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Diagnostic Imaging

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Focal Liver Lesions

Detection, Characterization, Ablation

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Foreword by

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With 268 Figures in 727 Separate Illustrations, 83 in Color and 39 Tables

Springer

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Foreword

The radiological diagnosis and management of focal liver lesions is a common problem confronting many radiologists in their daily clinical activity.

Moreover, during recent years numerous new developments have taken place in the non-invasive diagnosis of focal liver lesions due to the rapid progress in the cross-sectional modalities: ultrasonography, computed tomography and magnetic resonance imaging.Parallel to these important diagnostic advances, several innovative techniques for the percutaneous radiological management of malignant focal liver lesions have been introduced in clinical practice.

This volume comprehensively covers all these new and fascinating radiological techniques both in the diagnostic and the therapeutic field and represents an excellent up-to-date review of our current knowledge on the radiological approach to focal liver lesions. The eminently readable text is complemented by numerous superb illustrations.

The editors are world-renowned experts in the field with a longstanding dedication to imaging of the liver and percutaneous treatment of malignant liver lesions, as proven by their highly praised previous scientific work, including handbooks, book chapters and numerous articles on liver radiology .The department of diagnostic and interventional radiology of the University of Pisa is internationally known for its fundamental and innovative research activities in liver imaging and ablation techniques.

The authors of the individual chapters were invited to participate because of their outstanding experience and major contributions to the radiological literature on the topic.

I would like to thank the editors and the authors and congratulate them most sincerely for their superb efforts which have resulted in this excellent volume, a much-needed comprehensive update of our knowledge of focal liver lesions .This book will be of great interest not only for general and gastrointestinal radiologists but also for abdominal surgeons and gastroenterologists. I am confident that it will meet the same success with the readers as the previous volumes published in this series.

Leuven

Albert L. Baert

Preface

Few fields of medicine have witnessed such impressive progress as the diagnosis and treatment of liver tumors. Advances in imaging technology, the development of novel contrast agents, and the introduction of optimized scanning protocols have greatly facilitated the non-invasive detection and characterization of focal liver lesions. Furthermore, image-guided techniques for percutaneous tumor ablation have become an accepted alternative treatment for patients with inoperable liver cancer.

This book provides a comprehensive and up-to-date overview of the role of diagnostic and interventional radiology in respect of liver tumors. The volume moves from background sections on methodology and segmental liver anatomy to the main sections on the diagnosis of benign and malignant liver lesions. An integrated approach, focused on the correlation of ultrasound, CT, and MR imaging findings, is presented. Finally, an exhaustive section describes the principles, methods, and results of percutaneous tumor ablation techniques.

The volume is the expression of the efforts of many distinguished experts from throughout the world. We are greatly indebted to them for their enthusiastic commitment and support. Also, we would like to thank most sincerely the Medical Radiology series editor, Professor Albert Baert, for his confidence and advice. We sincerely hope that the book fulfills the expectations of our colleagues – radiologists, clinicians, and surgeons – who are interested in this important and rapidly evolving field.

Pisa

Riccardo Lencioni
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David O. Cosgrove

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1.1 Introduction

Ultrasound is a tomographic imaging technique that can provide anatomical and functional images with high resolution and great flexibility at low cost (Kremkau 1997; McDicken 1991). Structural detail down to around a millimetre is available without the need for contrast agents (Fig. 1.1). The high intrinsic contrast is produced by the tissues' structure at a submillimetre level and is chiefly attributable to the differences in rigidity and density between fluids, watery tissue, connective tissue and fat. The tomograms are formed very rapidly, allowing real time imaging so that studies are quick and interactive. Immediate viewing of tissue motion is intrinsic to ultrasound imaging; examples include the effects of respiration or palpation and the direct visualisation of the position of a biopsy needle (Pederson et al. 1993). The tomograms can be taken in any plane, allowing optimal display of critical anatomy and pathology. Small, self-contained scanners can be made and these can be taken to the patient's bedside (Machi and Sigel 1996). No or minimal preparation is required so that the procedure is well tolerated, the only practical problem for the liver being abdominal tenderness that may make probe contact painful. The hazards of ionising radiation do not exist and the acoustic powers used in diagnosis appear to be completely safe, though there are emerging concerns over the possibility that its interaction with the microbubbles used as contrast agents may produce free radicals that could be injurious.

The flexibility of ultrasound technique has led to several specialised applications. Small transducers can be mounted on an endoscope with the advantage that higher quality images are obtained because higher frequency ultrasound can be used (Bezzi et al. 1998). Endoscopic ultrasound is, of course, somewhat invasive and only tissues with a few centimetres of the gut wall are accessible. The same is true of intravascular ultrasound. Small transducers suitable for use in the operating theatre offer the benefit of higher resolution as well as of guiding needle placement for biopsies or cannulation of small portal vein branches while the development of transducers small enough to fit into standard laparoscopic instruments extends these advantages to minimally invasive surgery (Herman 1996; Barbot et al. 1997; Klotter et al. 1986).

Doppler has extended the role of ultrasound in the diagnosis and management of vascular pathology of the liver and is now an indispensable component of hepatic imaging (Grant 1992). It is particularly helpful in liver transplants, both pre-operatively [to establish portal vein (PV) and caval patency] and post-operatively (for the PV and hepatic artery) and in the Budd Chiari syndrome. In cirrhosis Doppler can establish the patency of the PV and of many types of shunts. For spectral (pulsed) Doppler, a sensitive gate is positioned over a vessel and the temporal pattern of flow analysed to display its velocity spectrum; volume flow can also be estimated, though with less precision (Fig. 1.2). In colour Doppler, a vascular map is presented as an overlay on the grey scale scan to provide a form of angiogram that gives a non-invasive picture of vascular anatomy (Fig. 1.3)

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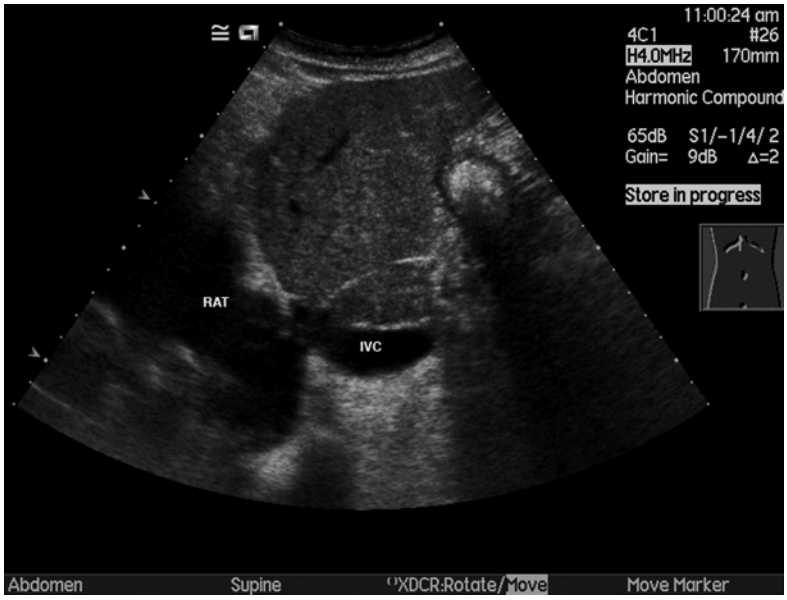


Fig. 1.1. In a sagittal section through the left liver, the caudate lobe (segment 1) can be seen posterior to segments 2 and 3. Note the fine stippled texture of the liver's parenchyma. *IVC*, inferior vena cava; *RAT*, right atrium

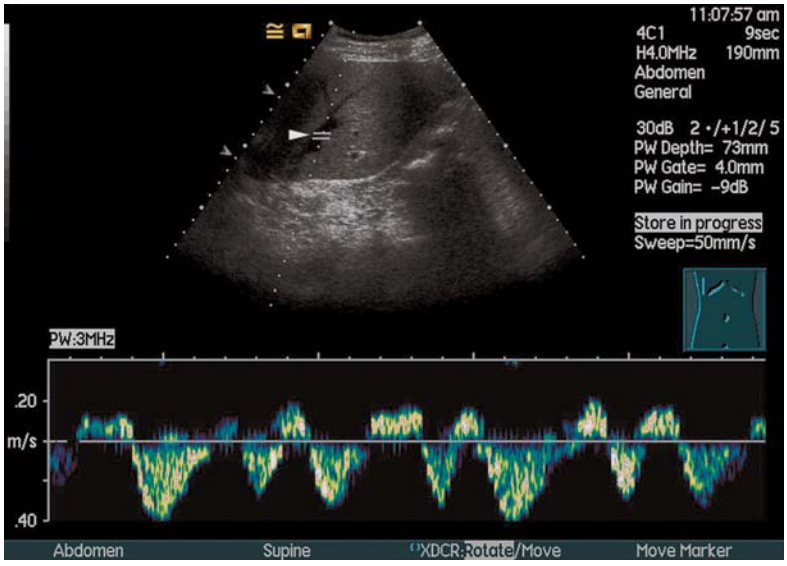


Fig. 1.2. In this spectral Doppler tracing the sensitive gate has been placed over the middle hepatic vein (*arrowhead*) and the trace shows the normal pattern where the predominant flow towards the heart (shown below the line to indicate flow away from the transducer) is interrupted by reverse flow as blood is returned to the liver in cardiac systole

(Foley and Lawson 1992). Though the haemodynamic information is limited (only mean velocity or, in power Doppler, the number of moving red cells, is presented) the anatomical information gained is an extremely valuable addition to imaging. Colour and spectral Doppler are complementary, the former providing images, the latter functional information on blood flow.

However, this description omits some important limitations to the uses of ultrasound. Image quality is affected by body habitus, slim patients giving the best images because resolution deteriorates with depth as inevitable result of the greater attenuation of higher frequencies; for this reason ultrasound is particularly valuable in paediatrics. This problem has been reduced by the development of non-linear (tissue harmonic) imaging and by the increasing bandwidth of newer transducers so that the most appropriate frequency can be selected electronically (Kono et al. 1997). Bone and gas are impenetrable; in practical terms this is only an occasional problem for the liver because the intercostal spaces allow adequate access in almost all patients if the subcostal route is difficult to use.

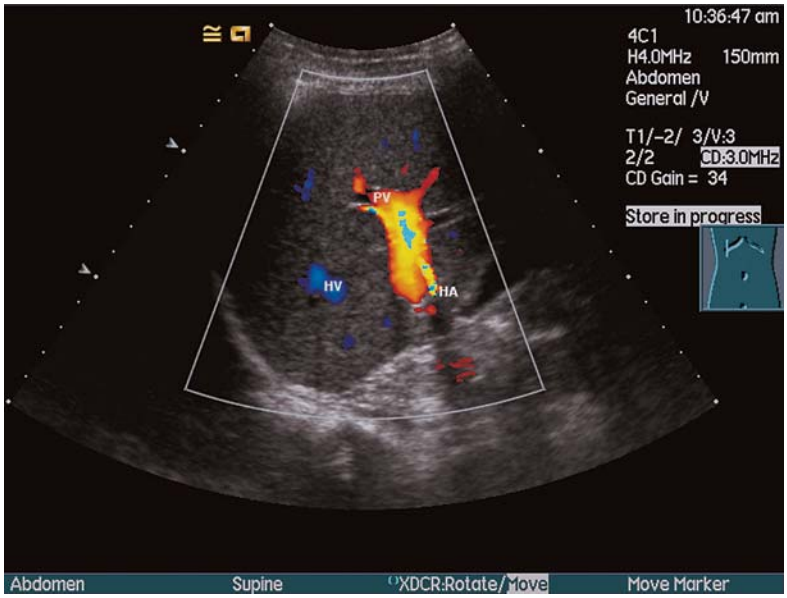


Fig. 1.3. In colour Doppler, flow towards the transducer is coded in reddish tints so that both the portal vein and the hepatic artery have similar colours. Hepatic vein branches are seen in blue. *HA*, hepatic artery; *HV*, hepatic vein; *PV*, portal vein

The small field of view of a real time ultrasound image makes the scan difficult to review and can also lead to difficulty in repeating the same tomogram for follow-up. It makes explanation to referring physicians and surgeons difficult; understandably, they find the more complete tomographic images of CT or MR more believable. Extended field of view displays have been introduced to minimise this limitation. Another interesting approach is to superimpose the real time ultrasound images on the appropriate slice derived from a previous 3D CT scan of the patient using. This virtual image co-registration is very promising for interventional applications such as tumour ablation because it combines the anatomical display of the CT with the interactiveness of ultrasound (Bryant et al. 2004).

The interactive nature of ultrasound renders it very operator dependent: a skilled and motivated operator can produce consistently good results but lack of experience and working without essential clinical information can severely devalue a study.

Recent technological developments have reduced some of these limitations. Tissue harmonic imaging, by selecting returning echoes at double the transmitted signals (these are generated as the ultrasound pulse propagates through the tissue, rather like the breaking of a wave as it approaches the shore), reduces the artefacts from heavily built patients and gives cleaner images. Intravascular contrast agents in the form of microbubbles not only rescues Doppler studies that would otherwise have been failures but also opens out important new diagnostic possibilities. Application of sophisticated transducer technologies and of powerful computer systems has resulted in better image and particularly Doppler quality.

Thus ultrasound is continuing to develop rapidly and its progress shows no sign of slowing down.

1.2 Technology

Ultrasound is a high frequency, mechanical vibration consisting of alternate waves of compression and rarefaction (Kremkau 1997; McDicken 1991). The waves are generated by piezo-electric crystals shaped into a transducer which focuses the ultrasound waves into a beam. Commonly used frequencies for the liver are 5.0 or 3.5 MHz corresponding to wavelengths in tissue of 0.3 and 0.5 mm respectively, and this is the theoretical best spatial resolution that can be achieved.

The small proportion of the ultrasound that is absorbed by the tissue disappears as heat. The remainder is reflected as the beam crosses between tissues of different acoustic properties, known as acoustic impedance, a complex of tissue density and rigidity. Both these components are familiar in that they are palpable; however, the ultrasound pulse responds to tissue structure in the sub-millimetre range. The smallest structure that can be resolved in practice depends on the contrast in reflectivity: well-defined structures such as ducts can be traced down to a millimetre or so

in calibre but low contrast lesions such as liver metastases must be much larger, perhaps 5–10 mm in diameter before they can be detected confidently.

The portion of the reflected sound beam that returns to the transducer is used to form the image. The depth (range) of a reflecting interface is calculated from the delay between the sending of the pulse and the detection of the returning echo, and its direction from the angle at which the transducer faces; this is the same "pulse-echo" method used in Radar and Sonar. The velocity of ultrasound in different tissues is not quite constant but varies so little that the minor errors in calculating the depth of reflecting surfaces can be ignored.

The strength of the echoes is proportional to the change in acoustic impedance at the interface. At risk of oversimplifying a complex phenomenon, the acoustic impedance correlates with tissue rigidity. In the body this ranges from gases at the one extreme, through fluids and soft tissue, to bone and calcified tissue at the other. For soft tissues, the collagen content is usually the main contributor and this is found in a condensed form in fascia and in a diffuse form as the micro-skeleton of the parenchyma that surrounds blood vessels. It is probably the characteristic vascular pattern as reflected in the ultrasound image that lends tissue-specific textures to sonograms. Fatty tissue is strongly echogenic because of the abundant lipid/watery interfaces at cellular or lobular level.

Real time scanners rapidly sweep the beam through the volume of tissue to be examined: the scan is repeated 10–30 times a second to give a moving image. The sweep may be angled from a point on the skin to form a triangular image in sector scanning. This method provides good access through small windows and so is particularly useful for intercostal scans of the liver. However, the triangular field of view does not display superficial structures well and linear arrays are more convenient in this respect. Here the ultrasound beam is swept electronically along a block of piezo-electric material some 2 cm wide and 5–10 cm long. Curved linear arrays combine some of the advantages of the two geometries and is used for all the ultrasound images shown in this chapter.

For Doppler a different type of signal processing is used to assess the movement of blood. By comparing the signals from a series of perhaps ten pulses sent along the same direction, changes caused by a moving structure (typically red blood cells) can be extracted. The slower the flow the more pulses must be transmitted and this, as well as the fact that solid tissues also move, sets a limit to the sensitivity of Doppler. The display shows motion along the line of the beam and so a correction for flow in oblique directions needs to be applied for flow velocity measurements. The spectrum from a pulsed Doppler scanner is displayed as a chart of (blood) velocity against time, in which flow towards the transducer is shown above the zero line. The amount of blood flowing at any particular point is indicated by the degree of whitening of the trace. Simultaneous imaging and Doppler (known as "duplex scanning", from their operation in two modes) allows the Doppler sensitive gate to be positioned precisely over the vessel of interest (Fig. 1.2).

In colour Doppler, similar processing is applied across the image. The colour Doppler signals are shown as an overlay conventionally coded in shades of red for flow towards, and blue for flow away from the transducer (Fig. 1.3). Another way to display flow information depicts only the Doppler signal intensity as a power Doppler scan. It has higher sensitivity than frequency-based colour Doppler but lacks directional information and so is more useful for the small vessels, for example, in tumours, than for the portal vein where flow direction is important.

Ultrasound guided biopsies make use of the real-time interactiveness of ultrasound (Chuah 2000). It may be used to plan the biopsy by marking the appropriate skin site for puncture; this is useful for simple procedures such as paracentesis where the main value of ultrasound is to check that loops of bowel in the ascites will not be punctured. For biopsy guidance two general approaches are the freehand and needle-guided methods. The former is simpler in that any transducer can be used. The needle site and path are chosen and the needle (or its tip) is monitored continuously as it is advanced into the lesion. Keeping the needle path in view requires a high degree of hand/eye co-ordination and is not feasible for small or deep lesions where the needle guide approach is more reliable. For this, an attachment to the probe with a needle channel constrains the needle along a path that runs diagonally across the scan area; its line is indicated on screen and, once this has been positioned over the lesion, the needle should pass in the correct direction.

To make a scan the transducer is contacted to the skin using a coupling gel, and the examination consists of moving the probe gently across the surface of the abdomen. For the liver, subcostal views in transverse and longitudinal directions are convenient and access may be improved if the patient holds a deep breath. No preparation is needed for liver scans but the gallbladder is easier to assess when distended in the fasting state.

For Doppler the main constraint is the fact that the signals are angle dependant, being maximal when flow is in the direction of the ultrasound beam and falling off with a cosine function to zero when the flow is at right angles to the beam. Thus, choice of the scanning angle is critical to obtaining good Doppler signals and avoiding misdiagnosis of absence of flow (Parvey et al. 1989). For quantitative velocity and volume flow measurements the beam-to-vessel angle must be measured; scanners are equipped with appropriate calculation packages to transform the Doppler shift into true linear velocity and to calculate the mean velocity from the spectrum of the velocities in the Doppler gate.

1.3 Microbubble Contrast Agents

Microbubbles represent a new class of contrast agent whose effects depend on the compressibility of gasses which is markedly different from the near-incompressibility of tissue (Goldberg 1997; Stride and Saffari 2003; Dawson et al. 1999). This difference can be exploited using multipulse sequences that cancel tissue signals and emphasise those from the microbubbles. As well as displaying major vessels, microbubbles within the microvasculature can be detected because these methods do not depend on microbubble flow but merely on their presence. In practice these specific modes have found major clinical application in the liver for detecting and characterising focal lesions.

Microbubbles are also ideal tracers because of the small injected volumes and this has been exploited in the liver to identify conditions characterised by arteriovenous shunting such as cirrhosis and metastases: an early hepatic vein transit time indicates a haemodynamic abnormality (Blomley et al. 1998). The dynamics of the wash-in and wash-out phases following a bolus injection can be calculated and used to form functional images which are truly quantitative (Eckersley et al. 1998).

1.3.1 Principles

The microbubbles used as ultrasound contrast agents are designed to be smaller than 7 μm in diameter so that they can cross capillary beds. These agents flood the blood pool after iv injection and are confined to the vascular compartment (unless there is ongoing bleeding). Both the gas they contain (usually air or a perfluoro compound) and the stabilising shell (denatured albumin, surfactants or phospholipids) are critical to their effectiveness as contrast agents and to rendering them sufficiently stable that they survive for several minutes after injection. The first widely used agent, Levovist (Schering, Berlin), is made of galactose microcrystals whose surfaces provide nidation sites on which air bubbles form when they are suspended in water; these microbubbles are then stabilised by a trace of the surfactant palmitic acid. A widely used albumen coated agent, Optison (GE-Amersham, UK), is filled with perfluoropropane, while a family of perfluoro gas-containing agents such as SonoVue (Bracco, Milan) and perflutren (Definity, Bristol, Meyers, Squibb, Billerica, NJ) that use phospholipids as the membrane are becoming important in clinical practice.

1.3.2 Interactions of Microbubbles with Ultrasound Waves

The change in density at the surface of a bubble in plasma forms a major impedance mismatch and the strong echoes this produces is exploited in the uses of microbubbles to improve Doppler studies, so-called Doppler rescue.

However, more specific responses of microbubbles to ultrasound arise because microbubbles undergo pulsatile contraction and expansion in the pressure changes of the ultrasound field (Mine 1998). All oscillating systems have a resonance frequency at which they vibrate most readily. For clinical microbubbles this turns out to correspond to the frequencies typically used in diagnostic ultrasound (2–10 MHz) and this is why they are so intensely reflective. These oscillations are symmetrical (i.e. their behaviour is "linear") at low ultrasound powers so that the frequency of the scattered signals is the same as the transmitted pulse. However, microbubbles resist compression more strongly than expansion so that, as the acoustic power is increased, the expansion and contraction phases become unequal and in this "non-linear" mode the returning signals contain multiples of the transmitted frequency (harmonics). At still higher powers (though within accepted limits for diagnostic imaging), highly non-linear behaviour occurs and the microbubbles may be disrupted and disappear from the sound field.

These harmonics can be detected by tuning the scanner's receiver circuitry to the second harmonic at double the transmitted frequency so that the harmonics can be separated from the fundamental signals. However, tissues also produce harmonics, especially when higher acoustic powers are used, and distinguishing between them is challenging; in practice in many of the simple contrast modes available, the two signals are inextricably mixed together.

Separating tissue from microbubble harmonics completely has been achieved in two ways. The high MI approach was the first to be discovered (Burns et al. 1995). The microbubbles are deliberately disrupted and visualised using colour Doppler or variations of it. The sudden disappearance of a signal from its previous location (loss of correlation between sequential echoes) is detected as a major Doppler shift and is registered as colour signals. Known as stimulated acoustic emission (SAE), it is particularly useful with contrast agents that show liver tropism in the late phase a few minutes after injection such as Levovist. Because it highlights the normal liver and spleen, lesions that do not contain functioning tissue, such as malignancies, are shown as colour voids. It is a very sensitive method and shows the microbubble signature exclusively in the colour layer overlain over the conventional grey scale image. However, the contrast agent is destroyed rapidly so real time scanning cannot be used, and a rather clumsy sweep-and-review approach has had to be been developed.

The alternative approach relies on the property of newer microbubbles, particularly those with phospholipid shells, to produce harmonics at much lower acoustic powers than are necessary to generate tissue harmonics (Burns 1996; Burns et al. 2000). Thus, when very low acoustic powers are used, the harmonics derive exclusively from microbubbles so that they can be separated from all tissue signals.

The phase inversion mode (PIM) was the first of these modes and was developed to avoid frequency filtering with which the narrower bandwidth degrades spatial resolution. In the PIM, a pair of pulses is sent along each scan line, the second being inverted in phase from the first. The returning echoes from the pair are summed so that the linear echoes cancel because they are out of phase, leaving only the non-linear components, mainly the second harmonic. PIM gives excellent quality images in both vascular and late phases. In its initial implementation, the PIM used a high MI and therefore tissue harmonics contaminated the microbubble signals. At the low powers needed to avoid tissue harmonics the image tends to become noisy and methods to minimise this have been developed. One approach is to send a stream of pulses with alternating phase and use colour Doppler circuitry to pick out the harmonics; essentially this method (known as power pulse inversion, PPI, and implemented on the Philips HDI 5000) exploits the high sensitivity of Doppler to overcome the signal-to-noise limitation. It has the advantage of displaying the microbubble image in the colour plane with the tissue image as a grey scale underlayer, in the same way as colour Doppler and allows either image to be viewed separately.

Another approach also uses a series of pulses, typically three per line, but here the amplitude of the pulses is changed as well as the phase; this preserves more of the non-linear content of the received signals and thus improves sensitivity. Implemented as contrast pulse sequences (CPS, Siemens Sequoia), the harmonics are displayed in a colour tint over the B-mode picture or as a split screen so that both can be viewed as required. In another approach the direction of flow in larger vessels is detected with low MI Doppler, while slow moving and stationary microbubbles are detected with a phase inversion sequence and depicted in green. This combined mode, known as 'vascular recognition imaging' (Toshiba Aplio), also allows the microbubble signature to be displayed separately from or combined with the B-mode and provides additional information on the flow direction in larger vessels.

All of these modes allow simultaneous display of the microbubble and tissue images. They operate at very low transmit powers and, as well as avoiding excitation of tissue harmonics, this has the important advantage that bubble destruction is minimised so that scanning can be in real time which makes contrast studies much easier to perform since no special scanning techniques are required.

1.3.3 Safety of Microbubbles

The safety of ultrasound contrast agents must be considered under two categories, the agents themselves and the effects of their interaction with the ultrasound beam (ter Haar 1999). The constituents of microbubble contrast agents have been carefully chosen to be inert with biocompatible membranes and gases that are either metabolised (oxygen in air-filled microbubbles) or breathed out (nitrogen, perfluorocarbons and sulphur hexafluoride) and are non-toxic. No toxic effects have been attributed to their compo-

nents. However, they are a form of particle and there is the possibility that they embolize, blocking microvessels though any blockage is likely to be transient since they dissolve within a few minutes of injection. Nevertheless, the product characteristics summary usually recommends caution in patients with severe heart failure or pulmonary hypertension. A well recognised though uncommon adverse event after injection of many microbubble agents is low backache; it has been suggested that this arises from microbubble emboli, either in the kidneys or in bone marrow. Some are hypertonic when reconstituted and this can cause pain at the site of injection.

Much more important is the possibility of harm arising from the interactions of ultrasound with the microbubbles. This may be mechanical or chemical. Microbubbles can expand to twice their resting diameter during the low pressure phase of the ultrasound wave and this has been shown to rupture capillaries in animal microscopy studies. While capillary rupture is a normal event (coughing and running usually rupture lung and foot capillaries), the possibility that this might cause permanent damage in some tissues such as the brain cannot be excluded. During the rebound from their expansion, microbubbles may collapse and fragment and in this phase very high temperatures can be reached. Though the heating is extremely short lived, surrounding molecules can be altered to release highly active free radicals such as atomic oxygen and ozone. These reactive species can damage macromolecules such as RNA and DNA. Free radicals are produced naturally by chemical and nuclear processes such as cosmic rays and cells are equipped with mechanisms that rapidly neutralise them. It is not clear whether free radical formation from microbubbles is actually harmful or not.

Sensible precautions suggest that the lowest dose and the lowest transmit powers consistent with the need to make a diagnosis – the "as low as reasonably attainable" (ALARA) principle – should be used.

1.4 Normal Appearance

The uniform stippled liver texture is interrupted by vessels which help define its segmental anatomy (Fig. 1.1) (Couinaud 1957). The hepatic veins, with their thin walls, appear as branching, tubular "defects" converging to the upper IVC. The portal tracts have strongly reflective walls from the associated vessels and fibrous tissue(Wachsberg et al. 1997). The left portal vein curves anteriorly from the main portal vein to supply the more anteriorly situated left liver. The liver vessels are clearly displayed by colour Doppler using conventional colour coding, normal hepatopetal flow is shown in red (Fig. 1.3). The accompanying artery is seen as a narrow red line lying anteriorly (Lafortune and Patriquin 1999). On spectral Doppler the portal vein has continuous flow with a peak velocity of some 15 cm/s while fasting; this can increase greatly in the postabsorptive state. The hepatic veins appear as blue bands on colour Doppler because their flow is away from the transducer. On spectral Doppler their flow pattern is complex being predominantly towards the IVC but reversed at each atrial systole (Fig. 1.2). This is because the IVC communicates directly with the right atrium, so that in systole blood is pumped retrogradely into the cava and hepatic veins.

1.5 Focal Lesions

A wide variety of focal liver lesions can be diagnosed by ultrasound, notably cysts, for which it is the most specific and sensitive test (Gaines and Sampson 1989). They are seen as echo-free spherical spaces with thin, smooth walls and a characteristic band of brighter liver distally, caused by the lower attenuation of ultrasound by their fluid compared to the liver (Fig. 1.4) (Bryant et al. 2004). The same appearance characterises the individual cysts of dominant polycystic disease except that they may be very numerous (Kuni et al. 1978). The lesions themselves and the heterogeneous liver texture that results from the numerous bands of increased sound transmission make the detection of co-existent liver disease difficult or impossible. Similarly, haemorrhage into a cyst or superinfection are not usually detectable with ultrasound.

Hydatid cysts have a variety of appearances depending on the condition of their contents, but consistently have a prominent capsule that is lacking around simple cysts (Haddad et al. 2001). In endemic countries, ultrasound guided aspiration (perhaps with injection of a sclerosant) is widely used for symptomatic control with good safety (Filice and Brunetti 1997). Abscesses are typically seen as shaggy-walled cavities that are often multiple (Moazam and Nazir 1998; N'Gbesso and Keita 1997; Dewbury et al. 1980). On Doppler the hyper-

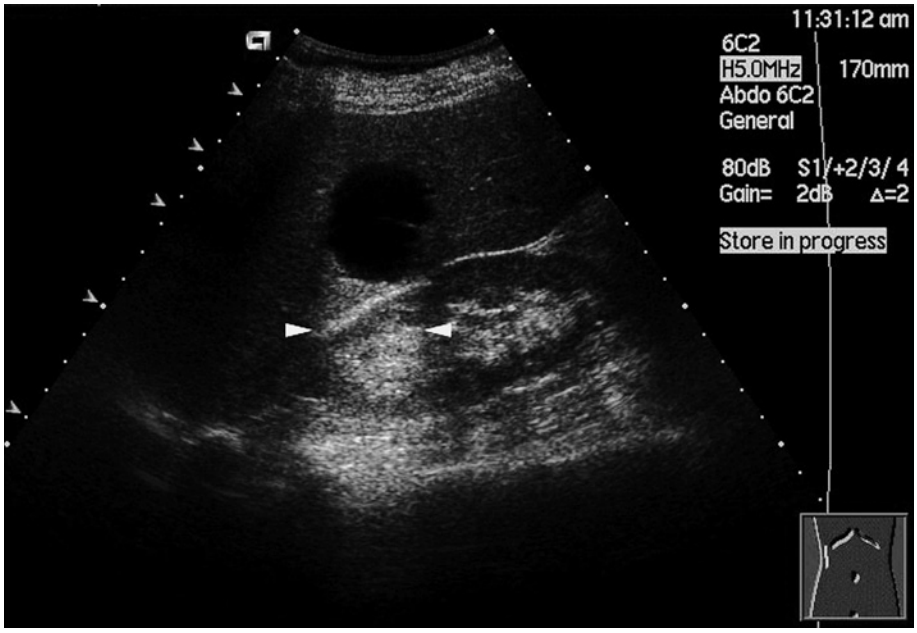


Fig. 1.4. Liver cyst. The typical features of a simple cyst, an echo-free space with smooth walls and increased sound transmission (*arrowheads*), permit a confident diagnosis and normally no further investigation is needed

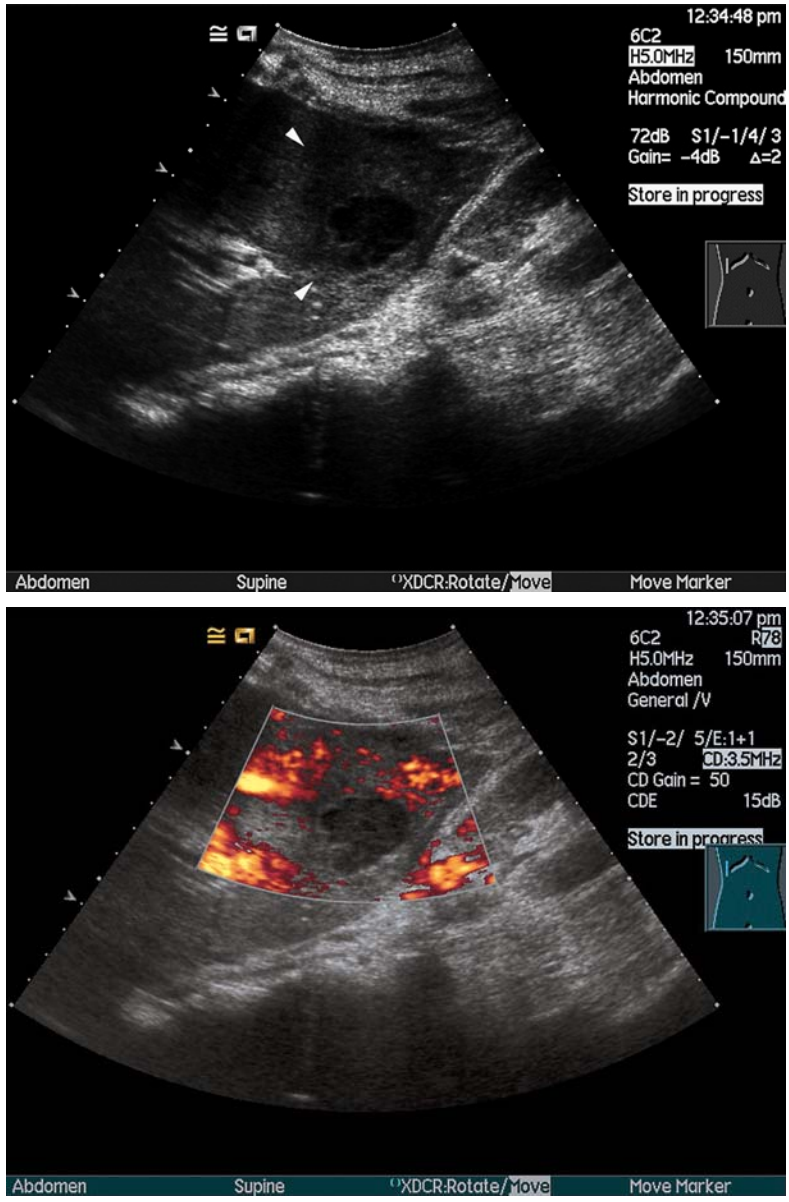
aemia of the surrounding tissue is often obvious (Fig. 1.5). However, in the initial stages of abscess formation, before pus has collected, a solid mass is found and the lesions can be very subtle (Dewbury et al. 1980). The microabscesses of fungal septicaemia often have a characteristic appearance of a cavity containing a central echogenic dot which is believed to be the artery in which the hyphae have embolized (Pastakia et al. 1988). However, the abscesses may be too small to detect with normal transducers used for liver imaging but may be resolved if a high frequency (small parts) transducer is used. Though these only allow the superficial 4 or 5 cm of liver to be imaged, the wide dissemination of these microabscesses usually allows a firm diagnosis to be made.

Haemangiomas are the commonest benign liver tumour and typically appear as uniformly echogenic masses (Kim et al. 2000). On Doppler they are hypovascular, only occasionally showing weak venous signals.

Focal nodular hyperplasia contains normal liver elements in an abnormal arrangement (Casarella et al. 1978; Di Stasi et al. 1996; Wang et al. 1997). Some have a vascularized central scar which is seen as an echo-poor streak with Doppler signals that typically radiate outwards in a spoke-wheel fashion and these arterial features are elegantly demonstrated after contrast enhancement (Wang et al. 1997).

Trauma may be very difficult to detect on unenhanced ultrasound unless there is a haematoma which is seen as an echo-poor cavity (Singh et al. 1997). However, there are interesting reports of the value of contrast agents here. Infarcts in the liver are uncommon except in the HELPP syndrome and following major liver surgery involving vascular reconstruction, such as liver transplantation (Christensen et al. 1997). They may be subtle on B-mode imaging but on colour Doppler are seen as non-perfused segments. Again, microbubble enhancement seems to improve the detection rate.

While fatty deposition in the liver is usually diffuse, producing a uniform increase in reflectivity, sometimes it is patchy. Focal fatty change produces echogenic regions, most often close to the gall bladder, that typically have a geometric shape (presumably reflecting the vascular territory that seems to underlie their formation) (Fig. 1.6). The reverse, focal fatty sparing, produces echo-poor patches. These changes can be confusing and may mimic metastases. Contrast enhancement is helpful because the lesion has normal haemodynamics and disappears as both it and the surrounding liver fill in the sinusoidal phase at around 2 min post injection.



a

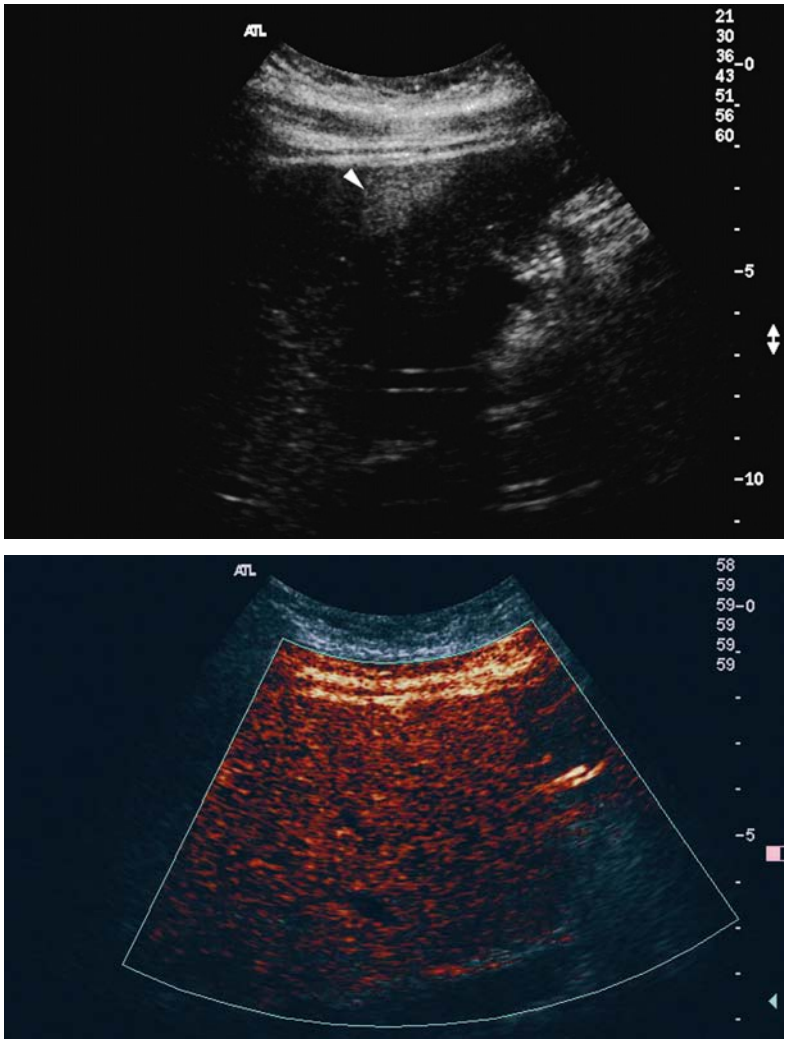
b

Fig. 1.5. a This liver abscess formed by extension from an aggressive cholecystitis is seen as a region of slightly reduced reflectivity (*arrowheads*) with a small central cavity that is multiloculated. **b** The inflamed tissue is markedly hyperaemic on colour Doppler

The variety of appearances of metastases on ultrasound is bewildering and remains largely unexplained (Fig. 1.7) (Middleton et al. 1997; Pain et al. 1984). Though there are trends, for example, echogenic metastases are typically of gastro-intestinal or urogenital tract origin and echo-poor lesions are usual in carcinoma of the breast and bronchus, it has not been possible to relate particular patterns with the primary site. The success of ultrasound in liver staging has been exaggerated in the past, quoted accuracies around 80% being calculated on a per patient basis rather than for individual lesions (Carter et al. 1996). Contrast enhancement offers a significant improvement.

Hepatocellular carcinomas can be detected as masses of varying echogenicity and often a heterogeneous texture (Itoh and Akamatsu 1998). Their typical hypervascularity can be depicted with colour Doppler (Fig. 1.8). However, HCCs are often multicentric and highly invasive so that they may not have well defined borders and this, together with the fact that they often arise in cirrhotic livers with an irregular texture, can make them difficult to detect and size. They may also be confused with regenerating nodules.

Cholangiocarcinomas are also often difficult to detect, probably again because they are infiltrative. For both these primary liver malignancies, microbubble contrast agents have proved useful.



a

b

Fig. 1.6. a An echogenic wedge-shaped region (*arrowhead*) of the liver was found in this patient being staged for a colorectal cancer. Its geometric shape projecting onto the liver's surface suggested the diagnosis of focal fatty change. **b** In view of the importance of establishing the diagnosis with certainty, a microbubble contrast agent (SonoVue, Bracco, Milan) was administered. The microbubble-specific mode Power Pulse Inversion (Philips-ATL, Bothel, Wa.) was used to demonstrate that the *lesion* vanished in the sinusoidal phase at 3 min. In this mode the distribution of the microbubbles is shown as a *red coloured overlay* on the grey-scale scan

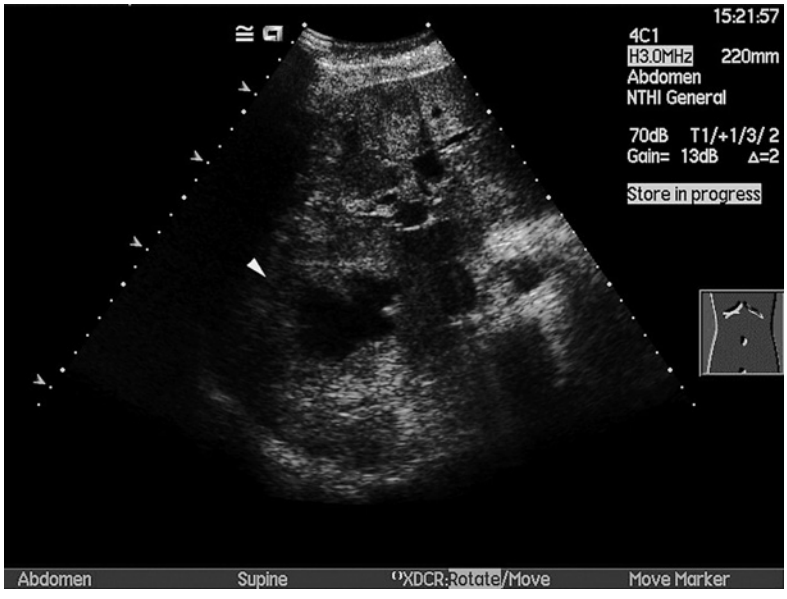
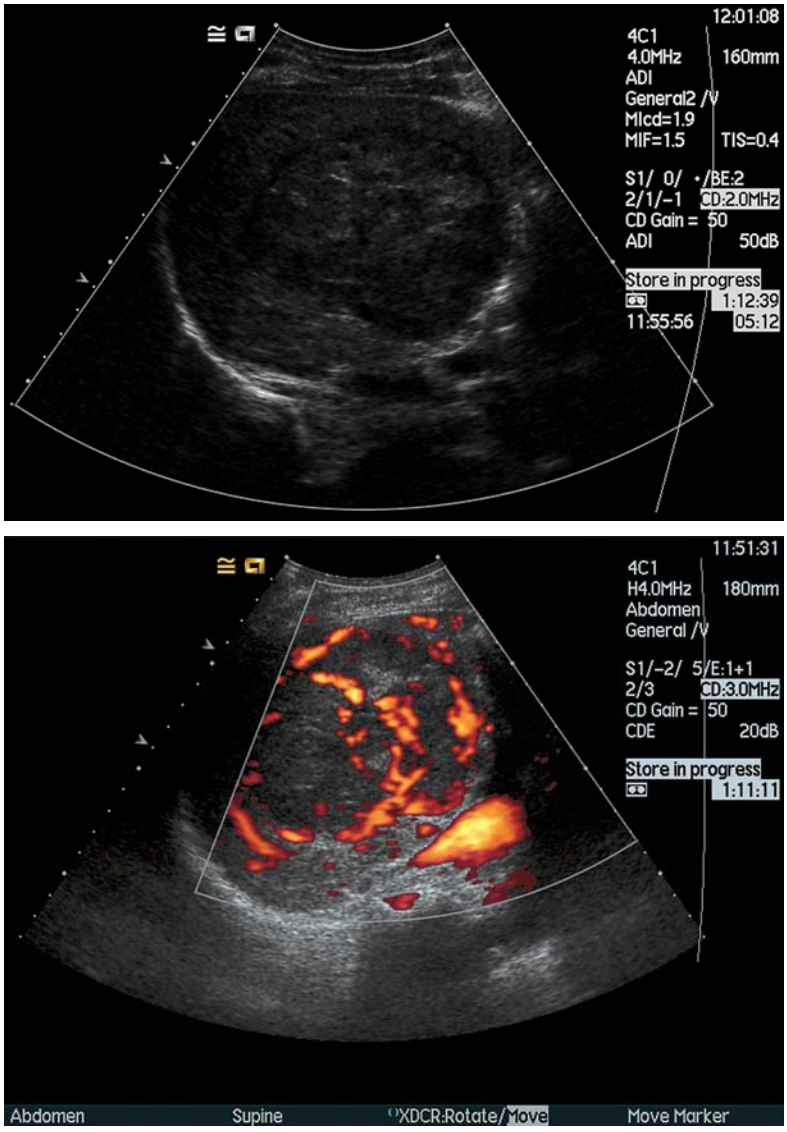


Fig. 1.7. Large heterogeneous masses occupy much of the right liver in this patient being staged for a colorectal carcinoma. One of the lesions has an echo free irregular central region (*arrowhead*) indicating haemorrhage or necrosis



a

b

Fig. 1.8. a The heterogeneous texture of large hepatocellular carcinomas is shown in this example which is typically hypervascular on colour Doppler. **b** The complex, chaotic pattern of the malignant neovasculature is well demonstrated

1.5.1 Contrast Enhanced Ultrasound

After injection of one of the newer contrast agents, the enhancement first appears in the hepatic artery and then some 20 s later in the portal vein (Wilson and Burns 2001). Gradually thereafter the liver parenchyma returns increasingly stronger signals until there is a near-complete parenchymal filling at around 1 min, the exact times depending on cardiac output as well as on the dose of microbubble administered; this late or sinusoidal phase is believed to represent pooling in the sinusoids or attachment to Kupffer cells. Contrast appears in the hepatic veins normally around 40 s after injection and 12 or more seconds after the artery lights up. Overall, the duration of useful liver enhancement is 4–5 min when a bubble-preserving low MI mode is used.

Microbubbles can also be used as tracers; in the liver the time taken for them to cross into the hepatic veins (normally 30 s or more, owing to the slow flow in the liver sinusoids) is shortened when there is arteriovenous shunting, as occurs in metastases and cirrhosis (Albrecht et al. 1999; Blomley 1997). This simple test seems to be able to detect occult metastases, for example in colorectal cancer, and might prove useful in selecting patients for adjuvant chemotherapy.

Since the parenchymal (late) phase depends on an intact functioning microcirculation, lesions that lack

this appear as dark defects; this applies to cysts and ischaemic regions such as trauma, scars and the rare infarcts and, importantly, to metastases which are detected with greatly improved sensitivity (Fig. 1.9) (Wilson and Burns 2001; Blomley et al. 1999). Even sub-centimetre metastases are readily detected against the enhanced background of normal liver tissue. Cholangiocarcinomas have the same appearance and this lesion, considered "difficult" for imaging in general, is well delineated with this technique.

Lesions that contain haemodynamically normal liver fill in the same way as the normal surrounding tissue and so tend to disappear in this late phase. Examples include focal fatty sparing/change, regenerating nodules in cirrhosis and focal nodular hyperplasia in which the central scar is often seen as a stellate defect at this stage (Fig. 1.6). The arterial phase is useful for characterising lesions based on their blood supply; hypervascular lesions such as hepatocellular carcinomas and vascular metastases (i.e. those from renal and neuroendocrine carcinomas) have one or more supply arteries that enter the lesion's periphery and fill rapidly in a centripetal fashion (Tanaka et al. 2001). FNH typically shows a different pattern with a single supply artery that feeds the mass from its centre in a centrifugal spoke-wheel fashion. Haemangiomas often have a pathognomonic haemodynamic pattern with arterial filling of the lesion's margin to form peripheral clumps from which the contrast slowly percolates towards the centre of the lesion. It may eventually fill completely and disappear in the sinusoidal phase but sometimes, especially with larger lesions, there are irregular non-filling regions which presumably represent thrombus or fibrosis. This centripetal slow filling also occurs in haemangiomas that are atypical on B-mode scans. Not all haemangiomas behave in this typical fashion on contrast ultrasound but when they do, no further investigation is needed.

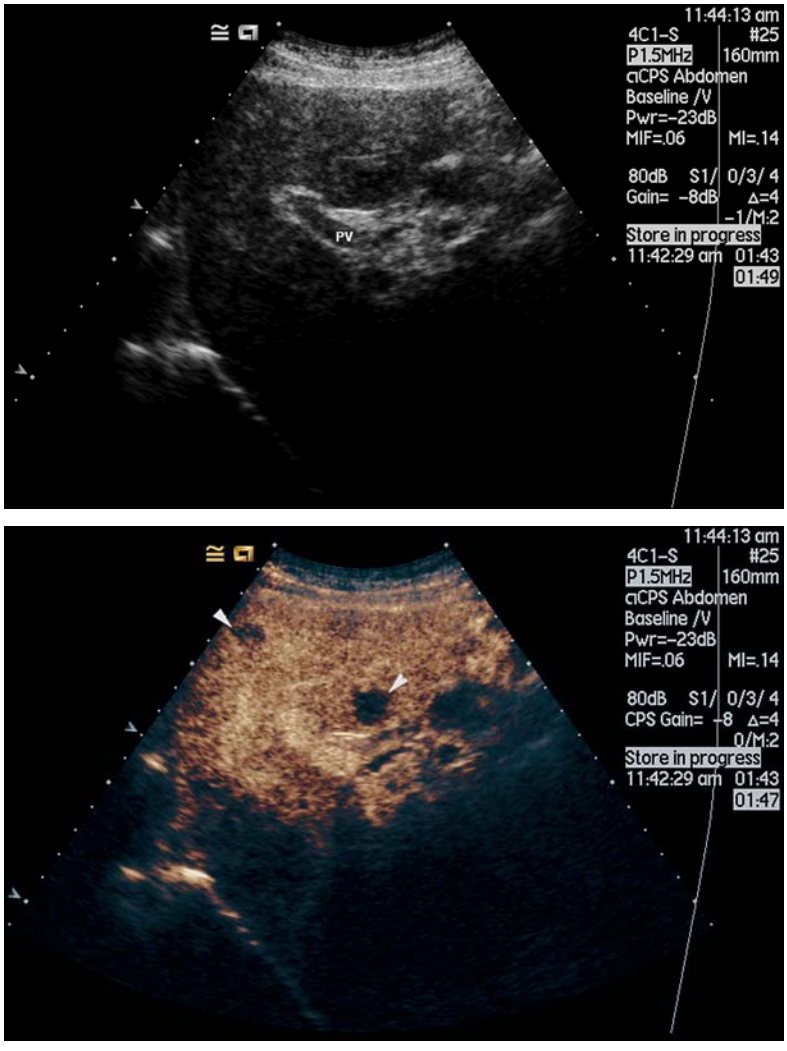


Fig. 1.9. a The staging liver ultrasound in this patient with a gastric carcinoma revealed a slightly irregular texture but no definite focal lesion. **b** In the sinusoidal (late) phase, almost 2 min after injection of 2.4 ml of the microbubble contrast agent SonoVue, several signal-free foci representing metastases were detected (*arrowheads*). The mode used was Contrast Pulse Sequences (CPS) which detects the presence of microbubbles whether stationary, as in the liver sinusoids shown here, or moving, as in the portal vein (*PV*). It operates at low transmit powers – an MI of 0.2 was used in this study – so that microbubble destruction is minimised

Metastases may be unimpressive in the arterial phase but sometimes have a peripheral artery that forms a halo; this must be distinguished from the nodular peripheral contrast around a haemangioma (Wilson and Burns 2001). Metastases that are hypervascular fill rapidly and often heterogeneously from their supply artery. The contrast washes out more rapidly than from the normal liver (a manifestation of their small vascular volume) so that metastases become prominent as enhancement defects in the sinusoidal (late) phase (Fig. 1.9).

Hepatocellular carcinomas have complex patterns that do not always allow a diagnosis on a contrast study (Kim et al. 2002). They are usually hypervascular and show rapid and sometimes spectacular increase in signal a few seconds after the injection, though some are hypovascular. Their late phase appearance is variable, presumably because of the spectrum of differentiation they show on histology. Many behave in the same way as metastases and become prominent as defects from around 45 s after injection and this finding is clinically useful. Unfortunately some (perhaps 25%) retain contrast to a greater or lesser extent in this phase and thus simulate benign lesions. This obviously limits the value of contrast studies in evaluating cirrhotic patients for HCC.

A particularly useful application of contrast agents is in evaluating the completeness of ultrasound-guided interstitial therapy: when all tumour appears to have been destroyed, microbubbles often reveal residual portions of perfused tumour that can be ablated immediately so that the patient does not have to be moved to CT (Lencioni et al. 1997; Solbiati et al. 1999).

1.6 Conclusions

Ultrasound technology has continued its rapid progress and many of the innovations have quickly become accepted as routine tools. Examples include tissue harmonic imaging and extended field of view scans. An important invention is the development of microbubble contrast agents that allow a contrast-enabled scanner to depict both the macro and microcirculation. In the liver they have proved to be especially valuable for detecting and characterising focal lesions and their use as tracers can reveal the arteriovenous shunting that is part of the metastatic process, even when the deposits are undetectable on conventional staging.

References

Albrecht TA, Blomley MJK, Cosgrove D, et al (1999) Non-invasive diagnosis of hepatic cirrhosis by transit time analysis of an ultrasound contrast agent. Lancet 353:1579–1583

Barbot DJ, Marks JH, Feld RI, et al (1997) Improved staging of liver tumors using laparoscopic intraoperative ultrasound. J Surg Oncol 64:63–67

Bezzi M, Silecchia G, De Leo A, et al (1998) Laparoscopic and intraoperative ultrasound. Eur J Radiol 27:S207–214

Blomley M (1997) Functional techniques with microbubbles. In: Nanda N, Schleif R, Goldberg B (eds) Advances in echocontrast. Kluwer, Dordrecht

Blomley MJ, Albrecht T, Cosgrove D et al (1998) Liver vascular transit time analyzed with dynamic hepatic venography with bolus injections of an US contrast agent: early experience in seven patients with metastases. Radiology 209:862–866

Blomley MJ, Albrecht T, Cosgrove D, et al (1999) Improved imaging of liver metastases with stimulated acoustic emission in the late phase of enhancement with the US contrast agent SH U 508A: early experience. Radiology 210:409–416

Bryant TH, Albrecht T, Sidhu P, et al (2004) Liver phase uptake of a liver specific microbubble improves characterization of liver lesions: a prospective multi-center study. Radiology (in press)

Burns P (1996) Harmonic imaging with ultrasound contrast agents. Clin Radiol 51 [Suppl 1]:50–55

Burns P, Fritsch T, Weitschies W (1995) Pseudo Doppler shifts from stationary tissue due to the stimulated emission of ultrasound from a new microsphere contrast agent. Radiology P197

Burns P, Wilson SR, Simpson DH (2000) Pulse inversion imaging of liver blood flow: improved method for characterizing focal masses with microbubble contrast. Invest Radiol 35:58–71

Carter R, Hemingway D, Cooke TG, et al (1996) A prospective study of six methods for detection of hepatic colorectal metastases. Ann R Coll Surg Engl 78:27–30

Casarella W, Knowles D, Wollf M, et al (1978) Focal nodular hyperplasia and liver cell adenoma. AJR Am J Roentgenol 131:393–402

Christensen S, Herold N, Ravn P (1997) Ultrasound examination of the liver in HELLP syndrome. Radiologe 37:170–172

Chuah SY (2000) Liver biopsy under ultrasound control: implications for training. Gut 46:583–584

Couinaud C (1957) Le Foie. Etude anatomiques et chirugicales. Masson, Paris

Dawson P, Cosgrove D, Grainger R (1999) Textbook of Contrast Media. Isis Medical, Oxford

Dewbury K, Joseph A, Sadler G, et al (1980) Ultrasound in the diagnosis of early liver abscess. Br J Radiol 53:1160–1167

Di Stasi M, Caturelli E, De Sio I, et al (1996) Natural history of focal nodular hyperplasia of the liver: an ultrasound study. J Clin Ultrasound 24:345–350

Eckersley R, Cosgrove D, Blomley M, et al (1998) Functional imaging of tissue response to bolus injection of an ultrasound contrast agent. Proc. IEEE Ultrasonics Symposium 2:1779–1782

Filice C, Brunetti E (1997) Use of PAIR in human cystic echinococcosis. Acta Tropica 64:95–107

Foley W, Lawson T (1992) Abdomen. In: Foley W (ed) Color Doppler flow imaging. Andover Medical, Boston
Gaines PA, Sampson MA (1989) The prevalence and characterization of simple hepatic cysts by ultrasound examination. Br J Radiol 62:335–337
Goldberg B (1997) Ultrasound contrast agents. Martin Dunitz, London
Grant E (1992) Doppler imaging of the liver. Ultrasound Quarterly 10:117–154
Haddad MC, Al-Awar G, Huwaijah SH, et al (2001) Echinococcal cysts of the liver: a retrospective analysis of clinicoradiological findings and different therapeutic modalities. Clin Imaging 25:403–408
Herman K (1996) Intraoperative ultrasound in gastrointestinal cancer. An analysis of 272 operated patients. Hepatogastroenterology 43:565–570
Itoh Y, Akamatsu K (1998) Relationships between echo level and histologic characteristics in small hepatocellular carcinomas. J Clin Ultrasound 26:295–301
Kim KW, Kim TK, Han JK, et al (2000) Hepatic hemangiomas: spectrum of US appearances on gray-scale, power Doppler, and contrast-enhanced US. Korean J Radiol 1:191–197
Kim TK, Kim AY, Choi BI (2002) Hepatocellular carcinoma: harmonic ultrasound and contrast agent. Abdom Imaging 27:129–138
Klotter H, Ruckert K, Mentges B, et al (1986) Intraoperative ultrasound study in surgery. Ultraschall Med 7:224–230
Kono Y, Moriyasu F, Nada T, et al (1997) Gray scale second harmonic imaging of the liver: a preliminary animal study. Ultrasound Med Biol 23:719–726
Kremkau F (1997) Diagnostic ultrasound: principles and instruments. WB Saunders, Philadelphia
Kuni CC, Johnson NL, Holmes JH (1978) Polycystic liver disease. J Clin Ultrasound 6:332–334
Lafortune M, Patriquin H (1999) The hepatic artery: studies using Doppler sonography. Ultrasound Quarterly 15:9–26
Lencioni R, Bartolozzi C, Ricci P, et al (1997) Hepatocellular carcinoma: use of contrast enhanced color Doppler US to evaluate response to treatment with percutaneous ethanol injection. Eur Radiol 7:792–794
Machi J, Sigel B (1996) Operative ultrasound in general surgery. Am J Surg 172:15–20
McDicken W (1991) Diagnostic ultrasound, physical principles and use of instruments, 3rd edn. Churchill Livingstone, Edinburgh
Middleton WD, Hiskes SK, Teefey SA, et al (1997) Small (1.5 cm or less) liver metastases: US-guided biopsy. Radiology 205:729–732
Mine Y (1998) Harmonic imaging. Nippon Rinsho 56:881–885
Moazam F, Nazir Z (1998) Amebic liver abscess: spare the knife but save the child. J Pediatr Surg 33:119–122
N'Gbesso RD, Keita AK (1997) Ultrasonography of amebic liver abscesses. Proposal of a new classification. J Radiol 78:569–576
Pain JA, Bailey ME, Bloomberg TJ (1984) Liver metastases: the role of preoperative ultrasound. J R Coll Surg Edinb 29:85–87
Parvey HR, Eisenberg RL, Giyanani V, et al (1989) Duplex sonography of the portal venous system: pitfalls and limitations. AJR Am J Roentgenol 52:765–770
Pastakia B, Shawker TH, Thaler M (1988) Hepatosplenic candidiasis: wheels within wheels. Radiology 166:417–421
Pederson J, Pederson ST, Karstrup S (1993) Ultrasound guided biopsies. In: Cosgrove D, Meire HB, Dewbury K (eds) Clinical ultrasound. Churchill Livingstone, London
Singh G, Arya N, Safaya R, et al (1997) Role of ultrasonography in blunt abdominal trauma. Injury 28:667–670
Solbiati L, Goldberg S, Ierace T, et al (1999) Radio-frequency ablation of hepatic metastases: postprocedural assessment with a US microbubble contrast agent. Radiology 211:643–649
Stride E, Saffari N (2003) Microbubble ultrasound contrast agents: a review. Proc Inst Mech Eng [H] 217:429–447
Tanaka S, Ioka T, Oshikawa O, et al (2001) Dynamic sonography of hepatic tumors. AJR Am J Roentgenol 177:799–805
ter Haar G (1999) Interactions between the ultrasound beam and microbubbles. In: Dawson P, Cosgrove D, Allison D, Grainger R (eds) Contrast agents in radiology. Isis Medical, Oxford
Wachsberg RH, Angyal EA, Klein KM, et al (1997) Echogenicity of hepatic versus portal vein walls revisited with histologic correlation. J Ultrasound Med 16:807–810
Wang LY, Wang JH, Lin ZY, et al (1997) Hepatic focal nodular hyperplasia: findings on color Doppler ultrasound. Abdom Imaging 22:178–181
Wilson SR, Burns PN (2001) Liver mass evaluation with ultrasound: the impact of microbubble contrast agents and pulse inversion imaging. Semin Liver Dis 21:147–159

2 Computed Tomography

Andrea Laghi, Ilaria Sansoni, Michela Celestre, Pasquale Paolantonio, and Roberto Passariello

CONTENTS

2.1 Introduction

Following its introduction in a clinical setting in 1974, computed tomography (CT) underwent an extraordinary technical revolution in terms of both scanning time and spatial resolution. Nevertheless, CT remained a cross-sectional technique with sequential acquisition of axial slices until the introduction of spiral (helical) CT at the end of 1980s. Spiral technology, made possible by improvements in tube technology and electronic computing, has transformed CT from a two-dimensional into a true volumetric imaging modality (Kalender et al. 1990). Faster image acquisition, more rational use of contrast agent administration as well as use of image reformation on multiple planes offered incredible advances in terms of lesion identification, characterization and staging and opened up new indications for CT study (i.e. CT angiography for arterial vascular assessment and replacement of catheter angiography; CT colonography for evaluation of colonic disorders).

A second revolution occurred when multi-slice (multidetector-row) CT (MDCT) was introduced (Klingenbeck-Regn et al. 1999). Although the first MDCT was a "dual-slice" scanner, presented already in 1992 and consisting of two parallel detector rows that allowed the simultaneous acquisition of two interwoven helices, the real impact of multi-slice technology was observed at the end of 1998, when the first four-slice CT equipment was introduced in a clinical setting (Berland and Smith 1998; Liang and Kruger 1996). MDCT, based on a four-row configuration of detectors, together with the development of sub-second gantry rotation time, offered the opportunity to overcome common limitations of single-slice CT scanners, especially in terms of scanning time and limited z-axis resolution (Hu et al. 2000). Technical evolution was followed by the development of 8- and 16-slice scanners, which became available between 2001 and 2002, and will continue with the 64-slice equipment expected by the end of this year (Prokop 2003a; Flohr et al. 2002).

Technological development was followed by a change in liver imaging protocols. The real advance in liver imaging was due to multiplanar and multiphasic capabilities of MDCT. Multiplanarity, due to the acquisition of 3D data sets with isotropic or near-isotropic voxels, resulted in the ability to analyse CT images on multiple planes (i.e. sagittal, coronal and oblique) making diagnosis of lesions in critical anatomic localization easier; isotropic volume also made the use of 3D rendering algorithms available, which is especially useful in the case of vascular reconstructions and virtual endoscopic views (Prokop 2003b). The multiphasic approach, made possible by fast scanning time, makes it possible to scan the liver parenchyma during pure vascular phases, offering a real arterial, portal and delayed phase (Brink 2003; Fleischmann 2003b). Optimization of vascular enhancement together with improved spatial resolution along the z-axis are expected to improve diagnostic accuracy in liver imaging (Kang et al. 2003).

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2.2 Technique

MDCT has transformed CT from a transaxial cross-sectional technique into a 3D imaging modality. Whereas single-slice CT took at least 5 years to gain general acceptance, MDCT has been more rapidly accepted in the radiological community, with exponential growth in the use of these scanners in clinical practice. Major improvements (z-axis coverage speed and longitudinal resolution) translated into rapid hepatic imaging and the use of new imaging protocols, not possible with single-slice spiral CT. Thin sections, that can now be routinely used within a single breath-hold, resulted in improved lesion detection and nearly isotropic image acquisition providing high-resolution datasets available for multiplanar reformations (Honda et al. 2002; Kamel et al. 2003). Moreover, the possibility to scan through the entire liver in 10 s or less allowed MDCT to demonstrate three clear separate and distinct hepatic circulatory phases of iodine contrast distribution, i.e. pure arterial, arterioportal, venous and equilibrium phases (Foley et al. 2000). MDCT with the improvements in morphological and functional information compared with single-slice CT enables a comprehensive approach to hepatic imaging within a single examination. MDCT brings new challenges, concerning contrast injections protocols (including optimal timing and rate of contrast injection, total volume of contrast agent and ideal iodine concentration of contrast medium) and patients' dose exposure (Fleischmann 2003b; Prokop 2003a).

2.2.1 Detector Configuration

The reason for a brief discussion about detector configuration, which might be beyond the aims of this chapter, lies in the differences among detector arrays of different CT constructors, especially when considering four-slice scanners; in fact, detector arrays of 16-slice machines are more homogeneous. The major consequence of a different design is the choice of scan parameters, which cannot be simply transferred from scanner to scanner, as with single-slice CT. This means that scanning parameters need to be optimized as a function of the available equipment according to only a few general rules.

At present, MDCT scanners may acquire 2, 4, 6, 8, 10 or 16 simultaneous sections. In all MDCT scanners, the number of slices that can be acquired is usually smaller than the number of detector rows (N), in order to obtain more than one collimation setting by adding together the signals of neighbouring detector rows.

The arrangement of detectors along the z-axis and widths of available slices vary among different systems. In particular three different detector array designs are currently available: "matrix", "adaptive" and "hybrid" detector arrays. "Matrix" detectors consist of parallel rows of equal thickness; "adaptive" detectors use detector rows with varying thickness. In the former type, the width of detector elements determines the thinnest possible section thickness and thicker sections are obtained by adding the signal from neighbouring detector rows; in contrast, in the latter type, various section thicknesses can be gained using partial collimation and addition of signal of adjacent rows. Finally, "hybrid" detectors use smaller detector rows in the centre and larger ones towards the periphery of the array. This design has been adopted mostly for 16-row scanners from all companies (Prokop 2003a; Kopp et al. 2002).

2.2.2 Scan Parameters

In single-slice CT, the most important scan parameters can be provided in the form of a triplet including slice collimation (SC, in mm), table feed/rotation (TF, in mm) and reconstruction increment (RI, in mm). Depending on clinical indications, a compromise has to be reached between z-axis resolution and required scan length. The effective slice thickness or slice width (SW) can be calculated from slice collimation and pitch, P (=TF/SC). The suggested scan parameters for single-slice spiral CT of the liver are 5/8/4 (SC/TF/RI) and the SW is 6.2 (Uggowitzer 2003).

In four-slice spiral CT the same acquired raw data set can be used to reconstruct two or more data sets of varying thickness. For this reason, it is important to distinguish between acquisition parameters, given as (NxSC/TF), and reconstruction parameters, expressed as (SW/RI) (Cademartiri et al. 2003). With multislice scanners, two definitions of pitch factor are used, depending on whether a section (P*=TF/SC) or total collimation of the detector array (P=TF/NxSC) is chosen as the reference (Prokop 2003c).

The image quality of any given four-slice CT system depends on collimation, pitch, reconstruction interval. Collimation should be tailored to the purpose of the study, because a decreased collimator width (thus, an increase in pitch) results in a narrow reconstructed section thickness and improved spatial reso-

lution, but in increased image noise and decreased length of coverage. However, maximization of pitch may also result in a decrease in contrast resolution (Wang and Vannier 1999). Thus, the most appropriate choice of scanning parameters depends also on clinical indication to CT study. In fact, for example, for CT angiography where imaging is devoted to structures with very high attenuation, loss of contrast resolution caused by maximization of pitch can be disregarded. This is not the case with liver imaging where both good spatial and contrast resolutions are required; a practical approach for liver imaging is to use relatively thin collimation, increasing the pitch as needed to cover the entire liver. A small reconstruction interval with overlapping sections is advantageous both for multiplanar reconstructions and for detection of small lesions, because the smaller the reconstruction interval, the greater the longitudinal (z-axis) resolution; one major drawback is the loss of z-axis coverage (Ji et al. 2001).

The choice of scan parameters with a four-slice CT scanner can follow two different approaches: "fast spiral acquisition", with the use of 5-mm slice thickness, similar to single-slice spiral CT, but with the advantage of much shorter scanning time; "volumetric imaging" using a high-resolution protocol consisting of thin collimation and lower pitch, necessary to acquire an almost isotropic volume that can be further post-processed using multiplanar reformations, maximum intensity projection and volume-rendering algorithms (Saini and Dsouza 2003). For liver imaging a compromise between fast scanning, necessary to obtain pure vascular phases, and high-resolution scanning, necessary to reformat the datasets, has to be performed.

This obligatory choice between scanning time and spatial resolution is not necessary any more with 16-slice spiral CT systems, as they combine the ability to acquire very thin slice images (narrow collimation) with a very fast scanning time.

2.2.3 Strategy of Dataset Acquisition

The major impact of spiral CT technology on liver imaging is represented in the short scanning time, allowing the evaluation of the entire liver parenchyma during a single breath-hold. Fast scanning opened the era of multiphasic protocols, consisting of multiple passes through liver parenchyma during different vascular phases. Using a single detector spiral CT the examination usually consists of a biphasic scan with images acquired during arterial dominant phase followed by a portal venous phase (Valls et al. 2004). The rationale of this imaging protocol is based on the differences of blood supply between normal parenchyma and liver tumours, as hepatic vascularization comes predominantly from the portal vein, whereas each kind of liver tumour receives blood mainly from the hepatic artery; exceptions to this rule are often represented by regenerating nodules and early well-differentiated hepatocellular carcinomas (Altmann 1978; Ferrucci 1991; Bernardino and Galambos 1989; Laniado and Kopp 1997; Hollett et al. 1995). Therefore, if the arterial dominant phase is acquired as part of the imaging protocol, diagnosis of hypervascular benign and malignant tumours (focal nodular hyperplasia, hepatic adenomas, hepatocellular carcinomas, islet cell tumour and carcinoid) is improved compared with analysis of delayed phase of enhancement alone (Ferrucci 1991; Baron et al. 1996; Oliver et al. 1997). On the contrary, hypovascular liver tumours (such as metastases), show low attenuation compared with normal parenchyma during both arterial and subsequent portal venous phases (Ferrucci 1991).

However, the scanning time of a single-slice spiral CT scanner is too slow to obtain a pure arterial phase; the result is a hybrid phase, with mixed arterial and portal venous enhancement (usually slices acquired first in the volume have a pure arterial enhancement whereas subsequent slices show portal dominant enhancement).

Only with the advent of MDCT could the entire upper abdomen be scanned within 10 s or less (Ji and Ros 2001). Fast acquisition offers the possibility to scan the liver during multiple phases of vascular enhancement. A complex multiphasic imaging protocol was optimized soon after the introduction of four-slice scanners (Fig. 2.1) (Foley et al. 2000). It consists of four separate passes through liver parenchyma following i.v. injection of contrast medium (Fig. 2.2). The first two passes performed respectively in craniocaudal and caudocranial direction following the arrival of bolus of contrast medium are acquired within a single breath-hold of approximately 24 s; the delay time for scanning is calculated with a preliminary bolus test or is automatically defined using a bolus tracking technique. The first pass, the so-called early arterial phase (EAP) acquires images where only arterial vessels are enhanced; the second pass, the so-called late arterial phase (LAP) obtains images during arterioportal enhancement. The first breath-bold is followed by a second 10-s scan during the portal enhancement (portal venous phase,

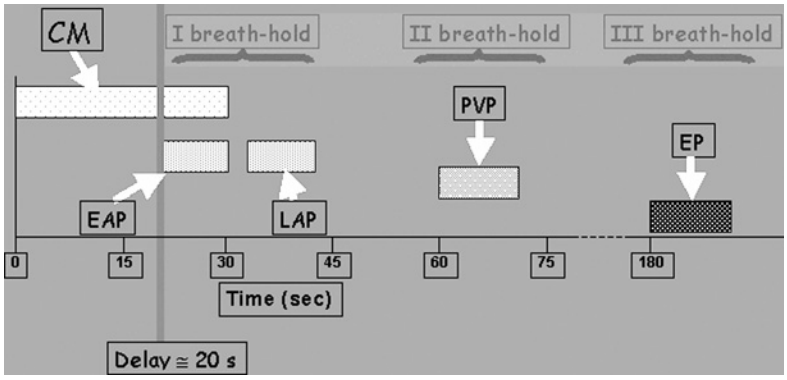

Fig. 2.1. Diagram of multiphasic vascular enhancement of the liver. Around 20 s (representing the average delay time usually calculated on the basis of bolus test) following the beginning of contrast medium injection first breath-hold acquisition of two consecutive scans is obtained. At around 60 s the second breath-hold scan is acquired followed by the equilibrium phase. *CM*, contrast medium; *EAP*, early arterial phase; *LAP*, late arterial phase; *PVP*, portal venous phase; *EP*, equilibrium phase

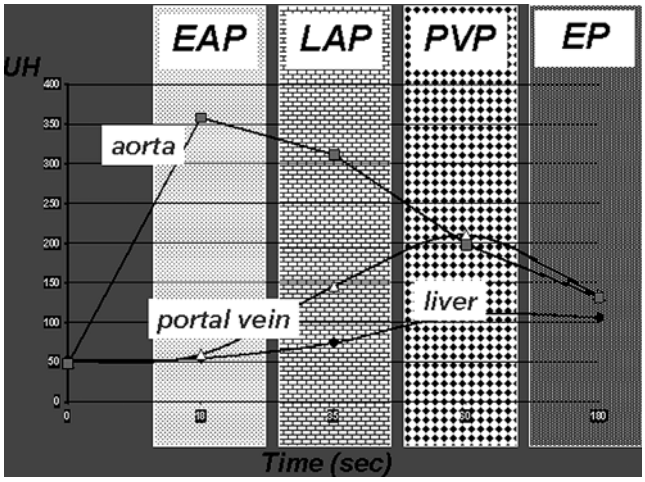

Fig. 2.2. Time-density curves representing enhancement of aorta, portal vein and liver parenchyma during each scan. Please note clear separation of different vascular phases with early arterial phase demonstrating exclusive enhancement of arterial vessels with absolutely no venous contamination. *EAP*, early arterial phase; *LAP*, late arterial phase; *PVP*, portal venous phase; *EP*, equilibrium phase

PVP) beginning 60 s after the injection of contrast medium. Finally, a 3-min delayed scan (equilibrium phase, EP) is acquired. The rationale for performing multiphasic examination is to maximize detection of hypervascular liver neoplasms, particularly in cirrhotic patients.

At this time, no consensus has been reached about the use of a so-called double arterial phase. Some authors reported that double arterial phase imaging of the liver with MDCT is effective for improving detectability of hypervascular hepatocellular carcinoma and for reducing the number of false-positive diagnoses (due to arteriovenous shunts); in particular sensitivity and positive predictive value for hypervascular HCC were 54% and 85% for EAP, 78% and 83% for LAP, and 86% and 92% for double arterial phase, respectively (Fig. 2.3) (Murakami et al. 2001). However, radiologists should recognize that the application of double arterial phase imaging to the liver may have crucial disadvantages for patients in terms of radiation exposure, as well as workload for personnel due to the huge number of acquired images, generating problems of filming, image interpretation and storage ("image pollution") (Ichikawa et al. 2002). On the other hand, other studies demonstrated that hypervascular neoplasms are best seen during LAP, with no contribution from EAP in terms of sensitivity (Foley et al. 2000; Ichikawa et al. 2002; Laghi et al. 2003). In our personal experience sensitivity and positive predictive value of respectively 48.5% and 96.4% in the EAP, 87.1% and 94% in the LAP were obtained, with no tumours detected in the EAP which were not visible in the LAP (Fig. 2.4) (Laghi et al. 2003). In another study, similar results were reported, with sensitivity of 88% with LAP and 90% combining EAP and LAP; both the values were statistically significant higher than 67% obtained with EAP alone (Fig. 2.5) (Ichikawa et al. 2002). The role of an EAP is the acquisition of pure arterial vascular datasets, where only arterial vessels are opacified. If the acquired volume is obtained with thin collimation and a reconstruction interval it can be used to generate high-quality vascular maps (CT angiography); these vascular maps may have an important role in pre-op-

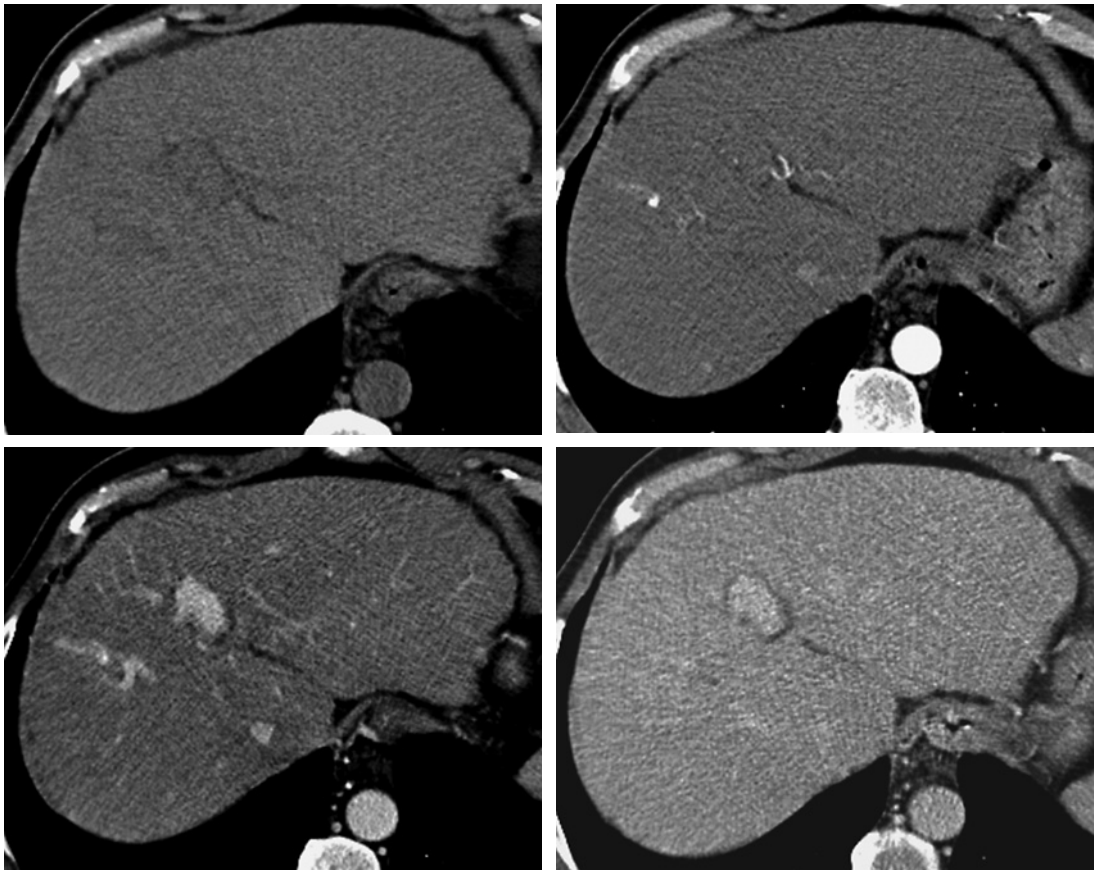

Fig. 2.3a–d. Arterioportal shunt. **a** On basal scan no lesion is detected. **b** On early arterial phase, intense enhancement of a pseudo-lesion is clearly depicted. **c** The enhanced pseudo-lesion follows vascular enhancement, with density similar to portal vein. **d** Delayed scan shows enhancement similar to surrounding parenchyma

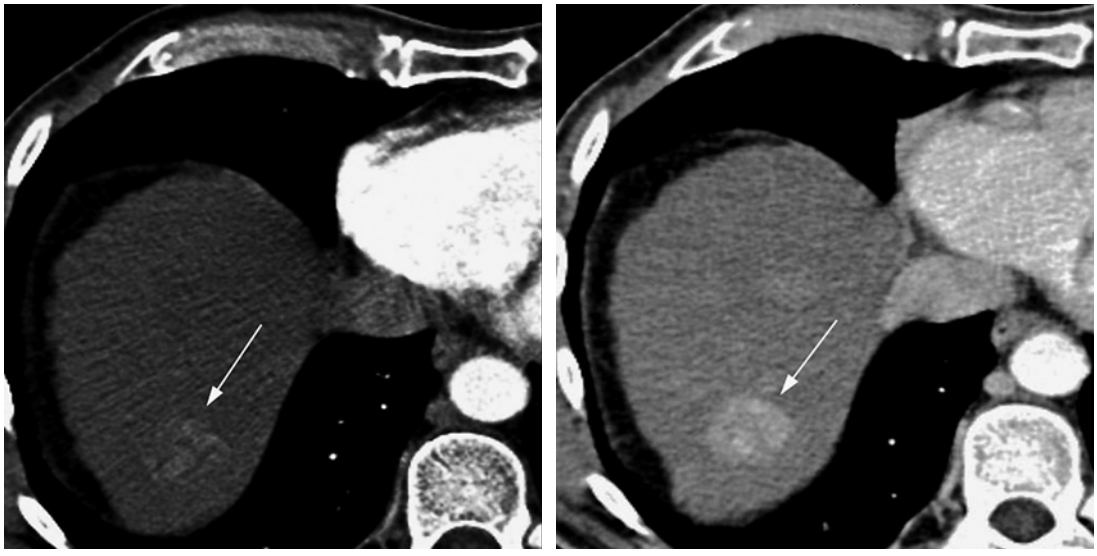

Fig. 2.4a,b. Hepatocellular carcinoma. **a** On early arterial phase hypervascular nodule is fairly seen (*arrow*). **b** Best conspicuity in lesion detection is obtained during late arterial phase (*arrow*)

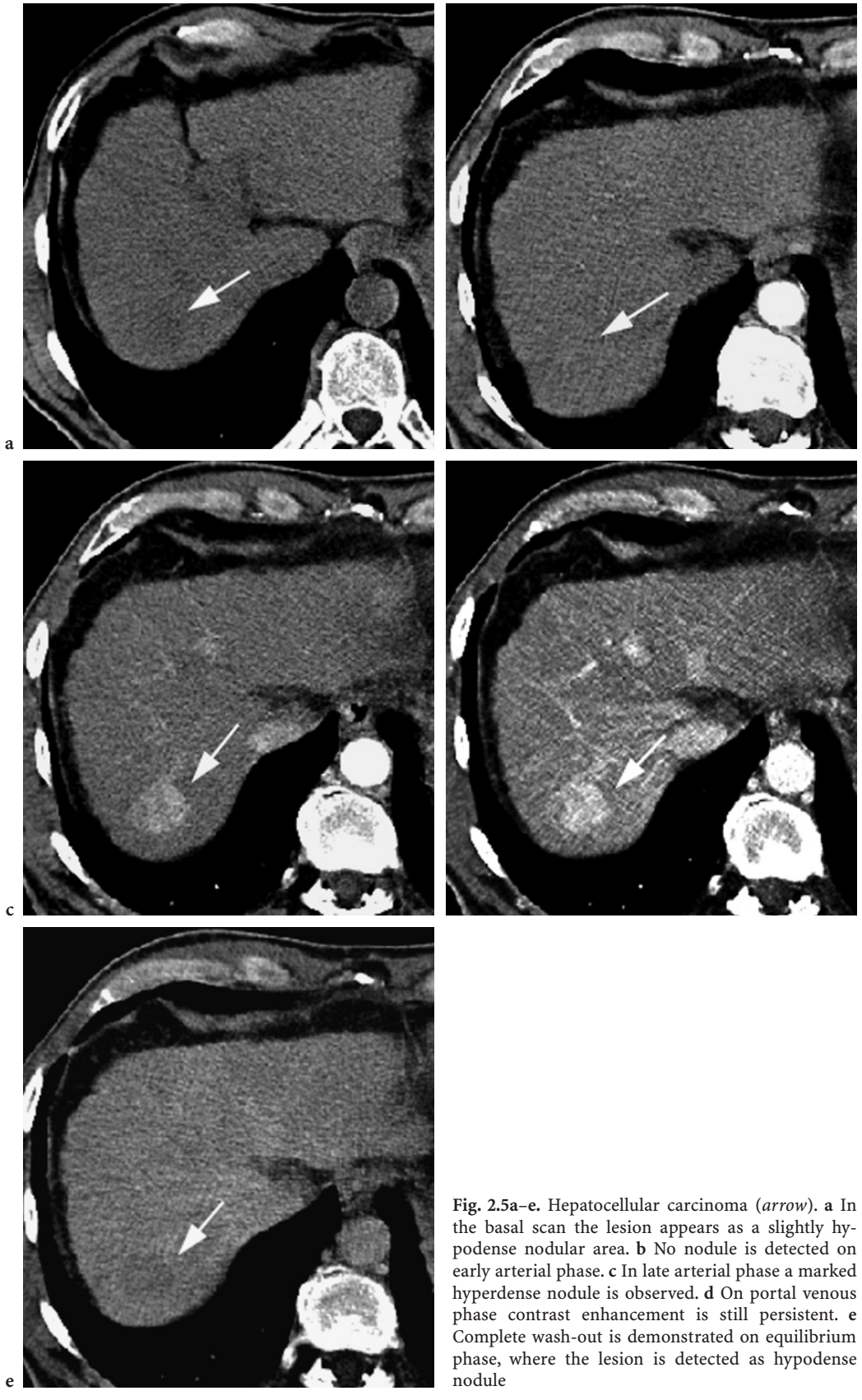

Fig. 2.5a–e. Hepatocellular carcinoma (*arrow*). **a** In the basal scan the lesion appears as a slightly hypodense nodular area. **b** No nodule is detected on early arterial phase. **c** In late arterial phase a marked hyperdense nodule is observed. **d** On portal venous phase contrast enhancement is still persistent. **e** Complete wash-out is demonstrated on equilibrium phase, where the lesion is detected as hypodense nodule

erative assessment of surgical candidates (liver resection or transplantation) or candidates for interventional procedures (catheter angiography) (Fig. 2.6) (Laghi et al. 2003).

The third imaging pass, the so-called portal venous phase (PVP), enables evaluation of isoattenuation or hypoattenuation of hypervascular lesions. In addition, in some patients, relatively hypovascular hepatocellular carcinomas and metastases from islet cell or carcinoid tumours may be detected only during this later acquisition scan (Foley et al. 2000). As is well known, the portal venous phase not only has the advantage of depicting hypovascular lesions but also is useful in demonstrating portal venous thrombosis, differentiating neoplasms from vessels, and identifying varices and shunts (Laghi et al. 2003).

Within the past decade, some investigators have advocated the use of delayed phase imaging for its potential added value in dynamic spiral CT imaging of the liver. Lesion detection and conspicuity has been reported to be higher in the delayed phase than in the portal venous phase, resulting in an improved detection rate of well-differentiated hypovascular hepatocellular carcinomas, depicted as low-attenuating lesions and sometimes missed when only arterial and portal venous phase scans are obtained (Hwang et al. 1997; Lim et al. 2002). Furthermore, delayed phase imaging has additional value in characterization of hepatic lesions because it offers better visualization of capsule and mosaic patterns seen in some hepatocellular carcinomas, delayed peripheral enhancement of cholangiocarcinoma and "filling-in" patterns of haemangioma (Figs. 2.7, 2.8) (Lim et al. 2002). In contrast, other authors demonstrated that the portal venous phase showed no significant differences in lesion detection compared with delayed phase imaging, or better still when combined, spiral CT of the arterial and the delayed phases revealed 91% of lesions, whereas a combination of the arterial and portal venous phases or the combination of all three phases revealed 92% of lesions; therefore, the combination of the arterial and portal venous phases is equal to the combination of three phases for detection of hypervascular hepatocellular carcinomas, and the delayed phase becomes superfluous (Choi et al. 1997). However, in this series of patients only hypervascular hepatocellular carcinoma was included, whilst in clinical practice, there are also cases of hypovascular hepatocellular carcinoma. This concept has been confirmed by other authors, who stated that portal venous-phase images are inferior to late phase images for detecting HCC nodules; in the same paper sensitivity of the unenhanced phase was also evaluated and it was demonstrated not to be necessary (Kim et al. 1999).

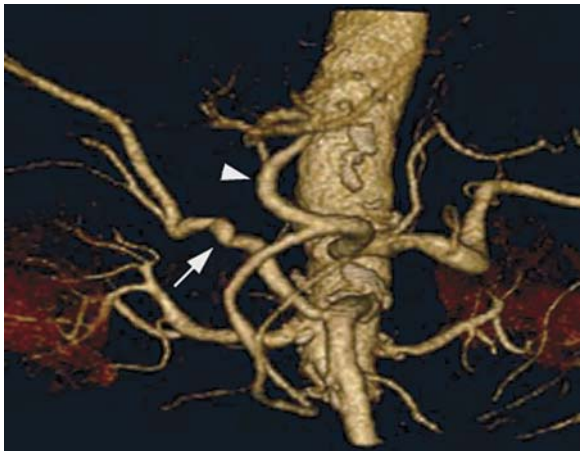

Fig. 2.6. Volume-rendered 3D reconstruction of celiac trunk and superior mesenteric artery. Anomalous origin of right hepatic artery from superior mesenteric artery is demonstrated (*arrow*). Left hepatic artery has a normal origin from common hepatic artery (*arrowhead*)

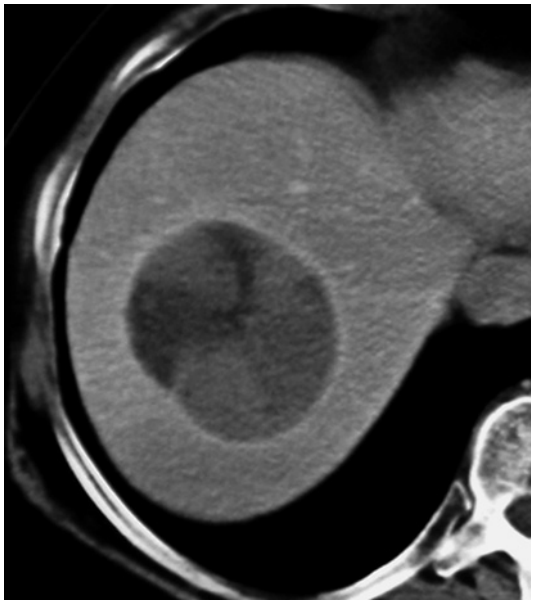

Fig. 2.7. On delayed scan better visualisation of capsule and mosaic pattern of hepatocellular carcinoma is demonstrated

Even with regard to the use of an unenhanced phase opinions are controversial with papers demonstrating no additionally detected lesions (hepatomas or metastases) compared with other phases and other experiences showing a 3% increase in the detection rate for hepatocellular carcinomas compared with arterial and portal venous phases (Miller et al. 1998; Oliver et al. 1996).