computerized contrast angiosonography; scan number 111 ≈ 36 s after injection; the blue lines correspond to ROI 1 (tumour) and ROI 2 (normal appearing renal cortex). **c,** the view from which the time-intensity curves (**d**) are calculated, showing the onset of increased mean pixel intensity at 10–20 s after injection, followed by a plateau phase related to the mean perfusion of the area marked as the ROI (red) and renal cortex (green).

influencing the time-intensity curve particularly later in the recording, as patient compliance decreases.

Discussion

The capability of US has increased, through both improved software control and the introduction of intravenous microbubble agents. Injection of these additional scattering agents into the bloodstream results in an increase in the back-scatter amplitude by 20–30 dB [5], i.e. signals can be detected that would be below the noise limit in unenhanced examinations.

If the microbubbles are exposed to sufficiently high acoustic pressure within the ultrasound field they start to emit nonlinear sounds containing harmonic waves. The initial implementation of these resonance phenomena led to the development of ultrasound systems that transmit in the normal way at one frequency and receive echoes in harmonic mode only at double that frequency. The effects on colour Doppler US are dramatic, allowing the detection of flow signals in previously undetectable small vessels [6].

Applying this new technology and analysing the recorded signals showed enhancement effects in all the present kidneys. Compared with the unaffected renal cortex, three different patterns of perfusion were apparent that not only correlated with the determined HU on CT, but were recognisably those determined by clinical routine CT. All tumours enhanced on US (as they did on CT) but most tumours enhanced less than did the cortical reference area, as during growth the avascular

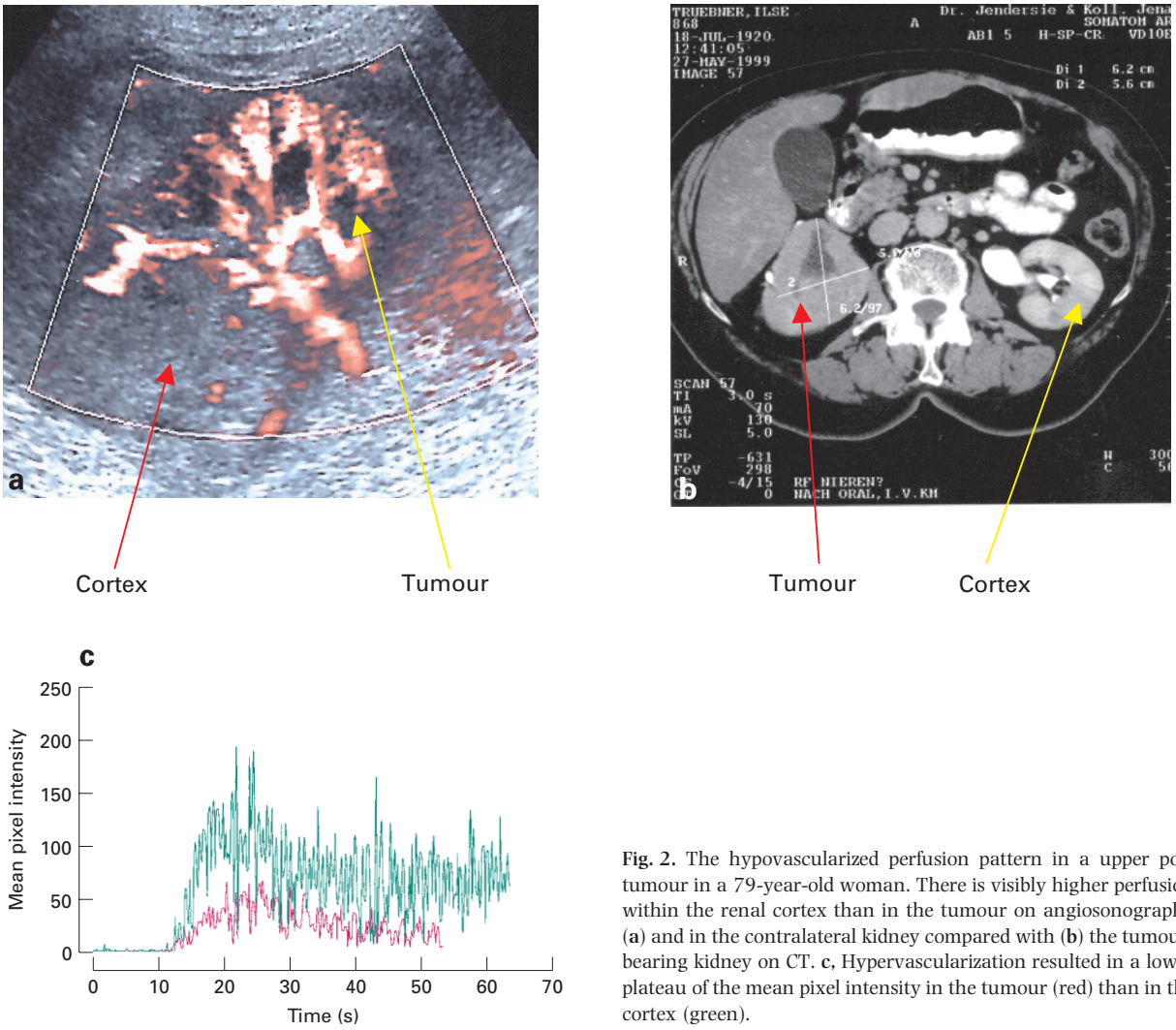

Fig. 2. The hypovascularized perfusion pattern in a upper pole tumour in a 79-year-old woman. There is visibly higher perfusion within the renal cortex than in the tumour on angiosonography (**a**) and in the contralateral kidney compared with (**b**) the tumour-bearing kidney on CT. **c**, Hypervascularization resulted in a lower plateau of the mean pixel intensity in the tumour (red) than in the cortex (green).

necrotic tumour centre increases, giving mean pixel intensity values below that of the renal cortex.

There are some limitations to US and computer analysis. As expected, none of the patients (mostly 50–60 years old) was able to hold their breath for 30–50 s, i.e. respiratory excursions of the kidney reduced the accuracy of counting of pixel intensity within the ROI. With increasing experience in using the method, the patients were allowed to breathe for up to 10 s after injection (lag phase), allowing more accurate recording during the enhancement phase. To optimize the examination it would be useful to develop computer software that analysed regular respiratory-related kidney movements before US started, thus making 'dynamic' respiratory-adjusted recordings possible.

Very small renal lesions (< 1–2 cm) were still difficult to detect. Even by scanning kidneys with power US to seek 'satellite' or small tumours, CT and especially MRI appear to be more sensitive. However, intraoperative US and other recently introduced and improved technology may help to visualize such tumours in the future; pulse-inversion techniques appear to be promising new tools.

Thus, using computed angiosonography, renal neovascularization becomes not only visible but also measurable. All renal tumours were visible on B-mode US but neovascularization, a characteristic of malignancy, is only detected using Doppler US. In some RCCs the signals are difficult to detect, either because the lesion is small (< 2–3 cm in the present study) or because the Doppler shifts are too small or too weak to be detected with current equipment; thus echo-enhancers are needed. However, there were visible Doppler shifts in 41 of the present 60 patients; this

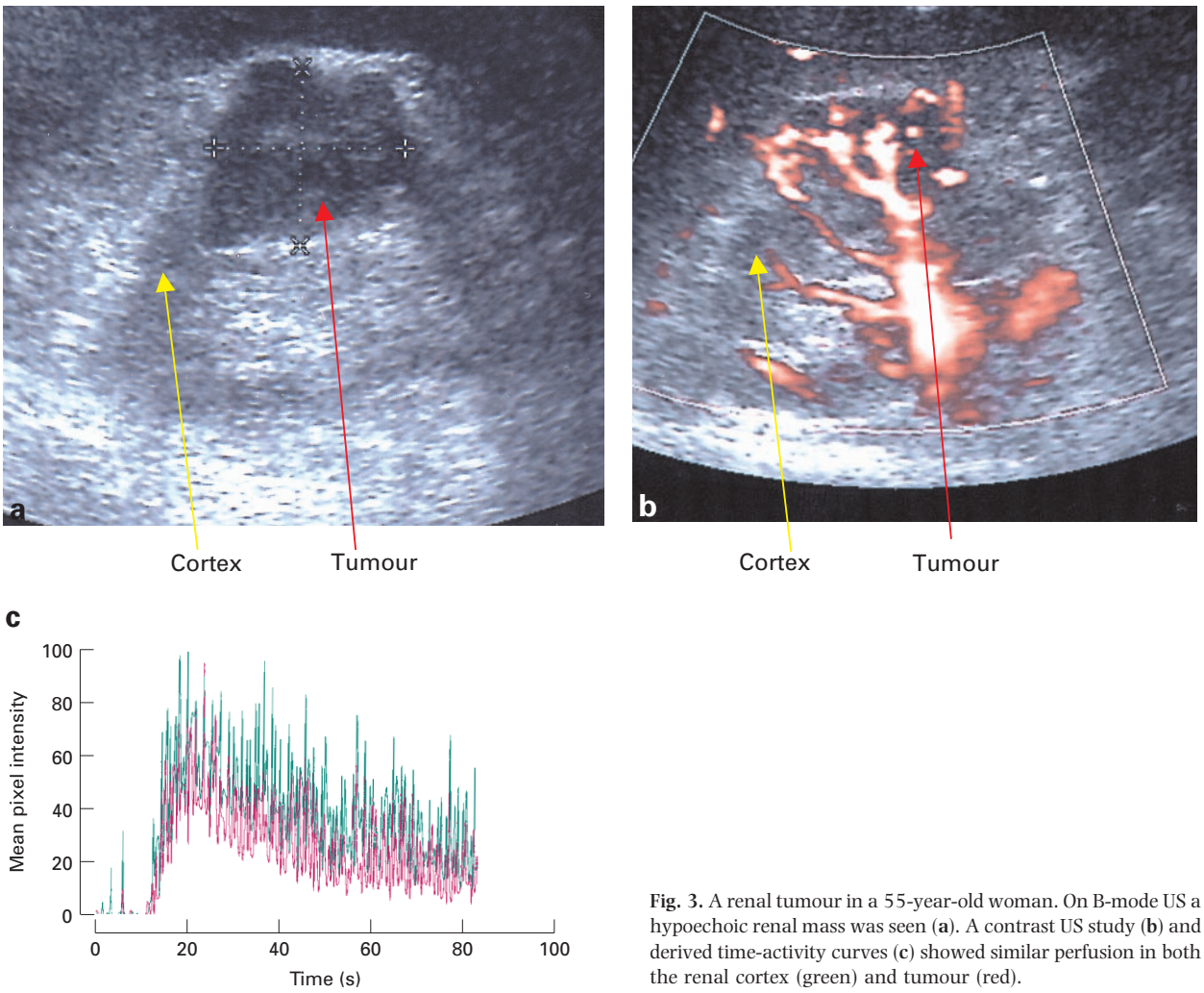

Fig. 3. A renal tumour in a 55-year-old woman. On B-mode US a hypoechoic renal mass was seen (**a**). A contrast US study (**b**) and derived time-activity curves (**c**) showed similar perfusion in both the renal cortex (green) and tumour (red).

was sufficient to diagnose a renal tumour and to exclude renal infarction or a thrombotic cyst, an important clinical conclusion.

As >90% of all kidney tumours are malignant and neither CT nor MRI can be used to safely diagnose oncocytoma (the most important benign renal tumour besides angiomyolipoma), US should be re-evaluated as a preoperative imaging method for patients presenting with renal tumours.

If further studies confirm the results of the present pilot study, angiosonography might be sufficient in the diagnosis of a patient awaiting radical nephrectomy, provided that there is a normal contralateral kidney and vena cava, a normal serum creatinine level and otherwise normal IVU. As echo-enhancers are not excreted in the renal pelvis normal renal function can only be evaluated indirectly. Thus, patients might be divided into three categories: (i) those presenting with a renal tumour and (on B-mode and Doppler US) a normal contralateral kidney and vena cava, normal serum creatinine level, ESR, urinary sediment and arterial blood pressure (subclinical glomerulonephritis), and contralateral ureteric jets into the bladder, who probably need no further diagnostic procedures; (ii) those in whom there is doubt (i.e. obese patients or patients with borderline serum creatinine levels), when isotope renography is recommended as an additional diagnostic procedure; (iii) those with microscopic or gross haematuria, when IVU is necessary.

The present method has the additional advantages of US as a cost-effective and widespread method that uses no ionizing radiation and harmless echo-enhancing agents. The results show the considerable potential of US in diagnosing RCC when combined with echo-enhancers, harmonic imaging and computer-based calculation of tumour vascularization.

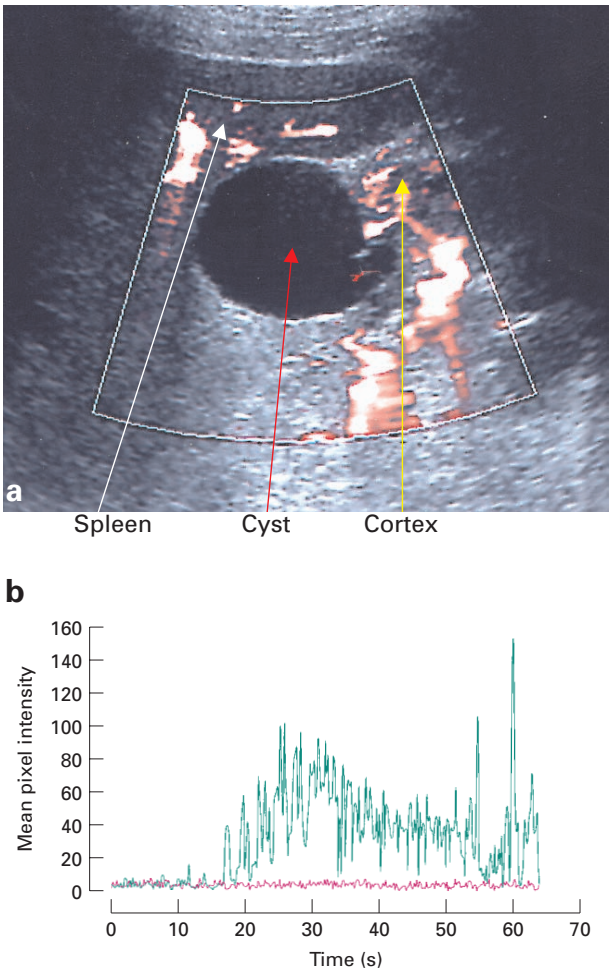

Fig. 4. A renal cyst in a man aged 47 years. **a,** No Doppler signals were detected within the cyst (in **b,** the mean pixel intensity was at baseline level, red) whereas there was contrast enhancement within the surrounding normal renal parenchyma (green).

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Abbreviations: **US**, ultrasonography; **HU**, hounsfield units; **ROI**, region of interest.