Diagnostics in Liver Diseases

9 Scintigraphic diagnostics

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► In 1951 examination of the liver using radionuclides was rendered possible through the development of an **automatic scanner** (B. Cassen et al.). In the same year, liver scintigraphy was also introduced by R.L. Wieland. The first proof of liver metastases was obtained in animal experiments in 1953 by means of ^{131}I-albumin (E. Yuhl et al.). As early as 1954, liver scintigraphy was applied in the clinical setting (L. Stirrett et al.). Since 1955, several ^{131}I-labelled substances excreted through bile, such as rose bengal (G.V. Taplin et al.), later also bromsulphane, have become available for functional assessment in hepatology. In 1958 G.V. Taplin et al. reported on their own clinical experience. • The development of the **scintillation camera** was a further major advance (H.O. Anger et al., 1959). Using the scintillation camera, sequential images could be taken in rapid succession. In 1971 C. Winkler et al. were the first investigators to use a scintillation-camera process-control computer system for studying the hepatic blood flow. • The following **radionuclides** were available: ^{198}aurum (L. Stirrett et al., 1954; H.N. Wagner et al., 1961), ^{99m}technetium (P.V. Harper et al., 1964), ^{133}xenon (J.R. Rees et al., 1964), and ^{113}indium (A.A. Goodwin et al., 1966).

Indications for scintigraphic methods may be given in specific situations: (*1.*) to evaluate certain partial liver functions, (*2.*) to clarify special issues when other imaging techniques (including laparoscopy) are not feasible, and (*3.*) to differentiate between benign and malignant tissue. The most commonly used short-lived radionuclide ^{99m}technetium (with a physical half-life of six hours) is associated with a strongly limited and justifiable radiation dose (total body < 1 mGy = 0.1 rad; screened organ 10−20 mGy = 1−2 rad). ^{99m}Tc may be marked both with colloids (proof of storage by Kupffer cells) and with erythrocytes (proof of perfusion and venous pooling); HIDA derivatives are tracers that can be excreted by hepatocytes and canaliculi. (s. tab. 9.1)

Colloids	storage capacity of Kupffer cells and of the RES (e.g. ^{99m}Tc sulphur or albumin colloids)
Iminodiacetate derivatives	uptake, transformation and excretion by the hepatocytes (e.g. IDA, HIDA, DISIDA)
Galactosyl neoglycoalbumin	hepatocyte-specific ligand
Erythrocytes	pooling and perfusion (e.g. $^{99m}TcO_4$)
Homotaurocholic acid	bile flow (e.g. ^{75}Se HCA)
Carcinoma antibodies	immunoscintigraphy in colorectal liver metastases (e.g. ^{99m}Tc AB CEA)

Tab. 9.1: Various radionuclides with their main characteristics and functions

Contraindications for scintigraphic investigations include pregnancy and lactation as well as intolerance to mucinous antibodies.

► The great value of nuclear medical examinations lies in the fact that the test results (including those produced by static scans) reflect biological functions. Furthermore, such sophisticated methods are generally helpful in defining the benignancy/malignancy and structural origin of the respective focal lesion.

1 Principle

The term scintigraphy describes the production of a planar, two-dimensional image showing the distribution of radioactivity in an organ in which a radioactive substance has been stored. Depending on the radionuclide used, **information** regarding the hepatic area is obtained on (*1.*) functional capacity of the RES, (*2.*) hepatocellular function, (*3.*) biliary excretion kinetics, and (*4.*) hepatic blood flow. (4, 8, 11, 12, 20, 22, 28, 38, 39) • The **images** taken by means of high-resolution large-area gamma-cameras are (*1.*) (static) liver scans or (*2.*) (dynamic) sequential scans. • Further technical and diagnostic improvements comprise: *positron emission tomography* **(PET)** and *single photon emission computer tomography* **(SPECT)**.

2 RES scintigraphy

^{99m}Tc-colloid: In the RES of the liver (as well as of the spleen and bone marrow), 80−90% of the radio-labelled colloids are usually taken up. This procedure is therefore also termed **static colloid scintigraphy**. Colloid particles of 200−1000 nm are usually taken up in the liver RES. The size and shape of the organ can be determined. Areas of the RES with reduced or no uptake of radioactivity appear as defective, i.e. silent or cold zones ("negative scan"). • The **extent of uptake** of the radiocolloids is reflected by different *shades of colour*, ranging from dark red ("hot") through yellow, light green, dark green, blue-green and blue to blue-black ("cold"). Multiple accumulations are a rare occurrence. These storage defects do not have any specific significance. • *Further evidence of centrally located defects is obtained by carrying out additional SPECT scintigraphy. (36)*

2.1 Liver cirrhosis

Following the administration of 100−200 MBq ^{99m}Tc-sulphur colloid intravenously, liver cirrhosis is characterized by a reduction in the uptake of radioactivity in the liver and an increased uptake by the spleen and bone marrow. Colloidal uptake in the liver is thus a valuable parameter for assessing any functional loss of the hepatic RES and for evaluating the residual parenchyma which is still functioning. The phagocytic capacity of the hepatic RES is closely related to the sinusoidal blood flow, the reduction of which is a result of the development of collaterals in the area of the hepatic sinusoids − this is an early sign of portal hypertension.

Scintigraphic proof of cirrhosis is based on (*1*.) enlarged rectangular liver, (*2*.) reduced and patchy uptake of radioactivity by the hepatic RES ("mottled liver"), (*3*.) shift in the maximum activity from the right to the left lobe of liver, and (*4*.) increased uptake by the spleen and bone RES. • The recorded scintigraphic findings permit *assessment of the course* of liver cirrhosis and provide information on focal complications such as (*1*.) occlusion of the branches of the portal vein with locally impaired perfusion and (*2*.) development of hepatocellular carcinoma.

► Thus the liver and the spleen form an anatomical and functional unit by being interlinked not only through the lienoportal vascular system, but also through the reticuloendothelial system. (s. fig. 9.1) *(see chapter 35)*

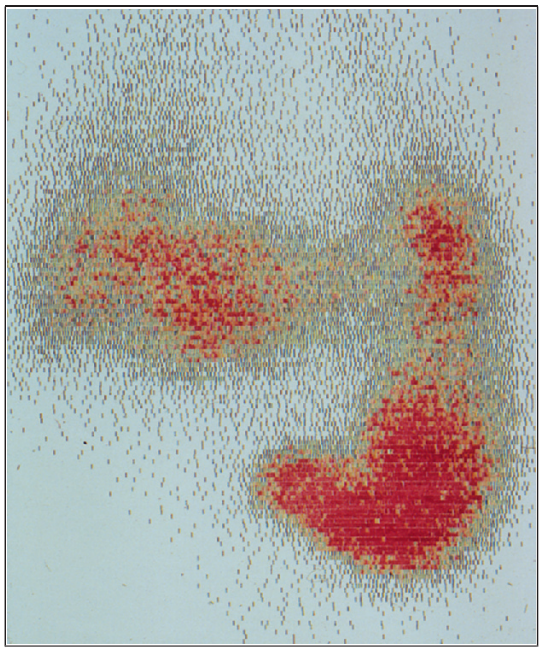

Fig. 9.1: Liver cirrhosis: diffuse decrease in the uptake of radioactivity by the liver with a markedly increased uptake by the clearly enlarged spleen (= colloid shift)

2.2 Budd-Chiari syndrome

In the Budd-Chiari syndrome, the central area of the liver shows a normal or even higher concentration of radioactivity, whereas the peripheral regions of both lobes of liver exhibit reduced or even no uptake ("hot spots" and multiple focal storage defects). Only the caudate lobe shows increased activity; due to its separate venous flow, it is not functionally affected by hepatic vein thrombosis. (27)

2.3 Focal liver lesions

Focal lesions with a diameter of > 1.5 cm can be detected with a sensitivity of > 80% and are visible as circumscribed storage defects, e. g. in the case of amoebic abscesses. (s. figs. 6.11; 9.2; 25.1) FNH is a liver tumour with maintained or even increased phagocytosis activity. • The nuclear medical diagnosis of *metastases* is now obsolete, having been replaced by more efficient imaging techniques. (s. fig. 9.3) (5, 9, 11, 23, 28, 30, 41) • If necessary, immune scintigraphy using antibodies (e. g. ^{99m}Tc-AB-CEA) may be applied in colorectal liver metastases. In HCC diagnosis, use of ^{99}Tc-anti-alpha fetoprotein produces a sensitivity of 90–95% in SPECT.

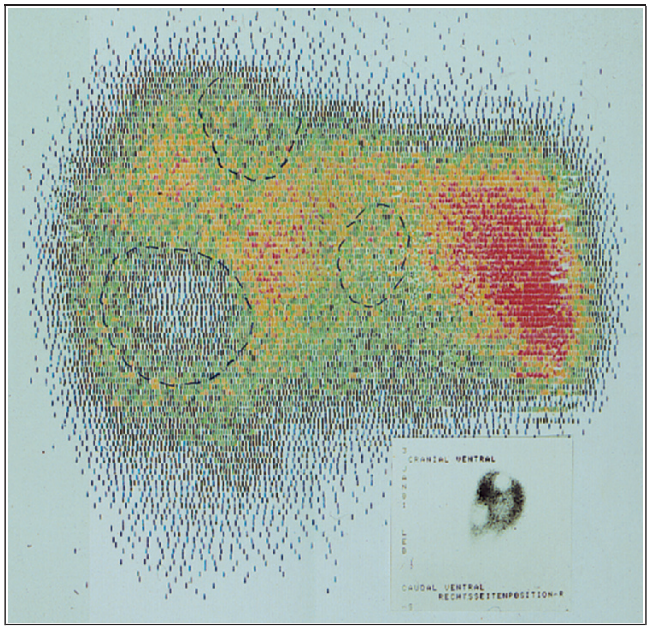

Fig. 9.2: Amoebic abscesses: storage defects and indistinct liver contours with hepatomegaly (s. fig. 25.1)

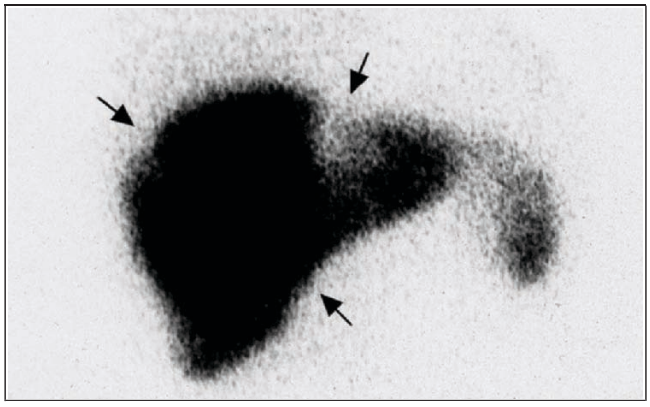

Fig. 9.3: Liver metastases: Anterior view during scintigraphy using Tc^{99m}-S-colloid (100 MBq): three foci in the right lobe of liver in colon carcinoma

3 Hepatobiliary sequential scintigraphy

^{99m}Tc-iminodiacetic acid derivatives (IDA, HIDA, DISIDA, BIDA) usually reach their maximum concentration in the hepatocytes 2–5 minutes after i.v. injec-

tion and are then excreted into the bile ducts. After 30−45 minutes, the radioactive substance has largely been cleared from the liver. (4, 14, 26) • ^{99m}Tc-mebrofenin correlates well with the ICG clearance test. It provides information of segmental functional liver tissue, which is of additional use when planning liver resection. (8) (s. tab. 9.2)

1. Examination of the hepatic perfusion of focal lesions
2. Evaluation of radionuclide uptake by hepatocytes (parenchymal phase): assessment of liver function (34)
3. Detection of biliary obstruction, such as in cholestatic syndrome with and without jaundice
   − search for (posttraumatic or postoperative) biliary leakage (e. g. following liver transplantation)
4. Examination of bilio-digestive anastomosis
5. Monitoring runoff after papillotomy
6. Follow-up after liver transplantation
7. Differential diagnosis of neonatal jaundice (below 10−12 mg/dl) vs. neonatal biliary atresia
8. Contrast-medium intolerance
9. Acute cholecystitis (exact visualization of the gall bladder excludes acute cholecystitis)
10. Focal nodular hyperplasia

Tab. 9.2: Indications for hepatobiliary sequential scintigraphy

3.1 Cholestasis

Differentiation between obstructive and parenchymatous cholestasis is possible in >90% of cases. A serum bilirubin level of up to 30 mg/dl is not seen as a methodological impediment to sequential scintigraphy. In incomplete obstruction with nondilated bile ducts, this technique provides more information than can be obtained using ultrasound. (17, 19)

^{75}SeHCAT: The homotaurocholic acid test using ^{75}Se to evaluate the hepatobiliary function (e. g. in the bile-acids losing syndrome) is also worth mentioning here. (42)

Scintigraphic assessment of **liver transplants** is helpful (e.g. perfusion, rejection, bile-duct obstruction or bile leakage). (29)

3.2 Focal nodular hyperplasia

FNH is the second most frequent benign hepatic tumour. It is a pseudotumorous regenerative node, most frequently occurring in women. Four-phase cholescintigraphy using ^{99m}Tc-IDA is currently the best method of detection. In 80−90% of cases, perfusion is good with hypervascular tumours of >2−3 cm in diameter. This results in initial enhancement of the FNH. However, the tracer cannot be discharged into the bile ducts quickly enough, because in FNH they only consist of irregular proliferations. This results in tracer retention in the excretion phase (so-called "trapping") in FNH, whereas the surrounding liver parenchyma is already tracer-free. Preserved colloid uptake by the RES is typical, whereas occasional uptake is deemed pathognomonic. • In 10−20% of cases, no intact RES is available in FNH. Thus the latter is scintigraphically "cold". (14, 40)

3.3 Hepatic adenoma

Hepatic adenoma consists of atypical, strand-like hepatocytes. It is characterized by normal perfusion and an extensive absence of Kupffer cells as well as irregularity of the bile ducts. Scintigraphically, it is possible to demonstrate that there is no elimination of iminodiacetates from the adenoma and that uptake of the radioactive tracer is prolonged compared with the normal liver parenchyma ("trapping" on IDA scans). (40) No colloidal albumin or ^{99m}Tc-colloid is taken up − this allows differentiation of an adenoma from focal nodular hyperplasia. • The additional use of the SPECT technique increases sensitivity.

3.4 Biliary leakage

Hepatobiliary sequential scintigraphy has proved useful in tracing biliary leakage, especially when it is posttraumatic or postoperative. With the help of this method, it is possible to demonstrate pathognomonic extrahepatic nuclide accumulation in the traumatized areas. A biliary leakage of 0.5 ml/min can be easily detected. Sensitivity and specificity are as high as 100%. This procedure is used as an initial screening modality in suspected biliary leakage. (29, 32, 42)

3.5 Liver blood flow

^{99m}Tc-DTPA: Arterial perfusion accounts for 20−40% of the circulation; in portal hypertension, cirrhosis causes arterial perfusion to increase to over 60%. In portal vein thrombosis, only an arterial curve is visible. Liver metastasis usually displays relatively high arterial perfusion. In (rare) occlusions of the hepatic artery, only a portal venous curve is visible. When a bolus injection of 400 MBq ^{99m}Tc-diethylenetriamine pentaacetic acid (DTPA) is applied, scintigraphy is able to reveal a biphasic time-activity curve. The initial increase of activity is produced by the arterial influence and the second peak by the portal venous inflow. Both curves can be evaluated quantitatively. (38) • Perfusion scintigraphy may be useful in the case of liver trauma, TIPS, hypervascularized hepatic tumours and partial liver resection as well as after liver transplantation.

3.6 Diffuse liver disease

^{99m}Tc-NGA: Hepatic binding protein (HBP) found on the hepatocyte surface can bind desialylated glycoproteins with terminal galactose residues. There is a close correlation between a change in HBP activity due to liver trauma and an increase in bonding inhibitors in plasma. • Galactosyl-neoglycoalbumin (NGA) belongs to a group of hepatocyte-specific tracers, whose accumulation is dependent upon HBP bonding; this can be measured scintigraphically using ^{99m}Tc-NGA (D.R. Vera et al., 1984). The lysosomes mark the end of the tracer take-up in the hepatocytes (> 90 %). • The first clinical findings in cases of liver trauma were reported on by the same group (R.C. Stadalnik et al., 1980). Results of the investigation into liver cirrhosis and HCC were presented later. It has not yet been possible to obtain any substantial findings in diffuse liver damage using conventional tracer methods. However, use of the hepatocyte-specific tracer ^{99m}Tc-NGA can be helpful in assessing liver injury and recovery. (16, 34, 37)

3.7 Hepatocellular carcinoma

^{67}Gallium: The uptake of ^{67}gallium by HCC is greater than in normal liver tissue. It is possible to differentiate foci in cirrhosis with the help of this radionuclide. In the case of a focus measuring more than 2 cm, specificity is 91% and sensitivity is 96%. This method should also be used for detecting early recurrent HCC. The tracer ^{67}gallium is, however, non-specific, since it is also taken up by non-hepatocyte-derived tumours and inflammatory lesions. (33) • Colloid scintigraphy and IDA derivates are not significant in HCC diagnosis.

3.8 Neuroendocrine tumour

^{111}In DTPA-DPhe-Octreotide: Neuroendocrine tumours show a greater expression of somatostatin receptors, which can be detected by means of this marked ligand. Such a form of szintigraphy makes it possible to locate a primary tumour as well as metastases; it is also indicated to monitor therapy.

4 Erythrocyte scintigraphy

Blood pool scintigraphy using a bolus injection of 750 MBq ^{99m}Tc-labelled erythrocytes may lead to a diagnosis of intrahepatic space-occupying processes which cannot be differentiated by US or CT. This applies especially to haematomas, haemangiomas and haemangiosarcomas. The SPECT technique helps to increase sensitivity. With regard to angiographic imaging reconstruction, however, the contrast medium-based imaging techniques available today produce by far the best results.

4.1 Haemangioma

Cavernous haemangiomas are the most common form of benign liver tumours. They occur in the form of a single lesion in approx. 90% of cases. When using ^{99m}Tc-pertechnetate labelling, haemangiomas exhibit a reduced uptake of radioactivity in the early perfusion phase compared with adjacent liver tissue; in the late phase, however, an increase in uptake is detectable. This "fill in" occurs faster in small haemangiomas than in larger ones due to the lower stasis. In the latter case, scanning should be carried out at a later phase. At 2 cm, a specificity and sensitivity of up to 100% is obtainable using a high-resolution three-headed system. (42) Smaller haemangiomas (< 2 cm) can be identified by interference-free SPECT in up to 90% of cases. (15, 35) The RES, hepatocytes and bile ducts show no scintigraphic reaction. (1–3, 15, 21, 25, 43)

5 Positron emission tomography

Positron emission tomography (PET) has two significant advantages compared to single-photon emission computed tomography: (*1.*) improved spatial resolution, and (*2.*) absolute quantification of tracer take-up.

Positron emission tomography with **^{18}F-fluoro-2-deoxy-D-glucose** (^{18}F-FDG) visualizes partial physiological and biochemical functions and thus also pathophysiological and pathobiochemical aspects at the molecular level in a nuclear medical procedure. PET may be a useful method for the differential diagnosis of hepatic foci (malignant/benign). Liver metastases of gastrointestinal tumours can be detected with significantly greater sensitivity using ^{18}F-FDG-PET. In relapse diagnosis of colorectal carcinoma, sensitivity is 93–100% and specificity 95–98%. (5, 35) Malignant melanoma takes up the most ^{18}F-FDG, enabling foci as small as 1.5 mm (as well as affected lymph nodes) to be identified with a high degree of accuracy. Hodgkin's lymphoma, which accounts for approx. 1% of all carci-

1. Lentodegenerative alterations in Wilson's disease
2. Biochemical changes related to hepatic encephalopathy
   - measurement of the blood-brain barrier by ^{68}Ga-DTPA
   - determination of neuroreceptors by ^{18}F-dopa, ^{11}C-dopamine, ^{11}C-serotonin
   - neurotransmitter mapping by ^{18}F in combination with metaraminol, *etc.*
3. Questions on protein synthesis
   - by means of ^{11}C-labelled methionine, leucine, phenylalanine
4. Hypoxia/necrosis markers
   - by means of ^{18}F-labelled misonidazole
5. Glucose metabolism-related activity patterns of liver cells
6. Measurable assessment of liver cell regeneration
   - by means of 2-^{11}C thymidine, *etc.*
7. Detection of hepatocellular carcinoma
   - by means of ^{11}C-acetate

Tab. 9.3: Application fields for PET scanning in (still experimental) hepatology with respective tracers

nomas, is a rare entity. In stages I and II, the 10-year survival rate is around 80%. PET has proved to be a useful tool in staging and monitoring. (6) • In the field of (still experimental) hepatology, a wide range of **scientific issues** may be amenable to PET. (s. tab. 9.3).

Tumour cells frequently display increased glycolysis. A radioactive-marked glucose derivative can therefore be taken up in the tumour cells and demonstrated using a PET scan after 40−45 minutes. The glucose cellular metabolism is measured after i.v. injection of ^{18}F-FDG. This tracer is easily absorbed by the cells before being converted by hexokinase into ^{18}F-FDG-6-phosphate which, after phosphorylation, is subsequently trapped inside the cells for a prolonged period ("metabolic trapping"). Its half-life is 110 minutes. In the field of hepatology, ^{18}F-FDG-PET has become clinically significant in staging, therapy follow-up and relapse diagnosis of liver tumours. (5, 7, 10, 13, 24, 31, 35)

^{68}Ga DOTATOC-PET: In PET, the gamma emitter ^{111}In is replaced by the positron emitter ^{68}Ga. This tracer is highly specific for detecting somatostatin receptors, particularly in combination with CT/PET.

^{18}FDOPA-PET: Neuroendocrine tumours are able to decarboxylate 5-hydroxytryptamin and L-3-4-dihydroxyphenylalanin. This tracer can therefore be used for diagnosis and monitoring therapy.

^{11}C-acetate: The application of ^{11}C-acetate PET led to far higher sensitivity and specificity than was the case with ^{67}Ga scintigraphy. Thus this technique may become a potential diagnostic tool. (18)

6 Flow diagram in suspected "liver tumour"

Various tumourous and pseudotumourous foci may form in the liver and hepatobiliary system. Differential diagnosis in thus more challenging. But a definitive diagnosis is necessary to be able to initiate therapeutic measures and to establish a prognosis.

After carrying out the imaging techniques (if necessary with contrast media) *(see chapters 6, 8, 9)* and laparoscopy/biopsy *(see chapter 7)*, the strategy of establishing a diagnosis by **flow diagram** is recommended in suspected **"liver tumour".** (s. fig. 9.4)

A flow chart should include echocomplex focuses and a distinction between single and multiple focuses. Haematoma and (especially) abscesses, are not always echofree; they may also be hypoechoic or reveal varied echoes. This must be taken into account in the diagnosis of these two conditions. Scintigraphy is becoming less significant, whereas MRI is considerably more important today. However, scintigraphy may be indicated when carrying out a differential diagnosis for adenoma and FNH. Economic constraints can make it necessary to omit some diagnostic steps regarding imaging procedures in order to produce a faster and more cost-effective diagnosis. As an alternative, targeted FNB, biopsies or laparoscopy are recommended. It may even be desirable in individual cases to obtain an earlier histological diagnosis and, if necessary, follow the flow chart in the opposite direction. • *All in all, an extremely careful and critical assessment is required, taking into account the risks, costs and benefits involved.* (s. fig. 13.2)

► In cases of suspected *"liver tumour"*, **ultrasonography** is the method of choice. If the type of focal process cannot be adequately identified even by very experienced investigators, sonographic monitoring should be performed within a short period of time. Even in cases where the differential diagnostic approach fails, pathological or potentially positive findings can still be obtained with a certain degree of reliability. If an exact diagnosis cannot be achieved, however, imaging techniques are then as a rule indicated. (s. fig. 9.4)

► In order to clarify pathological results or potentially positive findings, **computer tomography** is indicated. The use of CT may also be advisable even with negative sonographic findings if the clinical and laboratory parameters point to a focal process in the area of the liver or the biliary tract. (s. fig. 9.4)

► In the case of differential diagnosis of adenoma versus focal nodular hyperplasia, **scintigraphy** is indicated, whereas in the case of metastases, more reliable imaging techniques are preferred. (s. fig. 9.4)

► In suspected haemangioma, sonography, scintigraphy and MRI are the most efficient procedures. • In individual cases, these three imaging techniques might be interrelated with respect to diagnosis/indication. (s. fig. 9.4)

► Should the differential diagnosis of focal liver findings remain unresolved despite the use of imaging techniques, **laparoscopy** is indicated (possibly with targeted forceps biopsy or liver biopsy). Depending on the findings, *explorative laparoscopy* is also undertaken for the purpose of tumour staging. • Medical assessment of the clinical and sonographic findings may, in some cases, suggest laparoscopy with targeted tissue biopsy − even without previous CT − when an accurate diagnosis is required. (s. p. 158) (s. fig. 9.4)

► The indications for sonography-guided or CT-guided **fine-needle biopsy** (FNB) are (*1.*) contraindications to the use of laparoscopy (s. p. 149) or (*2.*) if it seems unlikely that previously unresolved findings will be clarified by laparoscopy. • In consideration of all relevant findings from sonography or CT as well as the patient's condition,

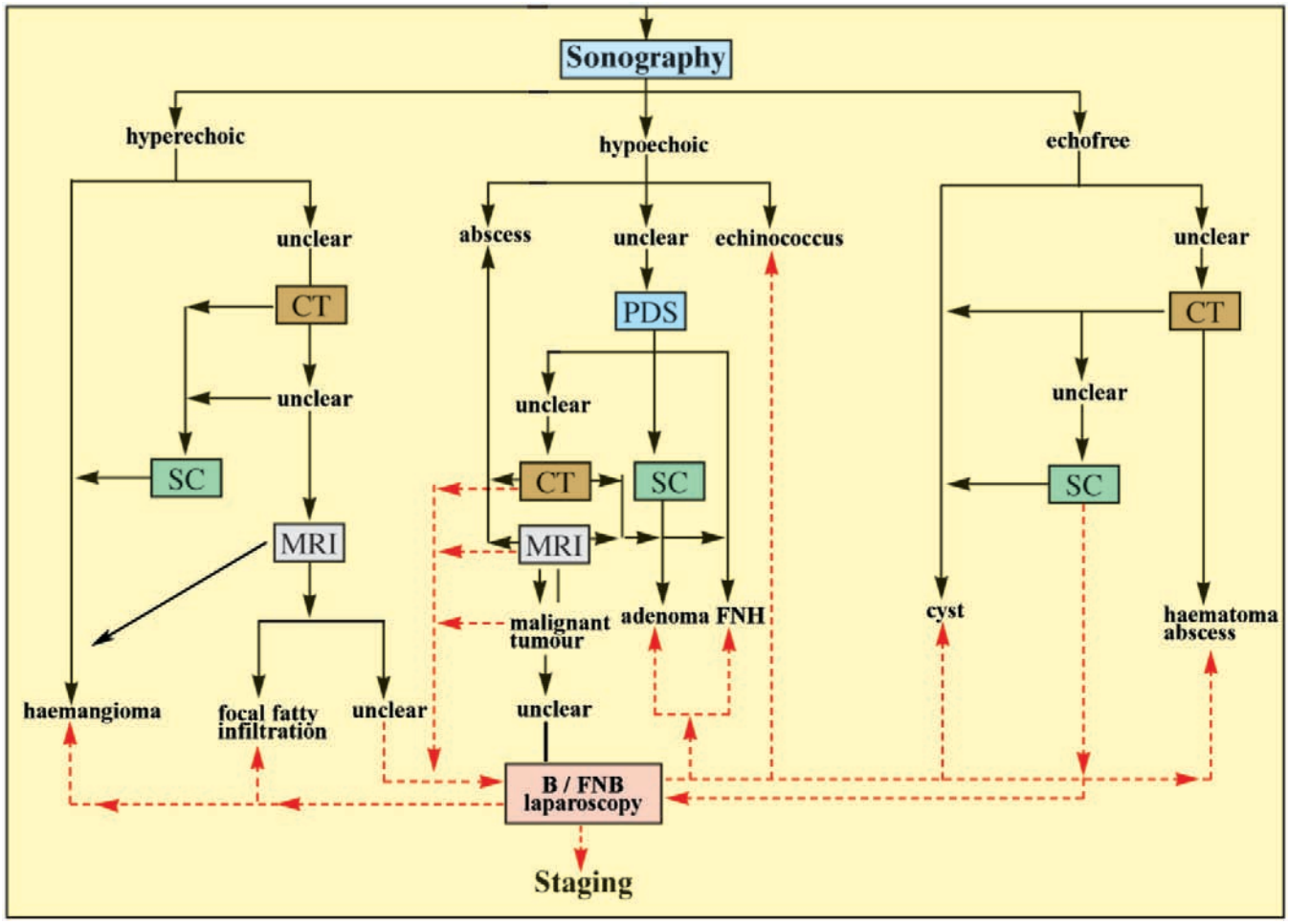

Fig. 9.4: *Flow chart for use in clinically suspected "liver tumour" with positive sonographic findings.* • Imaging procedures (—►) which may be indicated include power-Doppler sonography (PDS), computer tomography (CT), magnetic resonance imaging (MRI) and scintigraphy (SC). • Histological diagnosis is indicated in some cases in order to confirm or exclude imaging diagnosis. (---►)

it may be necessary in individual cases to resort to FNB as the primary approach instead of biopsy or laparoscopy. (s. fig. 9.4) • The non-availability of laparoscopy or insufficient experience with this technique are in themselves not an "indication" for percutaneous fine-needle biopsy. (s. fig. 9.4)

In view of growing financial constraints in many contries regarding the health service, the question of the cost/benefit ratio should also be taken into consideration. In the current economic situation, the **total costs** incurred for the respective examination methods can indeed be substantial.

Basically, the **prioritization of methods** within a diagnostic flow diagram should be determined by the question of whether (*1.*) use of an examination technique is indicated, (*2.*) indication applies at the given moment, and (*3.*) definitive diagnosis is likely to be obtained. • *Usually, only a definitive diagnosis allows statements to be made on therapy and prognosis!*

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