Chapter 5

Primary Liver Tumours – Presentation, Diagnosis and Surgical Treatment

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1. Introduction

Cystic lesions of the liver such as dysontogenic cysts and cystic disease of the liver, haemangioma, focal nodular hyperplasia (FNH), disturbed fat distribution of the liver, hamartoma and liver cell adenoma are summarized under the term primary benign hepatic tumours. On the other hand, malignant tumours of the liver are classified into primary and secondary tumours. Primary malignant hepatic tumours are hepatocellular carcinoma (HCC) and cholangiocellular carcinoma (CCC). In addition to the aforementioned tumours one also has to consider rare and very rare primary hepatic tumours, e.g. hemangioendothelioma and hepatosarcoma as well as hepatoblastoma in children. Secondary tumours of the liver, i.e. liver metastases, may result from various primary tumours located throughout the entire body and need to be discussed separately. Another important group of liver lesions are parasitic liver tumours, particularly Echinococcus cysticus and Echinococcus alveolaris, which also do not emanate primarily from the liver tissue.

From a surgeon's point of view, new scientific findings and developments in the surgical procedures of liver resection as well as additional emerging treatment strategies used for HCC, are worthy of note. Liver resection and liver transplantation as the surgical therapy options are competing with regard to the best clinical long-term results, but they complement each other in multimodal therapy concepts. Numerous new insights for the optimal concept of a multimodal therapy including surgical procedures, i.e. liver transplantation and liver resection, are to be expected. Life prolonging medical therapy with Sorafenib for advanced, inoperable HCC is particularly notable, highlighting an important medical therapy may play in the future development of multimodal treatment concepts. Laparoscopic procedures are used increasingly in liver surgery, and at least in the current literature, there is agreement that

skills in laparoscopic surgery will not only be expected for cholecystectomy, but also increasingly for liver resection

2. Preoperative differential diagnosis of liver masses

2.1. Presentation and symptoms

An abdominal ultrasound scan (US) is used frequently as routine examination in patients presenting for a medical check-up or for clarification of symptoms such as upper abdominal pain, weight loss, anaemia, power loss, icterus and/or fever. However, these symptoms occur only in very advanced stages of malignant primary and secondary hepatic tumours.

Confirmed individual risk factors for HCC include age, alcohol abuse as well as concomitant or primary diseases, e.g. liver cirrhosis, non-alcoholic fatty degeneration of the liver (NASH), hemochromatosis, autoimmune hepatitis and chronic viral hepatitis B (HBV) or C (HCV). Interestingly, a case control study in a patient population from the M.D. Anderson Cancer Centers in Houston suggests that liver cirrhosis and chronic hepatitis C are also potential risk factors for the development of an intrahepatic CCC (Shaib YH et al.) This was not the case for extrahepatic CCC, although alcohol abuse per se, rather than cirrhosis or hepatitis, was reportedly a risk factor for both intra and extra hepatic CCC. Elevation of the tumour marker CA 19-9, as well as CA 50, was evident in approximately 60 % of cases with CCC.

Fever and chills are typical symptoms of bacterial cholangitis, which can occur with increasing frequency in primary sclerosing cholangitis (PSC). After a prolonged course, PSC is a known risk factor for both extrahepatic proximal bile duct carcinoma (Klatskin tumour, histologically CCC) and intrahepatic CCC. Frequently, icterus is the first symptom of a Klatskin tumour. In case of fever and evidence of a cystic liver mass, differentially a liver abscess has to be considered. If extrahepatic symptoms are present at the time of diagnosis of a liver cancer, such as deterioration of the general condition with weight loss, anaemia and/or weakness, one also has to consider a possible hepatic metastasis.

In females oral contraceptives are frequently discussed as a risk factor for the development of liver adenomas and FNH. Depending on the origin of the patient from an endemic area or after visits abroad, chronic hepatitis B or C as risk factors for liver cirrhosis as well as parasitic cystic liver diseases (e.g. echinococcosis) need to be considered. Intravenous drug abuse also is a known risk factor for chronic hepatitis B or C, which in turn are known risk factors for the development of liver cirrhosis and HCC.

2.2. Medical imaging and the role of preoperative fine-needle biopsy

In approximately 20 % of all routinely performed US of the abdomen liver masses are noted. Generally, these masses can be either benign, such as. cysts, hemangiomas, disturbed fat distribution, hamartomas, FNH and liver adenomas or malignant (See Table 1). Malignant masses include liver metastases and malignant primary liver tumours, e.g. HCC and CCC.

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Particularly rare differential diagnoses are hepatoblastoma in children and in adults hepatic sarcoma and hemangioendothelioma.

After sonographic diagnosis of a liver mass other imaging procedures available for further differential diagnostic are US with contrast medium (CM), computer tomography (CT), magnetic resonance imaging (MRI), nuclear-medical procedures, US-guided liver biopsy and finally, the confirmation of the diagnosis following liver resection (Table 1).

Benign liver tumours	Characteristics demonstrated by radiological imaging
Cavernous haemangioma	Contrast medium-assisted US scan, CT, MRI: during the arterial phase discontinuous nodular enhancement at the tumour periphery followed by centripetal absorption of the contrast medium.
Liver cell adenoma	Under application of contrast medium early arterial wash-in and adaptation to the liver parenchyma in the late phase.
Focal nodular hyperplasia	Wheel spoke structure of the vascular architecture with central scar; under application of contrast medium star-shaped arterial vascularisation, homogenous adaptation to the liver parenchyma in the late phase.
Liver cysts	Conventional US: no echo, absence of a wall, dorsal intensified echo. In CT demonstration if septa and calcification in case of echinococcus.
Malignant liver tumours	**Characteristics demonstrated by radiological imaging**
Liver metastases	Good detection with US scan, CT and MRI. Very variable presentation.
Hepatocellular carcinoma	Early arterial hypervascularisation with quick wash-out during the parenchymal phase.
Cholangiocellular carcinoma	Difficult to detect, use of multimodal radiological imaging methods makes sense (US, CT, MRI, when suspecting a Klatskin tumour ERCP).

Table 1. Characteristics of focal liver masses in radiological imaging.

Today, presentation combined with medical imaging enables us to obtain the correct diagnosis in more than 90 % of cases before the final histological result is available. The algorithm depicted in Figure 1 shows the diagnostic approach under inclusion of modern imaging procedures.

Basically it would be most preferable to have an almost positive differential diagnosis prior to commencing surgery, particularly as extensive liver resection involves considerable risks, which are to be taken seriously. Furthermore, the choice of the best possible multimodal therapy often depends on the differential diagnosis of the malignant tumours. To date, incorporation of the surgical treatment options liver resection and liver transplantation in an interdisciplinary treatment concept can be considered as a standard. As presented below, this interdisciplinary treatment concept can vary considerably depending on the type of liver tumour diagnosed and possible additional diseases of the parenchyma, e.g. liver cirrhosis.

As a specialized centre for liver resection and transplantation, we personally have found cases in which, contrary to the results of the preoperative imaging, diagnosis of a malignant tumour could not be confirmed in the final histology. It is not rare that instead of the suspected HCC

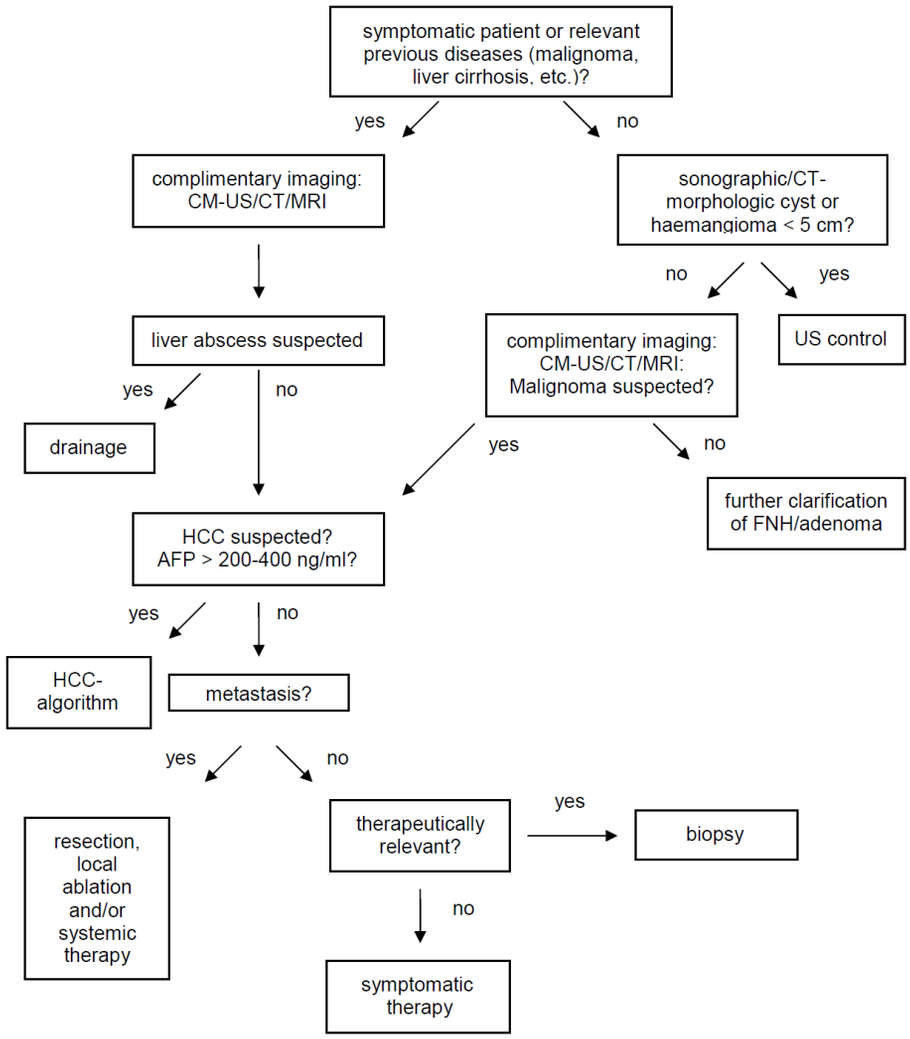

Figure 1. Algorithm for the clarification of a focal liver lesion (For HCC-algoritm see Fig 4 or EORTC EASL 2012)

the final histology shows an adenoma or intrahepatic haematoma, a haemangioma or a comparatively harmless hamartoma, none of which require urgent surgical treatment. The quality of the current preoperative radiological diagnostic together with the determination of the tumour marker alpha-fetoprotein (AFP) and the patient's anamnesis does not necessarily require a preoperative histological confirmation with fine-needle biopsy of the diagnosis of malignant liver tumour. Due to possible false negative results and the risk of potential implantation metastases in the puncture channel, today frequently a fine-needle biopsy is explicitly not desired. Therefore, one has to expect cases in which the preoperatively assumed malignancy is not confirmed histologically in the resection sample. In view of this fact, patients should be informed explicitly of this small but still existing risk. However, it has to be pointed out that in patients with a new liver mass and a history of a malignant tumour, the probability is great that this mass is a metastasis. In patients with the typical risk constellations for HCC, e.g. liver cirrhosis or chronic HBV or HCV or hemochromatosis, the risk of the new liver mass

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being a HCC is considerably higher, even when the serum AFP value is not verifiably elevated. In cases of doubt, an US-guided fine-needle biopsy makes sense, although it has to be considered that a negative histology cannot positively exclude a malignant tumour.

3. Indication for surgery for primary liver tumours

Primary malignant liver tumours and liver metastases are the most frequent indications for liver resection. When liver resection is indicated the patient's general condition and the comorbidity must not be disregarded. Particularly patients with cardiovascular and pulmonary diseases should receive the appropriate optimal treatment for these conditions prior to the planned liver resection to minimize the general risks, especially the post-surgical mortality. Preoperatively, it should be made absolutely clear to the patient that it is vital to avoid exposure to hepatotoxic substances, e.g. alcohol, paracetamol and drugs and preferably also to refrain from smoking. When deciding on the indication disease-specific aspects are also to be considered, e.g. type of liver tumour and degree of possible concomitant diseases of the liver parenchyma (Figure 1).

3.1. Evaluation of the risk of postoperative liver failure after liver resection and clarification of a possible indication for liver transplantation

Prior to any liver resection it is vital that the liver function is checked. If impaired liver function is evident (e.g. reduced serum cholinesterase or prothrombin time (PT), or elevated INR value without causal anticoagulative medication), an additional liver parenchyma disease should either be diagnosed or excluded (e.g. fatty liver, viral hepatitis, liver cirrhosis, NASH, hemochromatosis etc.). As a rule, these conditions have a considerable influence on the risk for potentially lethal postoperative liver failure. Further morphological indirect signs of a possible additional disease of the parenchyma are ascites and evidence of circulatory collaterals; these can be seen in either Doppler-US or CT of the abdomen.

Preoperatively unknown thrombocytopenia or hyperbilirubinaemia should also give cause to consider an additional liver disease other than a liver tumour. In such cases it is urgently recommended to consult an experienced hepatologist for detailed diagnostic purposes. Should in addition to the HCC a parenchymal disease and impaired liver function be diagnosed, depending on the individual case, the surgical treatment option should be liver transplantation instead of resection. In any case, such patients should be referred to a liver centre that can offer all relevant therapy modalities, including transplantation, for the treatment of HCC. Disregard of these basic principles can result in fatal errors, which can lead to the surgeon being confronted with a potentially preventable and difficult to treat postoperative liver failure. In addition, the surgeon would be unaware of the exact parenchymal damage that was the essential contributor; neither would he be in a position to consider liver transplantation as a possible alternative.

Today, the generally accepted standard in most cases is interdisciplinary treatment and a multimodal therapy concept. When combining multimodal therapy concepts with liver

resection, the general rule is to adhere to an interval of at least 4-6 weeks between chemotherapy and planned liver resection. This is vital to minimize the risk of postoperative liver failure as sequelae of resection combined with a more or less hepatotoxic chemotherapy. Such an interval will allow time for physiological liver regeneration instead of unnecessarily endangering regeneration through possibly still active cytostatic effects of the chemotherapy.

If extended liver resection is indicated and a remaining liver volume is expected to be small, means of minimizing the risk of postoperative liver failure should be considered, e.g. hypertrophy of the remaining liver tissue. When considering that this may be necessary, it can be useful in individual cases to perform volumetry with using digital CT-, MRI- or US-data to determine the remaining liver volume in relation to the liver volume to be resected.

Particularly difficult is the preoperative assessment and prediction of the function of the liver tissue remaining after resection, especially when extended resection is necessary, with the possibility of additional damage to the liver parenchyma. It is catastrophic for the patient and his relatives, as well as for the liver surgeon, if after liver resection the remaining liver 'fails' as a result of the so-called small-for-size syndrome. This syndrome has a high mortality. Currently, it is still impossible to forecast accurately the probable function of the remaining liver tissue. Here the surgeon's skills and experience still play a prominent role. Particularly in patients with malignant tumours for whom the primary liver transplantation as alternative to liver resection is out of the question (e.g. CCC or non-neuroendocrine liver metastases), the possible risk of a potentially lethal failure of the remaining liver tissue after surgery has to be discussed in detail with the patients and their relatives. In principle, when informing the patients of risks and chances of liver resection, this problem should also be discussed in detail. In some cases of postoperative liver failure after resection an emergency liver transplantation save life, if a suitable organ becomes available in time. Of course, it cannot be assumed that this presents a realistic option in each case of failure of the remaining liver tissue.

Fortunately, it is rarely the case that the established radiological and laboratory-chemical methods do not show any signs of a cirrhotic liver and cirrhosis is primarily discovered during surgery. If the standard preoperative preparations were performed, it is our opinion that it is not necessarily a treatment error if the diagnosis of liver cirrhosis is initially made during surgery. The reason for this being that it is widely known that in many cases there are only indirect clinical signs. Generally, cirrhosis only becomes clinically notable at the advanced stage, and ultimately can only be confirmed histologically as currently routine preoperative liver biopsy cannot be generally recommended.

3.2. Neuroendocrine liver tumours

In the case of liver metastases of neuroendocrine tumours, e.g. those rare primary neuroendocrine liver tumours, which however are usually metastases of a still undiagnosed primary tumour, instead of liver resection there is the alternative of liver transplantation. However, it has to be noted that according to the presently valid and binding guidelines of the Federal Medical Council liver transplantation is permitted as an option for neuroendocrine liver metastases after potentially curatively resected primary tumour. These guidelines categori-

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cally rule out liver transplantation as a treatment option for other liver metastases, e.g. for the comparatively frequent colorectal liver metastases.

3.3. Intrahepatic cholangiocellular carcinoma and Klatskin tumour

As currently there are no other potential curative therapy options for CCC (Figure 2), e.g. radiation treatment or chemotherapy, one should consider the indication for liver resection rather liberally. This also applies for the intrahepatic CCC and the proximal bile duct carcinoma at the hepatic bifurcation, the so-called Klatskin tumour. Particularly in the case of a Klatskin tumour it is necessary to take the risk to perform only an exploratory laparotomy. Especially this tumour frequently permits only intraoperatively to determine definitively whether it is technically viable with a justifiable risk and whether resection is potentially curative. In some cases one can only determine after the resection of the hepatic bifurcation and affected liver lobe that ultimately histologically tumour-free resection margins are not feasible without risking failure of the residual liver by a too greatly extended liver resection. In this context one has to consider that depending on the extent of resection, connecting the intrahepatic bile ducts of the 3rd order or bile ducts located even further peripheral to a biliodigestive anastomosis becomes increasingly more difficult or technically surgical impossible. The intraoperative assessment of the extent of resection necessary must in these cases clearly be left to the experience of the operating surgeon. In our opinion it is certainly not a treatment error to complete the intervention as R1-resection. We consider that in the case of a Klatskin tumour it is rather the question whether or not refusal of referral to a centre particularly experienced in the field of hepatobiliary surgery for an explorative laparotomy is regarded as a possible treatment error, e.g. in the sense this may be considered as refusing any patient his legitimate right to an indicated operation. It should always be kept in mind that for a Klatskin tumour there are no other surgical options with a potential perspective for long-term survival, and it is our experience that as a rule it is impossible to recognize whether or not a curative resectability of a Klatskin tumour is feasible solely by means of radiological imaging. It can occur that a patient with PSC develops a proximal bile duct carcinoma, e.g. a Klatskin tumour, while waiting for liver transplantation, or is suspected as the result of the cytological examination of epithelial tissue of the bile duct. Today, these patients still have the option of liver transplantation as well as the option of an application to EUROTRANSPLANT for an upgrade of the urgency based on the match MELD score. This could probably shorten the time on the waiting list for a donor organ. In such cases neglecting to submit to EUROTRANSPLANT the application for an upgrade of the match MELD score could possibly be considered as a treatment error. However, this option is currently not available to patients with a Klatskin tumour due to poor experience regarding their long-term course.

In case of an intrahepatic CCC it is unquestionable that liver resection is the only potential curative method of treatment and thus should always be intended despite the generally high risk associated with the surgical intervention, e.g. due to a congruently marked comorbidity. According to the currently valid and binding guidelines of the Federal Medical Council liver transplantation is no longer a treatment option available to patients with intrahepatic CCC; this decision is based on the poor experiences made in the past regarding the long-term courses of these patients.

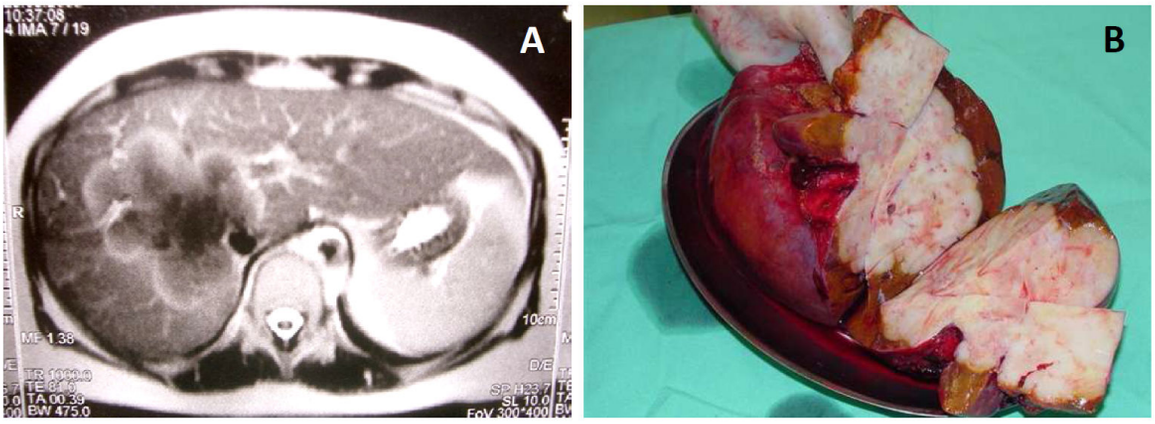

Figure 2. MRI scan (**A**) and surgical specimen (**B**) of a cholangiocellular carcinoma (CCC).

3.4. Hepatocellular Carcinoma (HCC)

For the treatment of HCC (Figure 3) the indication for resection and liver transplantation should be highly differentiated. One also has to consider alternative or complimentary therapeutic methods, which should or could be adopted multimodal with resection or transplantation (Figure 4). Here are meant particularly transarterial chemoembolisation (TACE), radio-frequency induced thermoablation (RITA) and percutaneous ethanol instillation (PEI) as well as chemotherapy with the protein kinase inhibitor Sorafenib.

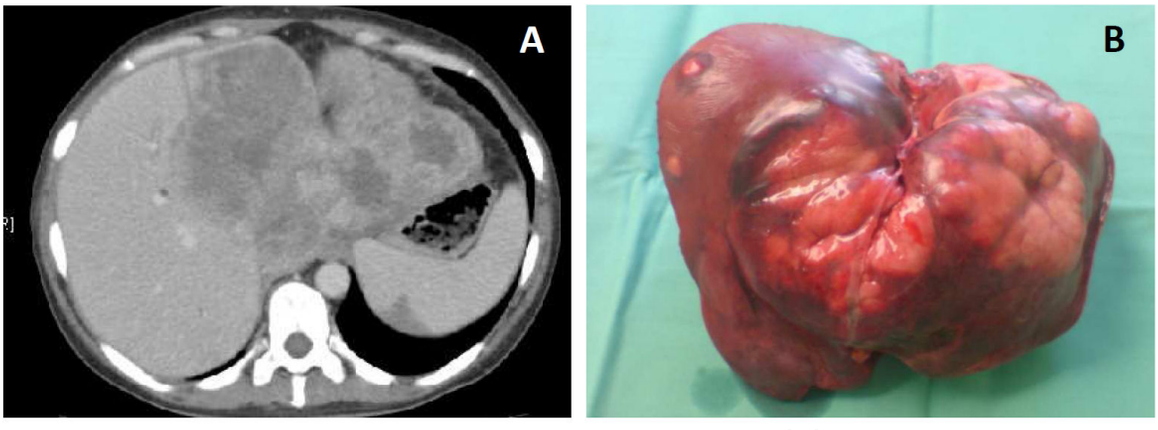

Figure 3. CT scan (**A**) and surgical specimen (**B**) of a hepatocellular carcinoma (HCC) without liver cirrhosis.

The interventional methods, e.g. TACE, RITA and PEI should be used in close interdisciplinary context with the surgical treatment options and be applied according to the individual case (Figure 4). Further consideration has to be given to additional diseases of the liver parenchyma, e.g. fatty liver, liver fibrosis, cirrhosis and hepatitis (viral hepatitis B and C, autoimmune hepatitis, NASH). Not to be disregarded is the drug treatment already applied for these conditions as this may have an influence on the risk of liver failure after liver resection or other interventions and in the case of a HCC this could well be an indication

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for liver transplantation. Furthermore, a prerequisite should be the most exact tumour staging possible with the modern imaging methods, e.g. to enable a positive exclusion of extrahepatic tumour growth or vascular infiltration prior to reaching the indication. Close interdisciplinary cooperation in the liver transplantation centre with regularly held case discussions has proven to be essential regarding avoidance of erroneous indications. Today such close interdisciplinary cooperations, including regular case discussions, should be made a requirement for the treatment of HCC.

For patients with HCC, liver transplantation presents a potentially curative therapy option depending on the tumour stage at the time of transplantation. However, in most transplantation centres the precondition is that these patients have to fulfil the so-called Milan criteria to be accepted on the waiting list (no extrahepatic tumour growth, exclusion of infiltration of the portal vein, a maximum of 3 tumour nodules with diameter of less than 3 cm, the size of a single tumour nodule must be less than 5 cm).

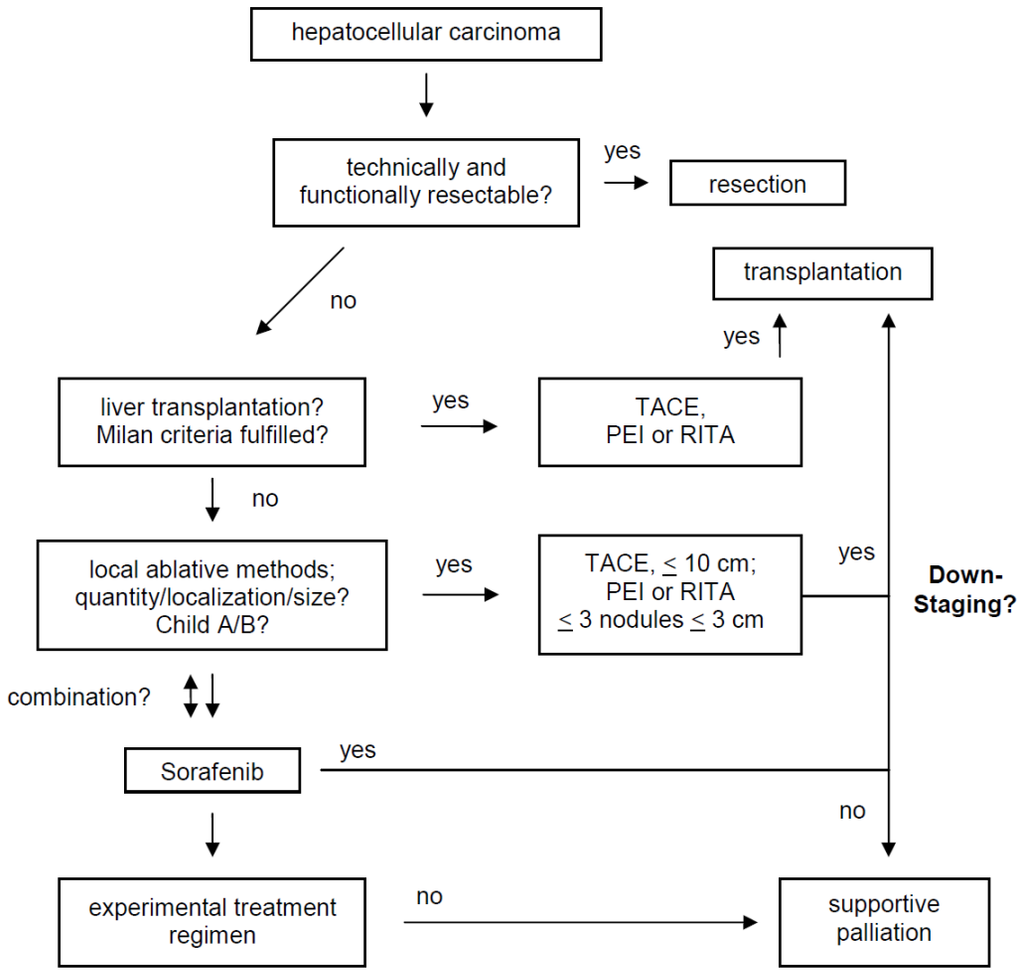

Figure 4. Algorithm for the therapy of hepatocellular carcinoma (HCC).

Liver transplantation is the treatment of first choice for selective patients with HCC, e.g. patients who are not candidates for resection and with tumour growth limited to the liver only. With transplantation optimal results can be achieved in patients with single lesions (diameter 2 – 5 cm or no more than 3 lesions with a max. diameter of 3 cm) without radiolocal evidence of extrahepatic tumour spread (Figures 5a/b). To achieve optimal results in patients with the above mentioned characteristics, it is imperative that a donor organ becomes available within 6 months (Figures 5c).

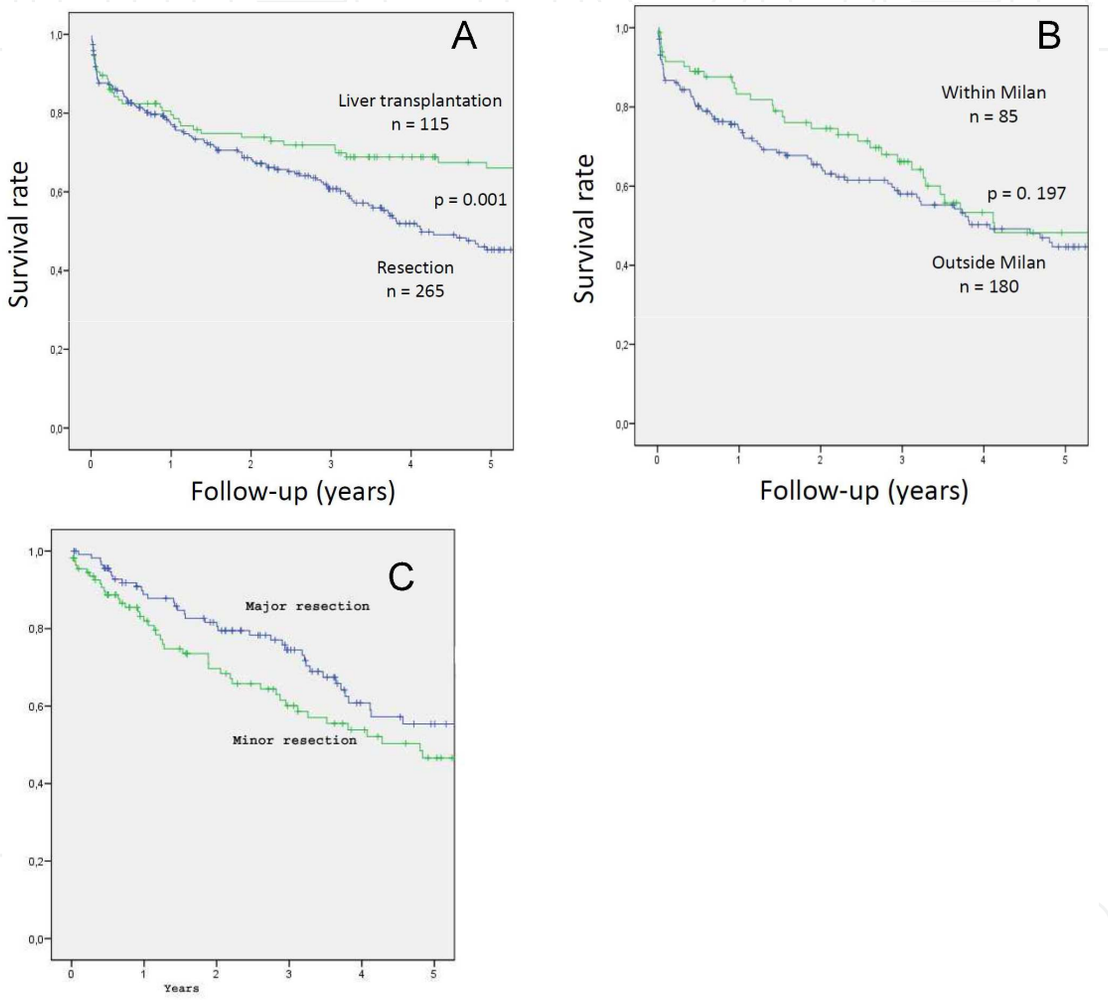

Figure 5. Outcome of surgical treatment for HCC: liver resection vs. liver transplantation (**A**), liver resection within Milan criteria vs. outside Milan criteria (**B**) and liver resection vs. explorative laparotomy only (**C**), for the years 1995 to 2006 at the Hannover Medical School.

The evident lack of donor organs from brain-dead donors regularly raises the question regarding the significance of liver donation from a living donor for patients with HCC. This discussion becomes particularly difficult when a healthy and suitable relative volunteers to donate part of his/her liver for a patient with HCC and an unfavourable prognosis (patient does no longer fulfil the characteristics necessary for a good prognosis after liver transplantation due to advanced tumour spread). In such situations the surgical risk for the healthy donor

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obviously becomes distinctly more important, and it is our opinion that in most of these cases transplantation is no longer ethically justifiable. Additionally, it has to be considered that a considerably longer waiting period for a matching donor organ (>1 year) has to be expected. Obviously, a great problem is the tumour progress while the patient waits for liver transplantation. TACE of HCC nodules is an established treatment method to prevent tumour progress and is used also frequently in our centre. A meta-analysis of all cohort trials and all prospective trials regarding TACE alone or in combination with additional percutaneous ablative interventions published in PubMed was recently performed. The result of this analysis was TACE alone performed in HCC patients prior to liver transplantation can effectively reduce the number of patients lost (so-called drop-outs) due to tumour progress while on the waiting list as they no longer fulfil the criteria for transplantation. The analysis also showed that a combined application of TACE and other percutaneous ablative methods can improve survival. It appears that a multimodal approach may provide the best results in the treatment of HCC.

For the surgical therapy of HCC the safety margin to be chosen for the resection plays a significant role for the surgeon. A prospective, randomised study performed in China compared a small (1 cm) with a large (2 cm) safety margin in a total of 169 patients in the sense of an intention-to-treat approach. The study showed that aiming for a safety margin of 2 cm lead to significantly improved survival rates after 1, 2, 3 and 5 years (Shi et al).

The results of the second interim analysis of the randomised Sorafenib study were published in the New England Journal of Medicine in 2008 (Llovet et al.) As the treatment with Sorafenib already showed significant advantages regarding the survival of patients with advanced HCC and the time span until progress was radiologically evident, the study was discontinued after the second interim analysis. Considering multimodal therapy concepts, these results will probably be relevant for the surgical treatment of HCC in the future. Currently, there are no study results that can show which role Sorafenib can play in adjuvant or neoadjuvant therapy concepts. A meta-analysis could show that patients treated with an adjuvant interferon therapy after liver resection due to HCC with concomitant viral hepatitis had a significant advantage regarding survival and tumour recurrence. This result is also supported by another meta-analysis concerning the same question. A retrospective analysis performed in France investigated the results after liver resection in patients with HCC, who fulfilled the Milan criteria at the time of resection. Here it could be shown that in case of recurrence after resection 61% of patients could be transplanted successfully (intention-to-treat analysis) (Bhangui et al., 2011).

3.5. Liver adenoma

For the principally benign liver adenoma (Figure 6) resection is generally indicated, when the adenoma measures >4 cm in diameter. The main reason for this is that an increase in diameter will raise the danger of a rupture. Furthermore, there is a risk of malignant degeneration in adenomas, although this can be hard to assess. Small adenomas can be mistaken for carcinomas, while needle biopsies suggesting and adenoma can be falsely negative.‘ Ultimately, the fine-needle biopsy only presents a random sample, which cannot exclude safely a malignant tumour if there is no evidence in the biopsy material.

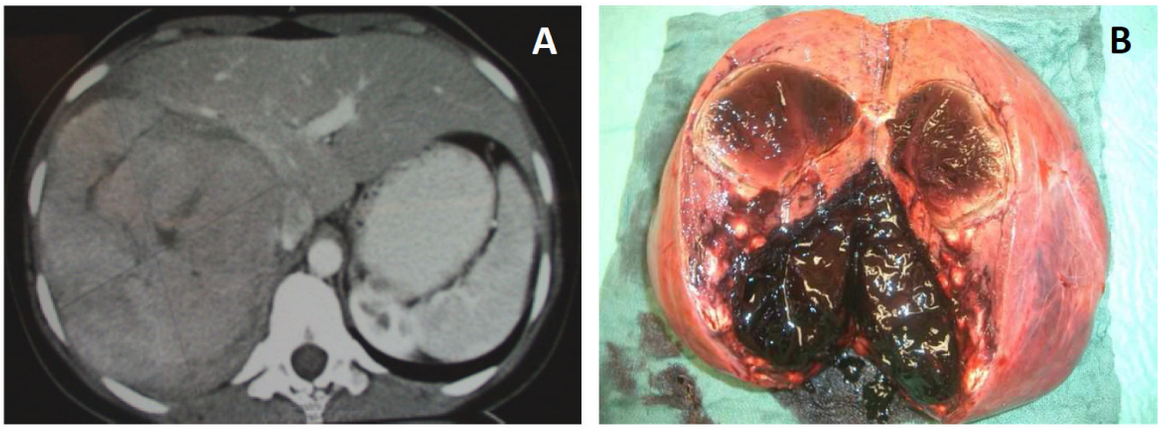

Figure 6. CT scan (**A**) and surgical specimen (**B**) of a partially hemorrhagic liver adenoma.

An American investigation analyzed retrospectively data of 5 hepatobiliary centres. A total of 124 mainly female patients were included, who were treated for liver adenomas between 1997 and 2006. The study resulted in the recommendation that patients with asymptomatic liver adenomas, which are >4 cm and/or patients taking contraceptive drugs therapy should undergo resection (Deneve et al.). A histopathological study performed in Bordeaux showed that the activation of beta-catenin in liver cell adenomas is associated with an increased risk to develop a HCC (Bioulac-Sage et al.)

3.6. *Dysontogenic cysts*, *Echincoccus cysticus* and *Echinococcus alveolaris*

Cystic liver tumours are either dysontogenetic cysts, biliary adenomas or infectious liver cysts. In principle, a cystic liver disease has to be considered differential diagnostically. Dysontogenetic liver cysts (solitary or multiple cysts) are benign, and approximately 1-7% of the ordinary population are affected. Most of these cysts are harmless and will only become symptomatic with increasing size. One has to differentiate between these normally solitary cysts and cystic liver disease. In cystic liver disease the complete liver is virtually infiltrated by cysts. During the late stage, when the patient becomes cachetic and liver failure is imminent, the therapy is liver transplantation. In most cases liver cysts are found incidentally when performing an abdominal US. Morphologically, the cysts show a smooth outline with a clear, liquid content (Figure 7). The walls of these cysts are delicate without calcification. The symptoms are mostly pain in the liver capsule with a sensation of pressure in the upper abdomen. However, considerable vascular compression can occur, e.g. compression of the retrohepatic caval vein or the portal vein. Frequently symptoms also result in compression of the stomach causing stenosis of cardia or pylorus as well as a displacement of neighbouring organs.

When echinococcosis is suspected, a serological exclusion or confirmation is required. Surgical therapy is indicated only when an increasing size causes symptoms or infections occur recurrently. Apart from open or laparoscopic marsupialisation or pericystectomy, partial resection of the liver is also a surgical treatment option. In most cases a simple liberal marsupialisation of the cyst is completely adequate to eliminate the symptoms permanently.

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However, it is important to ensure that the marsupialisation is performed in such a way that secondary adhesion of the roof of the cyst with subsequent persisting or recurring symptoms do not occur. Naturally, pericystectomy is not associated with this danger, but with a higher risk for a secondary haemorrhage or development of a bile leakage and therefore should only be performed in exceptional cases.

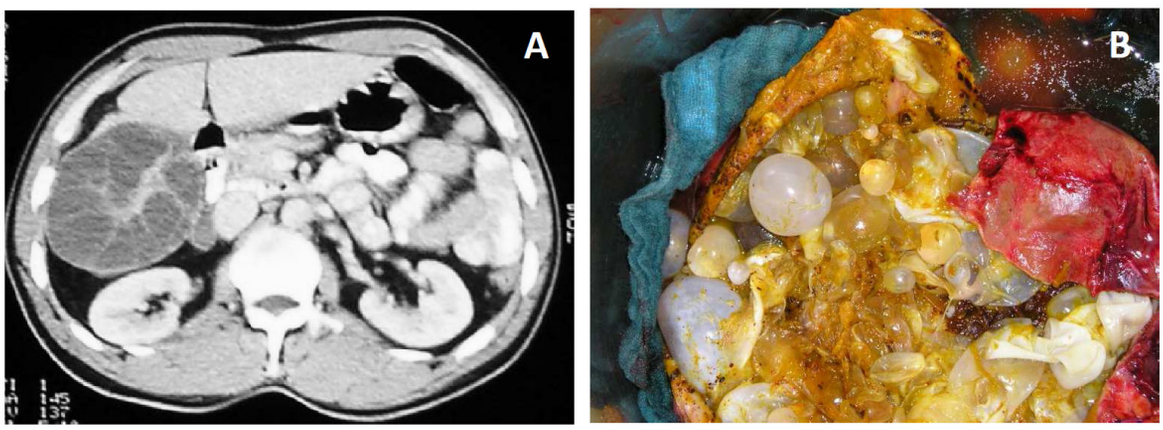

Figure 7. CT scan (**A**) and surgical specimen (**B**) of an Echinococcus granulosus cyst within the liver.

For the surgical treatment of Echinococcus cysticus a pericystectomy can be considered state-of-the-art. Echinococcus alveolaris requires an anatomical liver resection with an adequate safety margin similar to when resecting a malignant tumour. State-of-art surgical treatment for a large dysontogenetic liver cyst is marsupialisation. To perform a marsupialisation for cystic echinococcosis is obviously not per se treatment error, but due to the high risk of recurrence it is no longer performed by us and remains only an option in special cases. With respect to the surgical method applied treatment errors can occur when an Echinococcus cysticus is mistaken for an Echinococcus alveolaris or a harmless large liver cyst. Another reason for the wrong surgical procedure chosen may result when a preoperative echinococcus serology was not performed. This can result in marsupialisation of what is assumed to be a simple liver cyst with dissemination of still viable larvae into the free abdominal cavity, and often the catastrophic sequelae is a disease in the peritoneal cavity due to their free dissemination. Furthermore, the cysts can be joined to bile ducts. Therefore, when treating echinoccus cysts one should refrain from injecting high proof ethanol or formalin to destroy live larvae. Due to bile duct toxicity of ethanol or formalin these substances could cause secondary sclerosing cholangitis with subsequent chronic liver failure necessitating liver transplantation. In view of this risk, we necessarily consider injecting echinococcus cysts with high proof ethanol or formalin using the so-called PAIR method (Puncture – Aspiration – Injection – Reaspiration) as problematic, whereas the injection of 10% NaCl solution or 40% glucose solution by the so-called PAIR method to kill any viable larvae appears more justifiable.

3.7. Primary malignant hepatic hemangioendothelioma (hypertrophic endothelioma)

The etiology of these rare vascular tumours is unknown and the clinical appearance extremely variable. Data published show that in most patients a diffuse bilobate affected liver was evident, and thus the treatment was liver transplantation (44.8%). Whereas 24.8 % of patients received no treatment, 21 % received chemotherapy or radiation treatment and 9.4 % of patients underwent liver resection (Meharabi et al.). After liver transplantation the mean 1-year survival rate was 96 % and the mean 2-year survival rate was 54.5 %. Whereas the 1-year survival rate of untreated patients was 39.3 % and the 5-year survival rate was 4.5 %. After 1 year the survival rate of patients treated with chemotherapy and radiation was 73.3 % and 30% after 5 years, whereas the 1-year survival rate of patients who underwent resection was 100 % and the 5-year survival rate of still 75 %. Therefore, liver resection has to be the first choice for patients with resectable tumours, liver transplantation should be the first choice if both liver lobes are diffusely affected and there are no extrahepatic metastases.

3.8. Cavernous haemangioma

The cavernous haemangioma is the most frequently occurring benign hepatic tumour (absolute frequency of 0.5-7 % among the normal population), with a slight predominance in females (Galanski et al). The majority of these tumours are found accidentally by US scan. In most cases they cause no clinical symptoms, but become symptomatic once they increase in size. The symptoms caused by compression and displacement of blood vessels and neighbouring organ are similar to those experienced by dysontogenic liver cysts. Apart from US, other diagnostic methods used are MRI and CT (Figure 8). If further clarification is required, blood pool scintiscanning can be used as an additionally diagnostic tool. The only indication for surgical intervention is when the cavernous haemangioma becomes symptomatic. Generally, the danger of a haemorrhage caused by an accident, e.g. blunt abdominal trauma with ruptur of the cavernous haemangioma, is considered negligible, but cannot be categorically excluded. Ideally, whenever possible a haemangioma should be enucleated, e.g. this can be conducted in total vascular occlusion. When enucleation is impossible, the surgical treatment has to be resection of the appropriate section of the liver. It is vital to bear in mind the possibility of bile ducts being inside the wall of the haemangioma. Consequently, there is a significant risk ofbile leakage during enucleation.

During the last 10 years 49 patients (36 females and 13 males) were treated surgically for a haemangioma of the liver in our clinic (own unpublished data). The majority of patients were aged between 20 and 40 years. 55% of the patients presented for diagnostics due to pain, in 45% of the cases the tumours were detected accidentally during examinations for other complaints.

In 36 patients the tumours had a diameter of 10 – 20 cm. The surgical procedures performed were enucleation (n=27), atypical liver resection (n=7), segmental resection (n=5) and anatomical left or right hemihepatectomy (n=10). Due to postoperative secondary haemorrhage 2 of 49 patients required revision.

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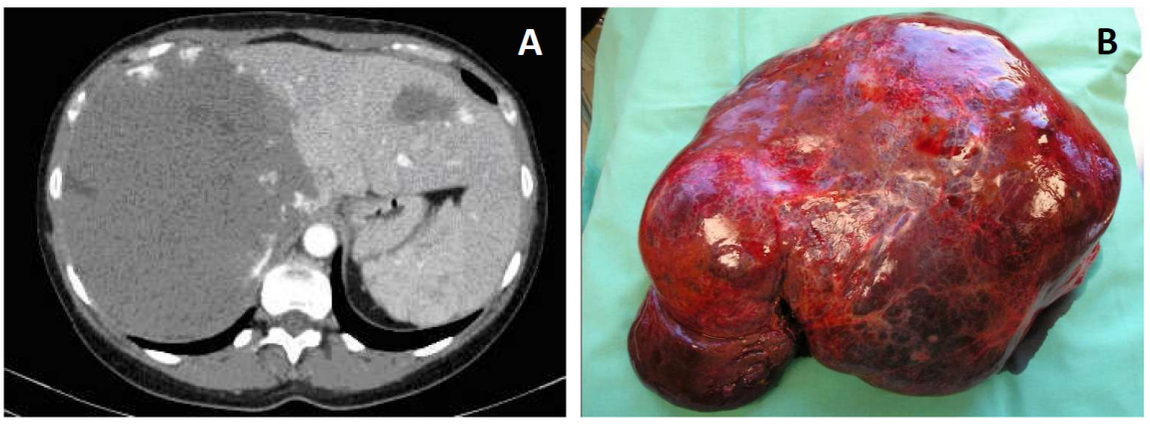

Figure 8. CT scan (**A**) and surgical specimen (**B**) of a large haemangioma of the liver.

3.9. Focal nodular hyperplasia

Hepatic FNH, a benign liver tumour, occurs approximately twice as frequently as hepatocellular adenoma. It is a disease affecting young, predominantly female adults (85%) with an incidence among the population of 20 per 100,000. In 15% of cases FNH can also be observed in mainly young adult males. As FNH predominantly occurs in females, the use of oral contraceptives is controversially suspected(Weimann et al.). Contrary to liver adenomas there is no description in the literature of malignant transformation. Without knowledge of the radiological findings it is often difficult to histologically confirm FNH due to the histologically normal, but enlarged structure of the hepatocytes. Vascular proliferation is evident, but is also observed for hepatic adenoma. Bile duct proliferation, on the other hand, is only evident in FNH. Both hepatic adenomas and FNH become symptomatic due to an increase in size and the subsequent compression and displacement of blood vessels and neighbouring organs. Apart from US, MR and CT can be used as diagnostic methods (Figure 9).

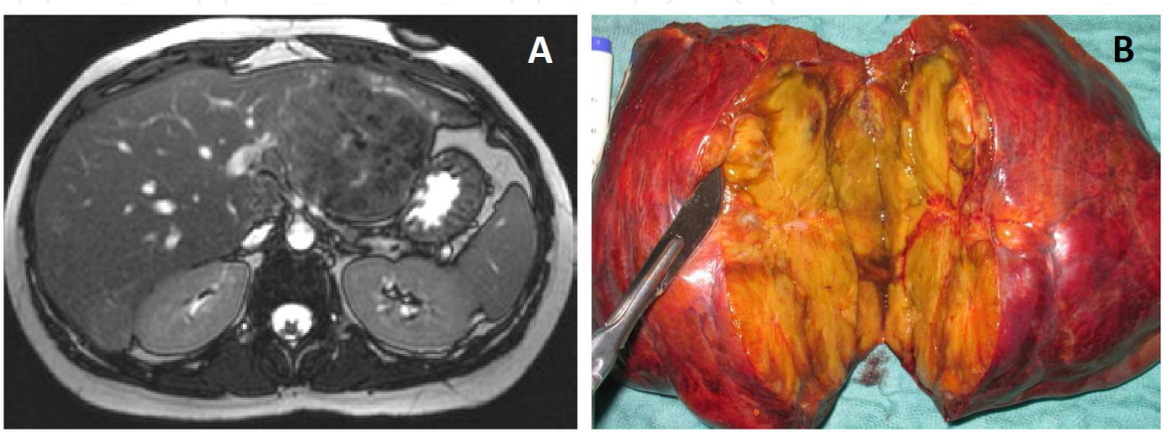

Figure 9. MRI scan (**A**) and surgical specimen (**B**) of a focal nodular hyperplasisa (FNH).

In approximately 95% of cases a hepatobiliary sequential scintiscanning can positively differentiate between FNH and hepatic adenoma. A definite sign is the central scar with its typical wheel spoke structure visible in the radiological image. Surgical intervention is only indicated when FNH becomes symptomatic. However, there are also cases when the explicit wish of a patient may be the indication for surgery. In these cases it is vital to inform the patient in detail of the possible risks and complications and the surgeon should seriously consider the possibility of carcinophobia.

In our opinion enucleation is the therapy of choice. Should this not be an option, the tumour can also be removed by either anatomical or atypical liver resection.

4. Special aspects of preoperative detailed information and informed consent

It is obvious that the patient prior to liver resection has to be informed in detail about risks generally involved in surgery, but also about those special complications usually associated with a liver resection (e.g. haemorrhage, secondary haemorrhage, thrombosis, pulmonary embolism, wound infection, injury of neighbouring organs). There is also the possibility of bile leakage, haemobilia, development of pleural effusion, icterus, chronic or acute hepatic insufficiency, pneumatohemia, acute pancreatitis as well as thrombosis of the portal vein or the liver artery.

In most cases of liver resection it is either imperative or advisable to also remove the gallbladder at the same time. The reason for this is that when performing an anatomical left or right hemihepatectomy the gallbladder is either directly at the designated resection site or during a segmental or typical liver resection denervation and/or devascularisation of the gallbladder may result. Furthermore, it may be advisable to simultaneously remove the gallbladder to prevent future occurrence of cholecystolithiasis. Subsequently this would at some stage require a cholecystectomy and adhesions at the operation site obviously present a higher operation risk. Therefore, it is advisable to inform the patient also of a simultaneous cholecystectomy prior to the planned liver resection. This is a point that is easily forgotten when informing the patient about the risks of the forthcoming liver resection as the gallbladder is not the primary surgical target.

During the preoperative informative discussion about the liver resection it should also be pointed out that intra- or postoperatively a blood transfusion may be necessary. Despite the present stringent and very safe quality controls, a residual risk of transmission of a viral or bacterial infectious disease cannot be completely excluded. In spite of today's safe determination of the blood group and bedside tests performed, there are rare cases of transfusion of blood group incompatible blood products resulting in serious transfusion incident. The patient should also be informed of the possible use of local hemostyptics (e.g. fibrin sealant) containing heterologous proteins, which may also transmit an infection.

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Neither should it remain unmentioned that after surgery the patient should refrain completely from taking any hepatotoxic substances (e.g. alcohol), at least during the several months lasting postoperative liver regeneration period.

5. Preparation for surgery

We would summarize the obligatory specific preparation for surgery as follows: laboratory (CHE, Quick, PTT, aminotransferase, bilirubin; blood count, coagulation, determination of blood group), assurance of sufficient provisioning of erythrocyte concentrates by the blood bank, CT or MRI images to plan the extent of resection, in case of cystic tumours echinoccoccus serology, existence of a written valid and adequate informed consent for the operation and anaesthesia by the patient. Depending on comorbidity and age of the patient additional investigations should be performed preoperatively, e.g. ECG, lung function test, endurance ECG and chest X-ray. When indicated one should also aim to consult the anaesthetist to assess the operational risk, and depending on the finding to consult the specialists for internal medicine to optimize the therapy of any comorbidity to minimize the risks prior to commencing surgery.

Furthermore, the cause for preoperatively elevated aminotransferases and/or evident impairment of the liver function categorically requires clarification in cooperation with an experienced hepatologist.

We believe that a 3-dimensional reconstruction of the hepatic vascular anatomy based on the individual digital CT data set is generally not absolutely necessary. It should be reserved for planning the operation of specific cases, for instance when the localization of the hepatic tumour is unfavourable, e.g. in direct proximity to the liver hilus or at confluence of right, central and left hepatic vein close to the confluence into the caval vein. In such cases this will enable the surgeon to decide whether an ex situ or ante situ resection to fully remove the tumour may be required or if primarily liver transplantation is the only option.

6. Anaesthesiological aspects

During liver resection the central venous pressure should not be too high as this would have a negative impact on the extent of bleeding from the resection area. Neither should the central venous pressure be too low when transecting hepatic veins and/or the caval vein as this would increase unnecessarily the risk of possible aeroembolism during the operation. This requires constructive cooperation with the anaesthetists. Therefore, during the liver resection the positive endexspiratory pressure (PEEP) should be around 8-9 mmHg and the amount of volume given should be in accordance with the measured central venous pressure. If possible, the anaesthesist should refrain from using potentially hepatotoxic medication to avoid increasing unnecessarily the risk of postoperative failure of the remaining liver.

7. Surgical techniques

It is vital for each liver resection to know in detail the functional anatomy of the liver, i.e. the definition of the hemodynamically independent parenchymal areas according to the Couinaud classification is an indispensible prerequisite for any surgeon performing a liver resection. The complete resection of functionally autonomous parenchymal areas perfused by one appending pedicle (branch supplying portal vein, hepatic artery and common hepatic duct) is termed anatomical resection. Here one distinguishes between sector orientated resections (e.g. right and left hemihepatectomy, left lateral liver resection of segments II and III, trisegmentectomy) and segment orientated resections (mono-, bi- and polysegmentectomy). Principally, a combination of different anatomical resections is often possible. This option should always be taken considered instead of extended resections, which are often associated with a greater loss of healthy liver tissue. On the other hand, even when choosing a combination, extending the parenchymal area to be dissected can increase the potential rate of complications (e.g. secondary haemorrhage, biliary fistula and necrosis of the wound lip). Extended resections transcend the anatomical en-bloc resection of segments II, III, IVa and IVb of a left hemihepatectomy (when necessary also including segment I). When extending the anatomical en-bloc resection of segments V, VI, VII and VIII, additional segments and/or the hepatic bifurcation and/or a cuff of the portal or the caval vein can also be resected. When performing a so called atypical resection the surgeon does not adhere to the anatomical segmentation of the liver. The reason for this is the aim to minimize the loss of functional liver tissue. An example is the enucleation of a hepatic haemangioma or FNH without safety margin or the atypical resection at different parts of the liver when resecting with a safety margin more than one liver metastasis. Depending on the individual situation, anatomical and atypical liver resections can be combined. A special technique is the analogue ex situ resection (i.e. outside the patient's body) of the liver. The liver is then perfused with a conservation solution (e.g. HTK) and cooled to ensure the organ survives the ischaemic time until autotransplantation. Another rare resection technique is the ante situ resection. In this case the liver is dislocated from caudal to cranial in front of the abdomen after the complete hilus and the infrahepatic caval vein have been dissected, and after perfusion with a conservation solution (e.g. HTK) and cooling analogue to an organ to be transplanted. Finally, the liver hilus and continuity of the clamped and dissected infrahepatic caval vein have to be reconstructed by anastomoses. However, this technique obviously requires a surgeon with adequate specific surgical experience in the field of liver transplantation.

7.1. Methods to control haemorrhages

During preparation close to the large hepatic veins and the caval vein aeroembolism and severe bleeding can occur should these veins be injured. Severe bleeding can cause considerable obstruction of vision and endanger systematic and safe anastomosing of the blood vessels. To avoid such a situation it is necessary to have a clear view of the suprahepatic and infrahepatic caval vein. This ensures that, when needed, the vessel can be manually compressed and if necessary vascular clamps applied for safe closure by controlled suture of a large lesion without unnecessary constriction of these veins. Far reaching sutures performed with large

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needles, when the vision is impaired due to a large pool of blood, can have catastrophic sequelae, and such situations may easily occur to surgeons lacking the required evidence to perform larger liver resections. Larger haemorrhages at the resection area caused by dissection of large hepatic veins or branches of the portal vein or the hepatic artery can be safely controlled by manual compression of the residual liver lobe. If this is insufficient due to the extent of the haemorrhage, the surgeon additionally can use the Pringle manoeuvre with temporary occlusion of the liver hilus and if necessary additional clamping of the supra- and infrahepatic caval vein. To ensure that this possible, the preparatory precondition prior to dissecting the parenchyma is provision of the appropriate vessel loop at the liver hilus in the region of the hepatoduodenale ligament and at the infrahepatic caval vein. Should, in spite of all safety measures, an uncontrollable haemorrhage still occur, according to the current state of surgical knowledge a treatment error can be assumed. In the worst case, one has to consider that often the temporary haemostasis by packing with an abdominal pad is the best strategy, as one would do in case of a central liver trauma with massive haemorrhage and typical poor surgical vision. However, to ensure effective haemostasis it is necessary to completely mobilise the liver into a position that permits compression of the liver with abdominal pads from all sides. After stabilisation and when indicated, transfer of the patient to a centre for hepatobiliary surgery, where these pads can be removed and the haemorrhage finally stopped in a second-look-operation. In such situations it is again vital to avoid deep sutures with a large needle as this would evoke the danger to compromise vital central structures (e.g. portal vein, hepatic artery and/or central bile duct).

In current studies it could be shown that there are significant differences with respect to morbidity or mortality regarding the application of Pringle manoeuvre and selective, total or modified vascular occlusion (Ishizuka et al.).

7.2. Prevention of postoperative problems

Particularly when performing a right hemihepatectomy or an extended right hemihepatectomy the surgeon should fixate the remaining liver lobe with a suture, i.e. reattach the remaining falciform ligament to the abdominal wall in order to avoid kinking of the portal vein with subsequent thrombosis. In case of the anatomical right hemihepatectomy, as well as the anatomical left hepatectomy, the surgeon should bear in mind the need to prevent iatrogenic stenosis of the portal vein. This can be achieved by ensuring that the distance been the branch of the portal vein and the branch that remains is great enough without causing an unnecessary constriction, e.g. hour glass stenosis.

7.3. Methods of parenchyma dissection

A systematic meta-analysis of the various techniques for dissection of the parenchyma could not identify any differences between CUSA, radiofrequency sealer and hydrojet when compared to the conventional clamp crushing. It is important during liver resection that haemostasis at the resection surface is adequate, and it is equally important to take adequate care of the dissected bile ducts during a liver resection, e.g. titanium clips. We believe that suturing larger bile ducts is the safer method, however, stringent attention has to be paid to

prevent accidental closure of the larger bile ducts of the remaining liver lobe. In a prospective, randomised study including 300 patients it could be demonstrated that the use of fibrin sealant on the resection area did not reduce blood loss, number of blood transfusions required, frequency of bile leaks, and neither did it improve the result of the resection. Therefore, considering also the cost we do not routinely apply fibrin sealant at our clinic.

7.4. Intraoperative US

Today, the use of intraoperative US is frequently used as standard procedure during liver resection to intraoperatively define exactly the resection margins and to detect possible additional masses in the liver. Should the histology report describe a margin forming malignant tumour, one has to consider at least that the tumour resection was microscopically incomplete. If in such a case no additional resection and no intraoperative US have been performed, it can be assumed that without detailed information the surgeon incorrectly assessed and defined the intrahepatic extension of the tumour and did not follow-up consequentially with further resection. However, in case of critical resections, when a postoperative failure of the small-sized residual liver has to be feared, it may be unavoidable to refrain from further extending the resection and/or it has to be accepted that an incomplete resection is inevitable. In such cases it is relevant that this deliberation is described and documented in the operation report to ensure that no treatment error (e.g. unnecessarily insufficiently radical oncologic resection) can be insinuated.

7.5. Laparoscopic liver surgery

During an international consensus conference on laparoscopic liver surgery held in Kentucky with 45 international experts from continents participating, the indication, patient selection, surgical techniques, complications and patient safety as well as further relevant surgical education aspects of laparoscopic liver surgery were specifically discussed (Buell, J. F et al). Hereby laparoscopic liver surgery included per definition solely the laparoscopic method (hand-assisted laparoscopic approach and hybrid technique). Mutual consent was reached on the point that this technique could be applied in patients with solitary liver lesions (<5 cm) in segments II – VI. The participants of this consensus conference agreed that already today the left lateral laparoscopic segmentectomy (liver segments II and III) should be considered the standard procedure compared with the open surgical technique. Concerning all forms of liver resection, including anatomical right and left hemihepatectomy, it was the opinion of the consensus conference that these types of laparoscopic liver resections should only be performed by particularly experienced surgeons who are sufficiently familiar with the more advanced extended openliver resections. The indication for conversion from laparoscopic to open surgical technique should be considered liberally in case of technically difficult, time-consuming resections and congruent aspects of patient safety. One should always attempt to initially control complications caused by haemorrhages laparoscopically before conversing to the open surgical approach. Using the combination of hand-assisted laparoscopic technique and the hybrid method may be quicker and more effective than the purely laparoscopic method. In case of benign liver lesions the indication for surgery should not just be considered

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because one can operate laparoscopically. For transplantation in children, the purely laparoscopic approach has already been used for the donation of the left lateral liver lobe (segment II and III), whereas for living donation for adult recipients only the hand-assisted laparoscopic procedure has been used so far. So far, safety and efficacy of laparoscopic liver resection have not been adequately analysed, particularly not in controlled studies comparing laparoscopic and open surgical techniques. Currently, it appears that a prospective randomised study cannot be realised due to logistic problems. However, there is agreement on the subject of initiating an international registry to document the role and safety of laparoscopic liver resection.

8. Postoperative treatment

In case of a rapid and unexpected postoperative rise of the liver enzymes (e.g. AST, ALT), a sudden thrombosis of the portal vein should be considered. Such prevalent complications occurring after liver resection are not necessarily evidence of a treatment error. However, it is important that these complications, if they occur, are not overlooked and that a quick and effective therapy is initiated. If a sudden postoperative elevation of aminotransferases occurs, the possibility of a thrombosis has to be considered and a Doppler-US and/or CT with i.v. contrast medium during the arterial and porta-venous phase should be initiated immediately. Evidence of a thrombosed portal vein requires the immediate performance of an emergency thrombectomy followed by PTT-effective heparinisation.

Particularly bilious peritonitis is a complication that should not be underestimated, even with good drainage. When in doubt as in the absence of distinct clinical improvement or in spite of CT- or US-guided placement of a system to drain the bilioma, the indication for a revision should be considered rather liberally.

Early mobilisation and adequate respiratory training should also not be underestimated as effective methods to prevent pulmonary and thrombo-embolic complications.

Early contact with a liver transplantation centre is recommended should failure of the residual liver occur. Generally, such a centre not only has the ability to perform transplantation, but often clinical experimental methods to assist the liver function are available.

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