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The Liver Biopsy During Organ Procurement

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1. Introduction

Hepatic steatosis is a commonly noticed and most prevalent condition among donated liver grafts. The pressing demand for organs and increased patient death rates while awaiting organ transplantation has led to the use of cadaveric livers with hepatic steatosis for transplantation. Recent data reported the use of steatotic liver grafts in 71% of cases (Noujaim et al., 2009). Moreover, to meet the organ shortage, the criteria for donation have been broadened to include donors with advanced age, hepatitis B and C viruses, neoplasms, and benign underlying diseases (Fondevila et al., 2009). The use of expanded-criteria donors (ECDs) and the donor risk index (DRI) are strategies that have been proposed to increase the donor pool (Feng et al., 2006). The Donor Risk Index (DRI) lists seven donor characteristics, together with cold ischemia time and location of the donor as risk factors for graft failure. DRI >1.7 is reported to be associated with shorter survival after liver transplantation (Palmiero et al., 2010). It is hypothesized that donor hepatic steatosis is an additional independent risk factor (Spitzer et al., 2010). It remains unclear which value micro and/ or macrovesicular steatosis have for the short and long term results after liver transplantation. Therefore, different papers report a safe use of grafts with a severe microvesicular steatosis (Fishbein et al., 1997; McCormack et al., 2007). However, steatosis is one of the most important factors affecting liver allograft function. Steatosis is common in several situations, including: obesity, diabetes, and alcohol abuse (Durand et al., 2008). Organ donation predictive factors for recipient survival were: age, viral status, and degree of liver steatosis. Liver transplantation for alcoholic liver disease showed the highest complication rate. Chronic liver rejection occurred more frequently in the AIH transplanted group. The most useful predictive factors for 1-year survival were urea/ creatinine and liver function tests. (Patkowski et al., 2009). In addition, transplantation of a liver with >25% steatosis was a risk factor for the development of a biliary complication (Baccarani et al., 2009). Nevertheless, macrovesicular steatosis is known as a risk factor for early graft dysfunction and graft failure. Most transplantation centres consider 60% the value limit for transplantability, while others have adopted 30% as a cut-off limit (D'Alessandro et al., 2010).

Organ donor shortage continues to pose a significant problem. To ensure fair and transparent allocation of too few post-mortem grafts, the model of end-stage liver disease (MELD)-based allocation was implemented in the Eurotransplant area in December 2006. This has decreased the waiting list mortality rate from 20 to 10 %, but at the same time has reduced post OLT survival (1-year survival from almost 90% to below 80%), which is largely

due to patients with a labMELD score >30. Following MELD introduction, the regular allocation threshold increased from a matchMELD of initially 25 to a current value of 34. At the same time, the quality of donor organs has seen a continuous deterioration over the last 10 - 15 years, e.g., 63% of organs have a donor risk index of > 1.5 (Schlitt et al., 2011). Among the several reasons that might play an important contributing role are the pressing organ demand and the increasing percentage of elderly donors with co-morbidities, such as steatosis hepatis, combined with a high MELD-Score of the recipient at the point of transplantation. MELD >30 currently represents a major risk factor for outcome after liver transplantation. However, risk factors differ in individual patient subgroups (Weismuller et al., 2011). There has been data supporting the use of ECD organs in good-risk recipients. These include grafts from donors that are 60 years old, with prolonged hypotension, or with mild to moderate macrovescicular steatosis (Amin et al., 2004). The frozen-section histological evaluation of biopsies from cadaveric liver donors is an accurate, time-effective, and predictive method for the assessment of graft suitability. Nevertheless, it is discussed controversially if frozen-section histological evaluation of biopsies is a safe and efficient method in detection of macro- and microvesicular steatosis. Therefore, it is reported that validated pretransplant frozen-section analysis is a reliable technique when the maximum value for organ transplantation was 60% steatosis. Thus, the usefulness of another technique to support a more precise steatosis evaluation is recommended (D'Alessandro et al., 2010).

2. Brain death, permission and intensive care treatment

When brain death is determined according to actual guidelines, donors are selected for potential organ donation after permission is given. The diagnosis of brain death requires the absence of brain-stem reflexes and respiratory drive in a normothermic, non-drugged, comatose patient with a known irreversible brain lesion and no contributing metabolic derangements. Permission for organ donation has to be given considering the current transplantation law in the procurement country. While the donor liver is allocated further intensive care treatment is still necessary. Hepatic function is impaired after brain death. There is depletion of hepatic glycogen and a reduction in hepatic sinusoidal perfusion that occurs because of leukocyte activation and accumulation in the microcirculation (Smith, 2004). It is unclear if the application of cortisone reduces the leukocyte activation in the liver tissue. Maintenance of cardiovascular, pulmonary and endocrinological stability is important for successful organ transplantation. The goals in managing the hemodynamic status of the donor are: to achieve normovolemia, maintain blood pressure, and optimize cardiac output, so as to achieve gradients of perfusion pressure and blood flow that promote organ function with the use of the least amount of vasoactive-drug support. Diabetes insipidus results from the absence of vasopressin after the destruction of the posterior pituitary gland. It contributes to hyperosmolarity, hemodynamic instability, and electrolyte abnormalities (e.g. hypernatremia) as a consequence of an excessive loss of free water. These effects should be prevented, because hypernatremia leads to osmotic gradients at the liver cell with consecutive cell swelling in the recipient after liver transplantation. However, recent data suggests that transplant measures of early liver function and risk of failure, up to 1-year post-transplant, do not differ significantly based on peak or terminal donor serum sodium levels. These results indicate that donor serum sodium level likely has little clinical impact on post-transplant liver function. (Dictus et al., 2009; Kutsogiannis et al., 2006; Mangus et al., 2010; Shah, 2008; Wood et al., 2004).

3. Surgical procurement

The surgical technic of organ procurement has been reported earlier by Rosenthal et al. in 1983. The following chapter briefly resumes the major important aspects. The necessary technical details, depending especially on the combination of organs to be removed, are: wide exposure, dissection of each organ to be removed up to disconnection from the circulation while the heart is still beating, placement of cannulas for in-situ cold perfusion, orderly removal of the organs with cold perfusion protection of the organs to be removed last. In instances of liver and kidney procurement only, a midline sternal splitting incision is not routinely used, but can provide immediate access to the heart if there is any instability and can help to remove the liver more gently. After wide abdominal exposure, liver mobilization is carried out first, since this is the most meticulous dissection and attention to hemostasis is strict. Careful inspection of the arterial anatomy is done first; any anomalous arteries must be preserved. A branch to the left lobe is sometimes seen arising from the left gastric artery and can be seen in the superior portion of the gastrohepatic ligament. A branch to the right lobe arises from the superior mesenteric artery. This artery has occasionally been the entire arterial supply to the liver. The hepatic artery is dissected from the aorta. The common bile duct is exposed at its entrance to the pancreas and transected. The portal vein is dissected after transection of the pancreas to facilitate exposure. The inferior mesenteric and coronary veins are ligated; the splenic and superior mesenteric veins are mobilized. The junction of the inferior caval vein and right heart is identified, to provide maximal length of upper cuff of the vena cava. The liver is essentially ready for removal at this point. Cannulas are then placed for in-situ perfusion and crushed ice is immediately applied for cooling the external abdomen. First, cannulas are placed in the vena cava and aorta at their respective bifurcations and the vessels divided distally. Heparin 300 units/ Kg is given to prevent clotting (Rosenthal et al., 1983). Today, liver procurement is mostly performed by local surgeons experienced in at least ten organ donations as required. Liver preservation is realised using Histidine-Tryptophan-Ketoglutarate solution (Custodiol®) or University of Wisconsin solution (Viaspan®) as preservative.

4. Surgical evaluation

A successful evaluation of a liver graft for transplantation is based on several essential criteria: donor medical history, laboratory data on liver function, virological analysis, sonography, as well as intraoperative liver exploration particular for colour and palpation. Identifying marginal from good donor livers is one of the most difficult surgical tasks. Thus, surgical experience and evaluation criteria have increased importance in liver transplantation. Visual inspection and palpation are the most commonly used methods for surgeons to establish liver quality. The positive predictive value of a surgical appraisal of liver steatosis has been reported to be 71% for severe; 46% for moderate; and 17% for mild steatosis (Adam et al., 1991). When donor surgeons suspect steatosis by inspection of a liver graft, a frozen section is only performed in 38% to 47% of cases (Nocito et al., 2006). However, for a successful evaluation and consequent transplantation, reliable and objective means are needed to assess the liver before transplantation. Histopathological examination should provide a helpful decision for the transplant surgeon whether or not the organ is suitable for transplantation. Therefore, in all cases of organ procurement a wedge biopsy of 1-cm side length should be performed in two liver segments, one for each liver lobe (i.e., segments 3 and 6 or 7) (Frankel et al., 2002; Rey et al., 2009).



Fig. 1. The surgical evaluation of organ donor livers before preservation in situ.

To evaluate liver quality is one of the most difficult surgical challenges during organ procurement. Therefore visual inspection and palpation are the most commonly used methods in situ before liver preservation. At this time liver biopsy is mostly required.



Fig. 2. After liver preservation and procurement surgical evaluation of graft quality will be repeated.

After liver procurement the graft´s quality will be evaluated again by the donor surgeon. Surgical and anatomical characteristics are documented and communicated to the transplant coordinator and transplant surgeon. So far the liver biopsy results should be available. Finally, the graft is packaged into three bags of aseptic fluid.

5. Frozen section

Frozen section examination is useful in excluding donor organs which may become dysfunctional after transplantation. It has been shown that primary non-function has significantly decreased using frozen section examination (Markin et al., 1993).
If a frozen section is required, the procedure consists of the following principal steps: the surgeon should take a wedge biopsy of 1-cm side length. The wedge will be split lengthwise; one half is snap frozen in liquid nitrogen from which 3 - 4-µm-thick sections are cut, briefly fixed in 4% buffered formalin (pH 7.4), rinsed, and counterstained with H&E. After dehydration in rising concentrations of alcohol, the section is coverslipped and analyzed by routine light microscopy.

In order to obtain a frozen section of high enough quality, a number of important aspects have to be considered in frozen section technique of liver tissue, being outlined in the following passage, even though we assume that any pathologist will be familiar with the principle of frozen section cutting. Once the wedge is split longitudinally, the obtained section should be placed with its cauterized side down, flatly upon the frozen section chuck. When placing the sectioned tissue, this thickness should guarantee cauterization artifacts extending to the freshly cut surface. This is increasingly important, if the actual tissue area is small, being crucial in wedges with less than 0.5cm wedge length. Irrespective of the actual wedge length, the area of the section should not extend beyond 1.0 cm^2. If the wedge is bigger, splitting it into two should be considered and each piece analyzed by frozen section separately to obtain a picture of the entire area. A biopsy is considered to be sufficiently large, if it contains at least 10 cross sections of portal tracts. The number of portal tracts has to be documented to ensure a sufficient quality control. In addition, at least 4 sections of 3 – 5 m each should be cut and stained with H&E, to be able to analyze tissue alterations on several sections in sequence and in order to evaluate their importance. This will help to properly identify artifacts due to the procedure itself, such as uneven cuts, folds, shattering or rips of the section.

The problems of inadequate equilibration to the correct temperature are several fold (Fig. 3). The temperature of the equipment, i.e. the knife, the chuck, and the cutting table itself as well as that of the frozen tissue should be at least -20^0C and kept constant. This means equilibration time for the frozen tissue and the newly introduced section blade. Ideally, the "optimal" temperature is reached, when the cut section flows over the knife in a smooth uniform sheet with minimal curling. This, however, may mean taking the time to make adjustments to the cryostat temperature, which is time well spent to optimize the outcome, considering the consequences of rejection due to bad sectioning technique. A block that is too cold will quickly curl in an unmanageable way or shatter, creating a Venetian blind-like artefact. The tissue can be condensed if it is too cold, and it will even be tougher to cut, resulting in thick and thin sections. In contrast, if the block is too warm it results in a crumpled section. Thus, when placing the section itself, a layer of freezing compound with a flat surface has to be provided on the pre-cooled, and well cleaned chuck first, on which the freshly cut section is placed and completely covered by freezing compound medium. To obtain optimal freezing results, either a pre-cooled (at $-20\ ^0C$) metal block is placed on top of the section or a freezing spray can be used. The former is helpful when larger tissue sections need to be frozen, the latter is best when the tissue section is small. Care has to be taken to avoid compression. Larger sections will not be satisfactorily frozen by spray, which may lead to uneven freezing with subsequent shattering of the section taken. In addition, using a spray leads to creation of an aerosol, which can be detrimental when the fumes are inhaled (i.e. cardiac arrythmia etc). To prevent inhalation, the lid of the cryostat compartment should be closed transiently to let the fumes settle.

Cutting into the frozen tissue block is best done when the block is placed in such a way that the knife starts cutting at one of the corners of the wedge, since the liver capsule is normally harder than the parenchyma, leading to the compression of the softer hepatic tissue, shattering or ripping of the section, if the capsule is transected longitudinally first. In addition, the frozen tissue should be well cut into with several sections before using any for analysis, in order to avoid freezing artefacts and guarantee that the entire area is well exposed and sectioned.

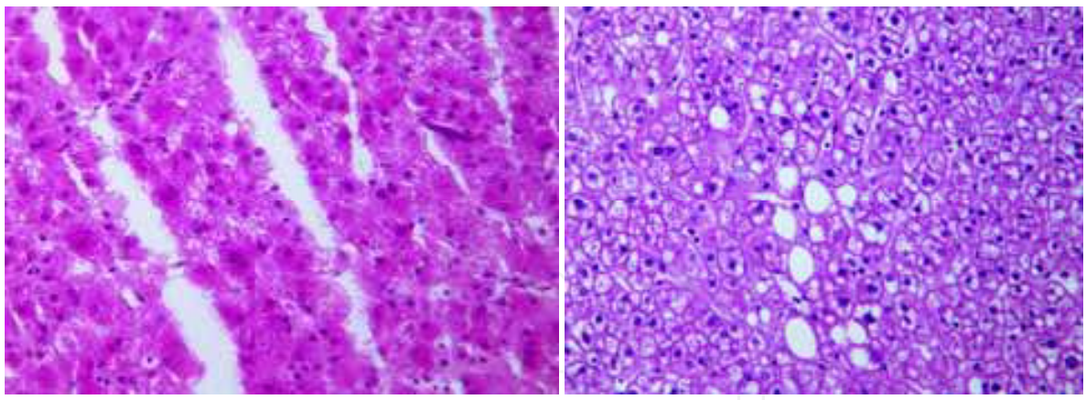


Fig. 3. Problems in cutting frozen section. Venetian blind – like artefacts (left), and sub-optimally preserved liver parenchyma (right) do not allow proper evaluation, particularly microvesicular steatosis

Besides technical problems, cutting a frozen liver section may cause unexpected trouble based on primary parenchymal alterations, such as increased hepatocellular fat deposition. In this case, lower cryostat temperatures of –25 ^{0}C can be helpful, provided there is time for equilibrating the equipment, the knife and the tissue to this temperature first, which may take about 20-30 minutes depending on the size of the frozen tissue specimen. This delay in processing being worthwhile on one hand, may be problematic on the other, when the allotted time for pathologic evaluation is short due to logistical problems of time consuming transport for the frozen section material or the delivery of the liver specimen.



Fig. 4. A wedge biopsy of 1-cm side length. The wedge will be split lengthwise; one half was snap frozen in liquid nitrogen.

For subsequent analysis of the frozen tissue, it is post-fixed in 4% buffered formalin and paraffin embedded. For that purpose, the frozen tissue should be taken out of the cryostat and allow to thaw just enough to be taken safely from the chuck. The majority of the compound medium starting to thaw should be removed and the tissue placed immediately into formalin. The remaining rest of the compound medium does not effect the subsequent fixation procedure. The procedure of subsequent analysis is equal to that of the rest of the wedge, namely being immediately fixed and paraffinized. It is prudent to wait with the fixation of the rest of the wedge tissue, in case a second frozen section is needed, which should not be a problem, if the wedge is of sufficient size. Meanwhile, the wedge tissue should be kept on ice.



Fig. 5. Several 3-4 µm thick sections are cut after the tissue block is well cut in to expose flatly its entire surface.

The most frequently encountered problem is the evaluation of hepatocellular, microvesicular steatosis (Fig. 6). If the tissue is not well preserved or suboptimally frozen, the subsequent frozen section may prove uncuttable at the thickness of 3 m, which would allow optimal identification but instead has to be cut thicker. This setting will prevent meaningful analysis of the percentage of microvesicular steatosis. In contrast, macrovesicular steatosis is less influenced by section thickness, unless it exceeds 5 m, but the accuracy of prediction will be lower, posing a possible problem in cases where the extend of steatosis reaches a critical level, potentially even leading to the rejection of the transplant in question. Staining methods for fat accumulation are available for frozen section as well as for paraffinized material. However, in a paraffin section, good (and thin) section quality is sufficient in our opinion to reliably recognize the degree of steatosis, while there is the danger that usually buffered, 4% formalin fixation and subsequent paraffin embedding will dissolve many fat droplets, particularly if they are of the microvesicular kind so that the fat stain will not show the true amount of deposition. The problem in frozen section lies again in the section's thickness: while thicker sections give better staining results, they do not allow good identification of the degree of microvesicular fat deposition, while macrovesicular fat deposition does not require a fat stain. In addition, the staining solution should be used within a week after preparation, which means that frequently the solution will have to be freshly made.

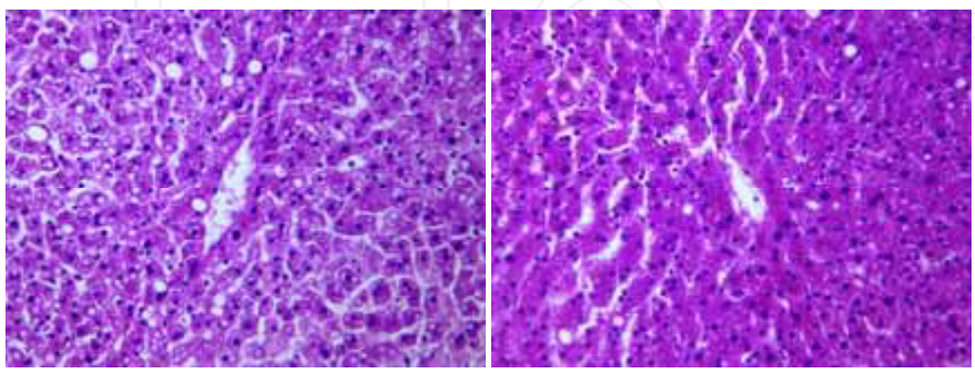


Fig. 6. Microvesicular steatosis: 3 µm thick sections on the left allow optimal evaluation, while the 5µm thick section on the right will lead to under estimation of steatosis. 250X; HE Stain

The other main finding in frozen section liver biopsies concerns the evaluation of parenchymal fibrosis. Here, an increased section thickness will lead to over estimation of the degree if fibrosis as well as potential misjudgement of the width of the liver sinus versus the hepatic trabeculae. While the sinuses will appear small, the trabeculae seem broader than is actually the case. This deception may be important to keep in mind, when the question of liver congestion with potential hemosiderin deposition arises.
In case focal, nodular lesions are encountered on an otherwise normal appearing liver, a frozen section is mandatory, if the organ is principally regarded as transplantable by the surgeon. Here, it is helpful when the entire lesion is excised such that the surrounding normal liver tissue is part of the excision, in order to be able to evaluate the edge of the lesional process (infiltrative or smooth). However, this resection is not sufficient for the histopathological evaluation: besides the excisional biopsy, the regularly taken biopsies from segment 3 and 6 or 7 should be also be performed, because they enable the pathologist to analyse the quality of the liver and its alterations independently from the lesion.

6. Histopathological evaluation during organ procurement

Standards for histopathological evaluation of liver biopsies are still lacking. We recommend, based on our experience that frozen section should be taken within a side length of 1 cm minimum and not only from the liver surface. The pathologist needs sufficient clinical and surgical data for diagnosis. The frozen section should be evaluated when material is post-fixed by a second pathologist for quality standard reasons. These results must be communicated to the transplantation center immediately. The pathologic evaluation, however, should not only include histopathologic findings, but also be extended to other primarily macroscopic findings such as: arteriosclerotic damage to the vessels, subcapsular cysts, and tumors, as well as bile duct abnormalities, since those findings may prevent transplantability despite a well preserved liver parenchyma.
One of the most frequently encountered problems is the size of the wedge itself. Occasionally, not a wedge but a crescent-like slice of hepatic tissue parallel to the surface is taken, and is almost always the only tissue for frozen section and only from the left liver lobe. This procedure is inadequate in several ways: (i) the amount of hepatic tissue is too small; (ii) there are clearly less than 10 portal tracts in this small excision; (iii) the closeness to the capsule may incorrectly suggest a fibrotic process, leading to rejection of the organ; (iv) a biopsy of only one (mostly left) liver lobe is insufficient; it cannot be assumed that the unbiopsied (mostly right) lobe is of equal quality or shows the same pathologic process. By analysing explanted but not-transplanted livers over the past 5 years, we encountered the practice of taking a crescent–like slice in several cases. In almost all cases, the evaluation resulted in rejection of the transplant organ, which after a complete work-up with histologic evaluation of all liver segments, could not be supported from the pathological analysis. The risk of prolonged bleeding with additional measures from the surgeon has been cited as a reason for taking a cresent-like slice in individual cases. While any procedure complicating the evaluation of the transplant should be principally avoided, this reasoning appears unacceptable since there should be sufficient time for arrest of bleeding while the frozen section is performed.

As far as differences between the liver lobes are concerned, we have learned from our study of explanted livers that in all but one case (out of 50) the degree of fibrosis or steatosis did not significantly vary among the different liver segments or the liver lobes (Rey et al., 2009). However, our single case with focal biliary cirrhosis in the right, but nor the left liver lobe, (Fig. 7) supports the concept of taking a wedge biopsy from both liver lobes.

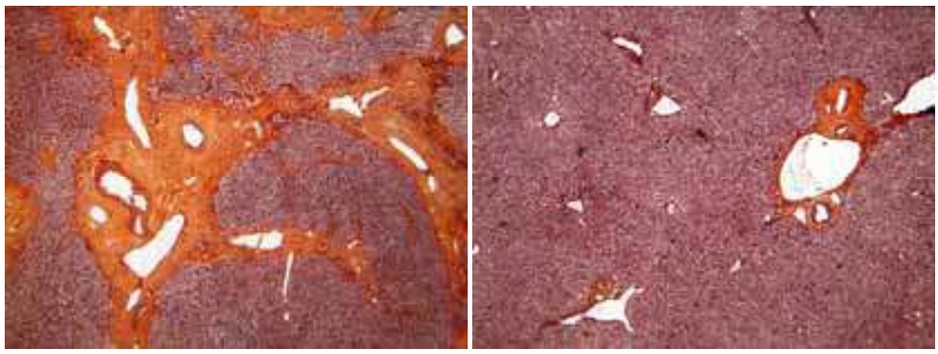


Fig. 7. Differences between liver lobes: Originating from the same liver, the left picture shows the parenchyma of the right lobe with bridging fibrosis and widened bile ducts due to focal bile duct obliteration, while the right picture shows a section from the left lobe with well preserved parenchyma. The liver was rejected from the surgeon with the argument that since the right lobe representing two thirds of the liver was "cirrhosed", (with no additional frozen section done), the "remaining" unchanged left lobe was not sufficient to transplant the organ. 40x; Gomori stain.

Similarly, a focal fat accumulation in alcoholic livers may be taken for an increased steatosis not present in the remaining liver. This opinion is in contrast to current literature which has demonstrated that a single liver biopsy adequately represents the histologic characteristics of the liver (Lo et al., 2008). It has been reported that left and right lobe biopsies obtained during diagnostic laparoscopy have a highly significant histologic correlation for necrosis, steatosis, inflammation, and fibrosis (Picciotto et al., 1983). Nevertheless, the overall importance for adequate histopathological characteristic of the liver parenchyma during organ procurement requires a wedge biopsy with at least 10 portal tractions, and not a superficial biopsy from the liver surface.

As we reported earlier, the colour of the liver surface is insufficient as major criteria in making the decision of transplantation or rejection. The quality of perfusion, the light quality of the operating room, the surgeons experience as well as different degrees of steatosis may greatly diminish the reliability of these criteria. Thus, if the quality of the organ appears doubtful, a frozen section is mandatory.

When a liver is biopsied in order to evaluate it's transplantability, several crucial questions have to be answered by the evaluating pathologist. The most important question is whether the tissue has a lesion or not. The answer depends largely on the quality of the tissue and particularly on the quality of the frozen section, as previously outlined. While highly abnormal lesions, such as a diffuse macrovesicular fat deposition or complete liver cirrhosis, pose hardly any problem even if the frozen section is suboptimal. In contrast, the so called marginal organ lesions, such as mild fibrosis or microvesicular fat deposition, will be under diagnosed (because the bad quality of the section does not allow identification of these

changes) and regarded as transplantable without restriction. This could pose a problem in posttransplant management. On the other hand, changes that are over diagnosed lead to a premature rejection.

Once the pathologist decides that there is a lesion, the question arises whether this lesion is focal or diffuse. Diffuse processes are expected to appear in all liver segments alike, as we could appreciate from our study from explanted, but not allocated livers, in which all segments were investigated histologically. The nature of these processes, such as: alcoholic damage, hepatitis B, or C, cannot be evaluated with certainty by frozen section.

Most important is the evaluation of focal lesions. As table 1 lists, there are several with different pathophysiology to be considered. The information from the primary evaluating surgeon is of great importance. It should state whether there is indeed a single focal lesion, its location (subcapsular; right versus left liver lobe), its macroscopic appearance (colour, size, tissue density), and most importantly, whether the excised tissue encompasses the entire lesion or only a part.

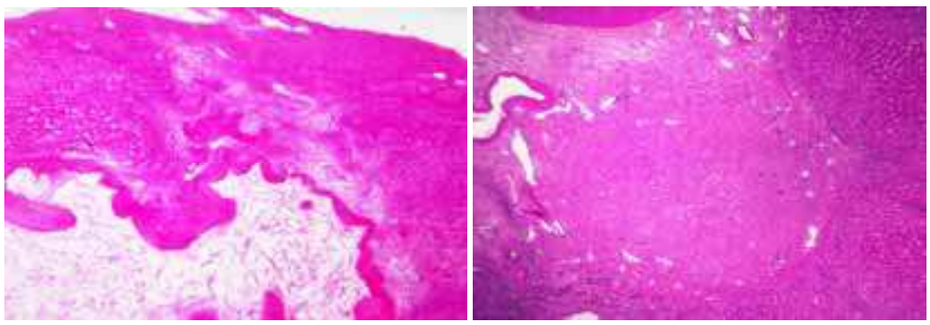


Fig. 8. Focal lesions: on the left, a thick walled cyst, differentially a simple cyst as well as an echinococcal cyst may be considered. On the right, a typical sclerosed lesion with a potentially difficult differential between a (rare) sclerosed malignant process or - as revealed itself on consecutive sections – a (frequently encountered) sclerosed hemagioma. 40x; H&E stain.

In the following section, the main focal lesions which may be encountered in a frozen section are briefly listed and their relevance outlined. At first, the pathologist must differentiate between malignant and benign focal lesions. Among the malignant lesions, the most important ones are *metastatic foci*, which may originate from a large variety of different sources, among them the gastrointestinal, the urogenital, and the respiratory tract. In women, breast and ovary have to be considered. However, in the biopsy these differentials cannot be made. Currently, such livers are regarded as non transplantable, but in the future with the tendency of increasing organ demands, the question to transplant a liver with a metastatic or malignant lesion may be reconsidered depending on the lesion and the clinical evaluation. The other differential of a focal malignant lesion arising in an otherwise normal liver is a *hepatocellular carcinoma (HCC)*. Albeit rare, the identification of such a lesion in a frozen section may be challenging or even impossible, if no normal liver tissue is included for comparison. While the typically thickened plates (being often more than 4 cells wide) are easily identified, the nuclear changes (increased size and nucleoli) can be hard to discern due to artificial swelling of the frozen tissue. Here, the transition from the tumour to the normal surrounding liver as well as plentiful mitoses is helpful. Rare tumour entities encountered are sarcomas, such as: *angiosarcoma, leiomyosarcoma, fibrosarcoma, rhabdomyosarcoma, as well as malignant fibrous histiocytoma.*

Simple cysts vs. Echinococcal cyst	prolonged ischemia (cold/ warm)
Congenital cystic disease	
Cystic mesenchymal hamartoma	Focal nodular hyperplasia
Hemangioma (capillary vs cavernous)	Liver Cell Adenoma
Hemangioendothelioma	Nodular, regenerative Hyperplasia
Biliary hamartoma	Peliosis hepatis
Lymphangiomatosis	Biliary adenoma
Angiomyolipoma	HCC in normal liver
Focal fatty change	Sarcomas
Heterotopia	

Table 1. Focal lesions in the liver as important differential diagnosis in frozen section

Benign focal lesions are numerous, but differ in the frequency that they are encountered. Among the most frequent are benign, simple cysts, hemangiomas and biliary hamartomas. All lesions can be found in subcapsular localization. *Non-paracytic cysts* are typically filled with a clear liquid, having an almost transparent wall and often a flat, sometimes a cuboidal or columnar epithelial lining. They are composed of mature connective tissue and are occasionally calcified. Macroscopically, they can be viewed as problematic when they are bled in. Differentially, an *echinococcal cyst* should be considered, although remnants of scolices may be undetectable. *Congenital autosomal dominant or recessive cystic disease* can be found in some cases; here the identification of renal and pancreatic cysts is important. Depending on the degree of cyst formation, even those organs may be considered transplantable (Rey et al., 2009). In children, a *cystic mesenchymal hamartoma of childhood* should be considered, whenever a pediatric liver transplant is in question. This occurs typically in the right liver lobe at the age of 16 months to 5 years. These hamartomas are mainly composed of connective tissue with small foci of remnants of liver cells, duct cells, even portal tissue.

Among angiomatous lesions, the *capillary and the cavernous hemagioma* are the most frequently accounted subcapsular lesions. Here, a predilection of the right liver lobe, and the female gender is found for the cavernous subtype. Histologically, the typical appearance is multiple, dilated blood-filled spaces lined with mature flat epithelium, separated by fibrous tissue. Problems arise from the tendency of these lesions to undergo regression and fibrosis, which may make it difficult to differentiate them from potential malignant lesions.

Hemangioendotheliomas can be found as focal lesions in childhood as well as in adult livers, although multiple foci throughout the liver may be encountered in childhood. Their histologic appearance is characterized by vascular spaces variable size, lined by immature plump endothelial cells.

Regarding the number of cases, the most difficult decisions to be made are those in which a sclerosing hemangioma has to be differentiated from hemangioendothelioma or bile duct adenocarcinoma. While the evidence of erythrocytes is helpful, all lesions are prone to bleeding and the evaluation of nuclear and cytoplasmic atypia can be severely hampered by the sub-optimal quality of a frozen section. Here, a series of sections should be taken. However, in the few cases encountered with some uncertainty left inspite of a frozen section, the liver was rejected as transplant organ. Subsequent analysis of these livers revealed that the lesion was a sclerosing hemangioma.

Biliary hamartomas, also called cholangiohamartoma or von Meyenburg complexes, are congenital lesions of a disturbed restructuring of the ductal plate (Chung, 1970). They

represent cystic spaces lined by bile duct epithelium and fibrotic obliteration of intrahepatic bile ducts (Woolf&Vierling, 1993). Depending on the localisation and prevalence of cystic ectasia and fibrotic obliteration, several disease entities can be differentiated ranging from the congenital hepatic fibrosis to the Caroli syndrome (Caroli, 1968). The lesions can be found as single or multiple subcapsular foci sharply demarcated and firm, being of grey-white colour and wedge-shaped; their size ranging from 0.5 to 1.0 cm. Cellular atypias are missing. Occasionally, small microhamartomas have to be differentiated from fibrotic portal tracts. However, the presence or absence of portal veins and arteries should enable the correct diagnosis.

Rarely, a *lymphangiomatosis* is found (Van Steenbergen et al., 1985). This solitary lesion is normally located intrahepatically and thus will normally not present itself to the evaluating surgeon. It has to be differentiated from a cavernous hemangioma since it can contain blood, besides cell debris and protein-rich fluid. If it is encountered, a systemic form (present in different organs) has to be recognized versus a sporadic, exclusively hepatic form.

Another benign but tumour-appearing lesion is a *nodule with focal fat accumulation* typically observed in livers from patients with high alcohol consumption (Brawer et al., 1980). This lesion can also be rarely found after tetracycline intake (Peters et al., 1967). Histologically, intrahepatic fat deposition and regional necrotic hepatocytes with inflammatory demarcation is seen.

An *angiomyolipoma* is yet another, mostly unexpected solitary finding, consisting of vessels, smooth muscle and fat tissue as well as medullary marrow. Normally of small size, it may be enlarged up to 20cm (Nonomura et al., 1994).

Ischemic transplant damage or damage to suboptimal organ perfusion, hypotonia and shock of the donor should be considered, if liver cell necrosis, hepatic fat deposition and cholestasis are observed. Prolonged cold ischemia will damage the sinusoidal cells; prolonged warm ischemia the hepatocytes (Schon et al., 1998).

Two other lesions can be challenging in frozen sections*: focal nodular hyperplasie (FNH)* versus adenoma (table 2). In ¾ of all cases, FNH represents an unexpected finding (Goodman, 1987) in women between the age of 20 and 50 years. Typically it is a solitary lesion (80%) and less frequently a multiple lesion (10% two foci, 10% >2 foci) predominantly in the right liver lobe. Star-like fibrotic strands have given the lesion the misnomer "focal cirrhosis". Thus, only a biopsy will be able to differentiate between this and genuine fibrotic/ cirrhotic lesions. The picture is characterized by fibrovascular and ductular areas radiating from the septa, accompanied by an expanding periphery of normal-appearing hepatocytes . While cells may appear polymorph, no dysplasia is seen. Glycogen and fat deposition is present. Intracanalicular bile cylinders can be found as well as bile duct proliferation. In contrast, a *liver cell adenoma* is a lesion almost exclusively found in women in their 3rd to 4th decade. Partially surrounded by a pseudo-capsule made from compacted liver cells, it consists exclusively of hepatocytes 2-3 layers wide lined with regular sinusoids, but without any portal tracts or bile ducts. If focal areas of immature connective tissue are found, a mesenchymal hamartoma should be considered instead.

Nodular regenerative hyerplasia or nodular transformation are small nodules, up to 0.6cm, which represent parenchymal regeneration present in non-cirrhotic livers versus multiacinar nodules without (type 1) or with (type 2) epithelial dysplasia mostly occurring in cirrhotic livers (Nakanuma, 1990).

	Focal Nodular Hyperplasia (FNH)	Liver Cell Adenoma
Location	right liver lobe, subcapsular; ev. multiple	subcapsular; solitary 80%
Central scar	present	absent
Fibrous septae	frequent	rare
Bile ducts and portal tracts	present	absent
Parenchymal lesion	nodular	homogenous
Hemorrhage and necrosis	rare	frequent
Cholestasis	mild	enhanced
Capsule	absent	Partial to ample encapsulation
Vascularity	Vessel with broadened walls	Thin walled vessels (sinusoids)

Table 2. Relevant findings for frozen section evaluation between FNH and liver cell adenoma

A *biliary adenoma* is a small, firm, white appearing nodule of less than 1 cm in diameter consisting of proliferating bile duct epithelium in subcapsular location. Focal inflammatory obliteration of a bile duct by may even lead to a cirrhotic alteration of an entire liver subsegment, which being located under the capsule, can be taken as a pars pro toto change of the entire liver. In our particular case, this resulted in rejection by the surgeon, again without further liver biopsy of other segments, which would have revealed the focality of the process.
Peliosis hepatis, often a 0.3 to 3.0 cm large lesion represents blood-filled, cystically dilated sinusoids without cellular lining (Zak, 1950). They are randomly distributed throughout the liver. Thus, the decision to transplant will largely depend on their size and number as well as their potential negative effect on liver function, particularly since etiologically different infectious diseases have to be considered (Bartonella Henselae, tuberculosis, HIV, S. aureus). Two subtypes are important (Yanoff&Rawson, 1964): the parenchymatous subtype is associated with hemorrhagic necroses, while the phlebic subtype is characterized by dilated sinusoids. However, peliosis has to be differentiated from other lesions such as biliary hamartomas, liver cysts and most frequently from all lesions resulting from acute congestion due to acute right heart insufficiency. Here, the lesion's pericental accentuation, and the lack of cystic structures are important in the diagnosis.
Heterotopias in the liver are rarely encountered, such as ectopic pancreatic tissue within heterotopic duct cysts (Schaefer et al., 1989).
Again, in most cases, a frozen section of the lesion after total excision will bring a satisfactory answer. However, livers were rejected on the ground of such a lesion described by the transplant surgeon, which were not biopsied as part of the decision process, although the subsequent histological evaluation of this liver (analyzing all 8 segments, and the vessels/ bile ducts of the hilar region histopathologically) clearly indicated that this had been a benign process, which should not have led to transplant rejection. There may have been other reasons unknown to us leading to the rejection of the liver. Considering the organ shortage and cost and effect of a frozen section, potentially supporting a decision of rejection, we would advise to perform a frozen section of such lesions in most cases, even if it would be only for providing an irrevocable proof of non-transplantability to the relatives of the decreased. Any rejection has to be seen as disregarding the last wish of the deceased

or the relatives, which in our opinion should be well justified. Furthermore, for future efforts to improve the transplantation rate it seems prudent that the transfer of information potentially leading to a decision of rejection are becoming more transparent and accessible in an epidemiologic databank for future analysis.

Once the histopathological evaluation is performed, the result should be documented on the appropriate transplant form, including the number of frozen sections taken, the quality of the tissue and whether it is sufficient for analysis, the actual histologic evaluation separately for each frozen section/ each segment, and the final assessment, whether or not the liver is good/ acceptable/ poor as transplant organ from a histopathological perspective. This last addendum is important in cases in which the evaluation between transplant surgeon and pathologist differs to the point that the organ is rejected. Pathological evaluations may result in transplantable appearing organs; however, several other reasons may prevent the surgeon from following this advice. Among them are problems with the donor organ concerning the reconstruction of the hilar vessels (anomalies) and the bile ducts (major bile duct too small, anomalies) as well as problems concerning the transplant acceptor. Thus, in the databank regarding the evaluation sheet from a rejected organ, the reasons and the person responsible for the rejection should be clearly stated.

7. Histopathological evaluation after organ procurement

Once the histologic evaluation of the frozen section is concluded, the remaining tissue is postfixed overnight as is the remaining part of the wedge biopsy in buffered, 4% formalin, pH 7.4. The pH of the formalin used should be pre-monitored: commercially available formalin solution may differ in its pH from highly acidic to basic values, all of which being sold as "buffered". The day after paraffin embedding, 3 to 4-µm-thick sections should be cut and routinely stained. A typical standard series of stains (besides H&E) should include: a Gomori's stain (as fibrotic marker), a PAS stain (for best histologic resolution of hepatocytes and sinuses) , and an iron stain such as Berlin blue (for iron deposition). An elastic van Gieson stain may be added, however, it does not provide any advantage; in contrast, it proves less sensitive in detecting fibrosis. If microvesicular staetosis is a major feature - at least if it was one major reason for rejection – a Sudan stain for fat should be included in the list.

One should carefully select the tissue sections to be stained. It seems unnecessary to stain every single one with all stains to be considered. Instead, a representative postfixed section from the primarily frozen tissue as well as one of the primarily formalin-fixed tissue should be selected for this purpose. The remaining tissue (mostly rest tissue from the wedge) should be evaluated primarily by H&E. If there is any question, one still has the opportunity to analyse these tissue portions by additional stains as well.

A discrepancy between the frozen sections analysis and the histopathologic analysis after organ procurement should be reported immediately to the transplant centre. In our experience, this is a very rare occasion: in revaluating the biopsy sites of previous frozen section excisions, we found only one out of 50 biopsies, whose basic diagnosis and evaluation mismatched distinctly. In this case, however, the diagnosis of a major degree of steatosis was made on biopsy, which could neither be found by re-evaluating the former (single!) biopsy site in the third liver segment nor by analysing all other segments of the rejected liver. Unfortunately, the biopsy could not be retrieved to be re-analysed as well, which should be the recommendation in such cases so as to learn more about the reason.

Another aspect of evaluation is the analysis of hepatocellular iron deposition. By frozen section and without further stains, the differential of hemosiderin (containing iron), and

hematoidin (containing no iron) is impossible. Therefore, we recommend a Berliner blue reaction, which will provide a blue precipitate in cases of hemosiderin, but not with hematoidin deposition.

8. Conclusion

Continuously collecting clinical, surgical, and histopathologic data in a central registry of all transplanted livers may provide valuable information as to whether the evaluation at time of transplantation was correct. If a posttransplant biopsy is taken after liver transplantation, the results of its histopathologic evaluation should likewise be collected in the same registry. This measure will improve our knowledge of the importance of morphological alterations and their significance at the time of transplantation. If the liver is rejected as transplant organ, these pieces of information may provide the basis for consoling relatives of the deceased about the reasons for not transplanting the organ and thus acting against his or her last will.
Furthermore, routine control biopsies, in intervals such as 12 months, three years and beyond, may provide valuable information whether or not organs regarded as marginally suitable due to histologic alterations, especially microvesicular versus macrovesicular fat accumulation, are able to recover. In case of death of the transplant recipient, liver evaluation by biopsy or autopsy should become a routine investigation in order to retrospectively control the transplant decision.

9. Addendum

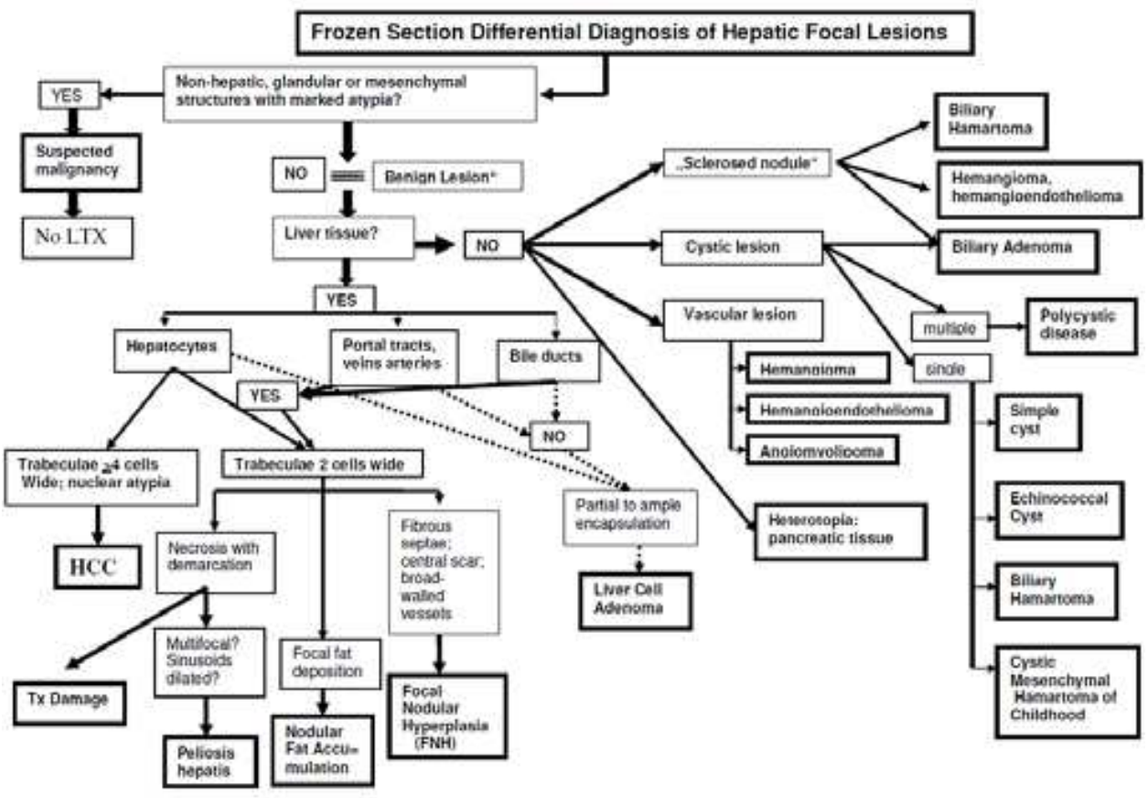


Fig. 9. Flow sheet: "Frozen Section Differential Diagnosis of Hepatic Focal Lesions"

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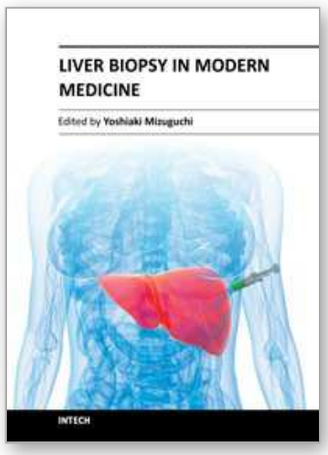
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Edited by Dr. Yoshiaki Mizuguchi

ISBN 978-953-307-883-0
Hard cover, 378 pages
Publisher InTech
Published online 10, October, 2011
Published in print edition October, 2011

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