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Extended hepatic resection in advanced hepatoblastoma

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1. ABSTRACT

Complete surgical resection of the primary tumor is one of the most important prognostic factors for hepatoblastoma (HB). This goal can mean a relevant challenge in some cases of advanced HB, especially since an anatomical resection should be realised. Over recent years several surgical techniques for advanced liver resections in children have been developed and refined. In this article the authors summarize their own experience with advanced liver resections for HB and give an overview over indications and specifications for the different approaches.

2. INTRODUCTION

Hepatoblastoma (HB) is the most common pediatric liver malignancy. In Western countries there exists a constant annual incidence of 0.5-1.5 cases per 1 million children below 15 years of age. The stage independent overall survival rate could be improved from 25% in 1960 to 80% presently based on the treatment progress of different international trials(8;16;33;38). The key to improved therapeutic results was the discovery that HB is sensitive to chemotherapy together with the implementation of risk stratification of the tumors following different treatment concepts. Especially in

Table 1. HB for extended hepatic resection as alternative approach for liver transplantation

Tumor extension	Proximity to major vessels	Procedere
Unifocal PRETEXT III	yes	Right / Left TSE
Unifocal PRETEXT IV	yes	Righ / Left TSE; mesohepatectomy
All three hepatic veins	yes	Extended atypical left hepatectomy
Portal vein	-	Right / left TSE + partial resection of portal vein
Cava vein	-	Right / left TSE + resection with patch or prosthesis , optional CPB
Hepatic vein	-	Right / Left TSE + partial resection with patch, optional CPB

advanced HB and / or high risk tumors the resection rate and outcome could be improved through preoperative chemotherapy resulting in significant decrease of tumor volumes and decline of AFP level. Different drugs or combinations of agents such as Cisplatin, Doxorubicin, Vincristine, Cyclophosphamide or 5- fluorouracil were highly effective for treatment of HB and are used in different international trials(9;11;21;31). However, HB cells are able to develop a drug resistance after multiple courses of chemotherapy(43).

Nevertheless, the most important prognostic factor for survival is the complete surgical resection of the tumor. Despite the excellent treatment results in low risk HB (5 year overall survival over 90%), the local treatment of advanced or multifocal HB is a surgical and partially unsolved challenge(31). Meanwhile liver transplantation is an established treatment option for children with multifocal, bilobular or otherwise unresectable HB without extrahepatic extension of tumors with good response to chemotherapy(29). However, from the surgical point of view exists a relevant number of so called borderline indications for tumor resection, where extended hepatic resections have analogue results as liver transplantations (Table 1). The burden put on the surgeons lies in the fact that – if local relapses occur due to residual tumor after major hepatic resections - rescue liver transplantations are associated with a far worse outcome compared to primary liver transplantations(2;27). The aim of this article is the evaluation of prediction of extended hepatic resection in advanced HB.

2.1. Challenges in liver tumor surgery

Challenges in liver tumor surgery are advanced tumors where a trisegmentectomy is necessary, tumors infiltrating large vessels (portal vein, hepatic veins, and retrohepatic cava vein) or the central bile ducts, multifocal HB, and central liver tumors. A fundamental question for the surgeon is the time point of surgery and the surgical strategy for these tumors. Due to the excellent results of primary liver transplantation for children suffering from advanced tumors, it is necessary to evaluate the role of extended hepatic resections in comparison to primary liver transplantations in all children with advanced tumors.

2.2. Assessment of resectability in HB

Resectability is predicated upon a patient´s status, functional liver remnant, existence of extrahepatic disease, tumor extension, and tumor biology. Tumors are deemed resectable if they can be removed with margin of uninvolved liver tissue while leaving an adequate liver remnant. Children without cirrhosis - and this is the typical constellation in HB - can tolerate resection of up to 80% of the liver.

CT scan (or MRI) of the abdomen is the basis for assessment of the resectability of liver tumors. These diagnostic tools are standardized procedures with a high sensitivity and specifity(5). Finally, intraoperative ultrasound has added further aspects to assess resectabiltiy and to exclude the presence of tumors beyond the planned resection. Ultrasound scan is essential to evaluate the relationship between major hepatic vessels and the tumor(8).

Under these aspects the preoperative assessment of the resecability of advanced tumors is an essential issue which requires a reproducible staging system.

Until 1990, all staging systems of primary liver tumors were based on findings at surgery or after surgery. The best known staging system so far is the TNM classification, which was adopted from the International Union Against Cancer. This system is simplified as a post-surgical staging system and is used by the COG as well as the German Liver Tumor Study Group.

The SIOP group established a system which described the pretreatment extent of disease. The system distinguishes between four PRETEXT categories, which reflect the number of sections of the liver, which are free of tumor. Additionally the PRETEXT system describes the extension of disease beyond the liver using the following letters: V-inferior cava vein, hepatic vein, P-portal vein, E-extraheptic disease, M-metastases (Figure 1)(1).

This is an excellent tool to judge the response to chemotherapy and in part the resectablity of liver tumors. A disadvantage of this system is the tendency to overstage the tumors, probably as a result of the difficulty to distinguish parenchymal ingrowth of the tumor(23). This is relevant in unilocular tumors in PRETEXT III and IV with regard to the subsequent decision between tumor resection versus liver transplantation. Another issue is the "understaging" which occurred for instance in 10/91 cases in the SIOPEL 1 study. In 4 of these 10 cases an incomplete tumor resections were performed(1;4). The PRETEXT system was modified in 2005 based on advances in imaging and clinical experiences over the last 15 years with additional criteria for risk stratification. New parameters are caudate lobe involvement (C), tumor focality (F), tumor rupture (H) with different subdivisions(35).

The PRETEXT system also proved to be of highly prognostic value for overall and event free survival in HB(4). On the other hand, the postoperative staging systems do not take into account the feasibility of complete

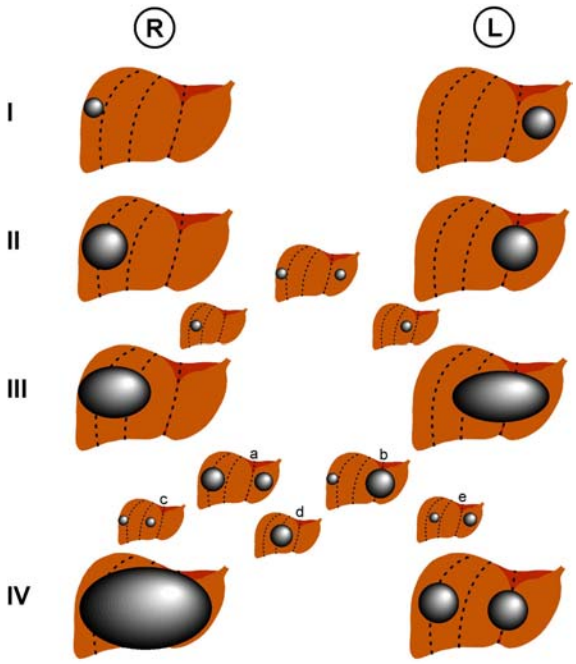

Figure 1. PRETEXT system of SIOPEL.

tumor resection especially keeping in mind the aspect of primary liver transplantation.

Meanwhile all international trials use the PRETEXT system and this decision offers the possibility to collaborate and compare the treatment results.

A new option for an improved assessment of the resectability of liver tumors is the three dimensional reconstruction with identification of specific risk areas in relation to the liver vessels and a clearly defined correlation to the Couinaud liver segments. This system was established for living related liver transplantation in adults and is meanwhile also used for planning of difficult liver resections in adults (7;20;34). Fuchs *et al* published an adaptation of this technique in pediatric solid tumors based on conventional multislice CT scans using a specific software from MEVIS/Bremen. Another advantage of this technique is the possibility of a virtual tumor resection (Figure 2)(12). Despite its impeccable contributions to advanced liver surgery, this diagnostic tool is by now not applicable on a regular basis, mainly due to economic reasons. However, with increasing experiences and numbers this approach will eventually be usable to further developing the preoperative tumor staging in HB.

2.3. Risk stratification of HB

Since 1994 the SIOPEL 2 study defined low and high risk groups for HB. In 1999 the German Liver Tumor Study Group also identified two risk groups with different treatment concepts for HB. Both systems are not comparable due to the different staging systems (Table 2). Otherwise most of the advanced HB are assigned to the high risk group. However, the unifocal PRETEXT III disease where proximity to major vessels makes adequate tumor resection doubtful is an exception. These tumors are relatively common and are usually stratified as low risk tumors. In children with HB, special care must be taken to distinguish between invasion and compression of the apparently uninvolved section of the liver. However, the SIOPEL concept recommends liver transplantation in cases of involvement of the hepatic veins or inferior cava vein whenever possible (4;35). These aspacts are relevant for analyzing the oncological outcome of HB under the aspect of liver transplantation versus extended liver resection.

3. SURGICAL TECHNIQUES IN ADVANCED HB

Major hepatic resections in HB are indicated in children with PRETXT III and unifocal PRETEXT IV tumors with persisting metastasis after preoperative chemotherapy. On one hand some international study boards suggest a primary orthotopic liver transplantation in cases of PRETEXT IV tumors after clearance of metastases through chemotherapy (18;26;27;28;30). Heroic liver resections with a high probability of leaving behind residual tumor should be avoided(4). On the other hand centers of excellence in liver surgery could demonstrate an excellent outcome in children with unifocal PRETEXT III and partially IV tumors after extended major liver resections(7;13;19;24;42). Other aspects are the availability of liver transplantation in the different countries of the world and the lack of prospective randomized studies for analyzing the outcome of liver transplantation versus major resection in HB surgery. Last but not least present retrospective analyses do not allow to draw clear conclusions for indications of liver transplantation based on the different biological behavior of HB, initial AFP level, vessel involvement, and risk stratification.

The well known advanced or major hepatic resections such us trisegmentectomy, mesohepatectomy and resection of HB with reconstruction of the main hepatic vessels are described in the following focusing on selected technical aspects of surgery and the oncological outcome.

3.1. Extended right and left hepatectomy (Trisegmentectomy)

The indications for trisegmentectomies (TSE) are cases of unifocal PRETEXT III and IV tumors. There exists a controversial discussion regarding radical partial hepatectomy and liver transplantation especially in cases of PRETEXT III where the tumor in direct spatial relationship to the main hepatic vessels. The SIOPEL group recommends primary liver transplantation for such conditions whenever possible. Within one study period (SIOPEL 2 to SIOPEL 3) the 3 year overall survival of high risk HB could be improved from 53% to 73% (71). There exist several reasons for the improvement of treatment results in the SIOPEL group. One point is the modification of chemotherapy and another point is the large number of liver transplantations, but also the influence of different numbers of patients with lung metastases. Nevertheless, all mulifocal PRETEXT IV tumors were included in these analyses and it is difficult or impossible to give detailed information on unifocal PRETEXT III/ IV tumors (Table 3) based on the international literature. Other groups such as the German Cooperative Liver Tumor Stud

Table 2. Criteria for high risk HB in the SIOPEL 2/3 study versus German Cooperative Liver Tumor Study HB 99

	SIOPEL	**HB 99**
Staging System	PRETEXT IV	Stage III/ multifocal
Vascular invasion	Major hepatic vessels	Major hepatic vessels
Presence of metastases	yes	yes
Lymph node involvement	yes	Yes
Tumor rupture	yes	yes
AFP < 100 µg/l	yes	no

Table 3. 3 year overall survival rate (OS) and 3 – year event free survival (EFS) with resection rate (R0 and R1) in high risk HB of SIOPEL 2/3 and German Cooperative Liver Tumor Study HB99

	SIOPEL 2(32)	**SIOPEL 3(44)**	**HB99 (GPOH)(14)**
Time intervall	1994 - 1998	1998 – 2008	1999 - 2008
No. of patients	58	158	42
Response to CT (%)	78	89	75-84
Resection rate (%)	67	74	70
No. of LTX	?	34	8
OS (%)	53	73	55
EFS (%)	48	65	55

Table 4. Macroscopic tumor residuals after TSE in HB (* stage in depended overall survival of the whole study group)

Author	**No. of TSE**	**No. of R_2 resections**	**Overall survival***
Schnater(37)	37	6	75%
Fuchs(11)	18	3	77 %
Towu(42)	11	0	73%

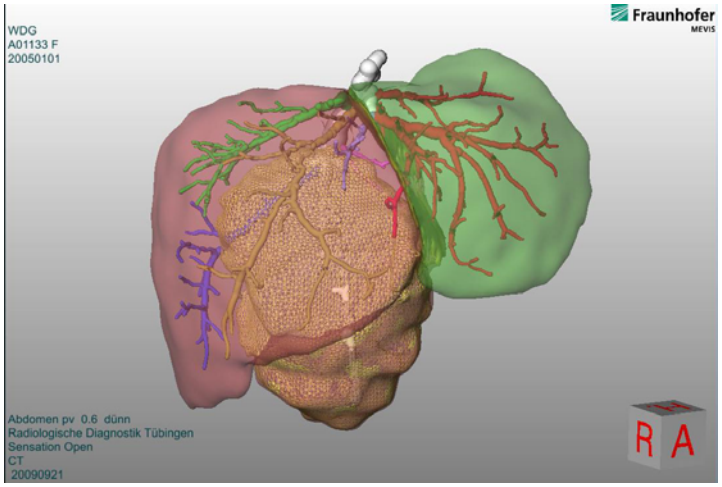

Figure 2. 3 –D- reconstruction of an HB with virtual tumor resection.

Group or single centers in the USA or France report on the same rates of R_0- and R_1-resection after extended hepatic resections and lower numbers of liver transplantations(3;25).

An essential point for success under the aspect of long term outcome in both treatment options is a good response to chemotherapy. Presently pre-existence of extraheptatic disease (tumor thrombus in the portal or cava vein) is a contraindication for liver transplantation. Meanwhile there exists a controvers international discussion about this difficult aspect. The recently established PLUTO registry (Pediatric Liver Unresectable Tumor Observatory) might help to give an answer to this open question in the future. At the same time, this is only a retrospective registry without central radiological and surgical review, without possibilities of evidence based analyses.

All international trails request the completeness of tumor resection in cases of extended liver resections. If there is any doubt, frozen sections of the resection margins should be obtained both, from the tumor side and from the remnant liver tissue. Otherwise, it is often necessary to remove the encapsulated tumor from the wall of main hepatic vessels without relevant safety margin. However, the presence of microscopic residual disease at the resection margin is not a major adverse prognostic factor for survival(11;32;33;37). These data justify trisegmentectomies as surgical approach in advanced HB (Table 4).

Macroscopic tumor rest is associated with an impaired outcome and therefore not acceptable.

The trisegmentectomy is a surgical challenge from the technical point of view. Especially significant intra-operative blood loss during extended left hepatic resection remains a problem even for experienced liver surgeons. Therefore, total vascular exclusion should be

carefully prepared. Since the implementation of the Pringle maneuver which is easy for the porta hepatic, total vascular exclusion can be realised after securing the infra- and suprahepatic cava vein. Total vascular exclusion has not been widely adopted by liver surgeons because of the concern regarding the associated ischemic injury to the liver remnant. The available data on total vascular exclusion in childhood liver surgery are very limited. Through the work of Huguet, liver surgeons have noted that of inflow occlusion can be tolerated up to 60 minutes even in the presence of cirrhosis(17). The time can be prolonged to over 80 min using a clamp –free interval of 5 min. In a series of 67 children undergoing liver resection with or without clamping during, Szavay *et al* could demonstrate that the operating time was significantly longer in the non-clamping group. There were no statistical differences regarding postoperative liver function between both groups(41).

Reduced blood loss is achievable by using modern technical devices such as CUSA® or harmonic knife in the parenchymal phase However, the correct knowledge about the segmental anatomy of the liver remains essential for the surgical success(10). Another important observation is the remarkable rate (9/11 patients) of tumor resections with microscopic residual disease in the SIOPEL 1 study by using the CUSA® device(37).

Another aspect is the difference between left and right trisecmentectomy. The technical demand is higher in the group of left trisegmentectomies due to the dissection of the subsegment vessels of the right portal vein in the Glisson´s capsule. Occasionally, in large tumors the resection of segment I (caudate lobe) is required in both types of resections. The dissection of the paracaval veins should perform carefully. Otherwise the protection of the segmental hepatic arteries can be challenging during extended hepatic resections in small children.

The low percentage of liver remnant after left or right TSE can be problematic for the initiation of postoperative chemotherapy. Mortality after TSE due to chemotherapy is are known problem. In the HB94 study,2 children died due to side effects of chemotherapy. In both cases a TSE had been performed and the chemotherapy started with a delay of 3 months and with a reduced dosage (11).

3.2. Mesohepatectomy

Another well known technique is the mesohepatectomy. This procedure is often performed in adults in cases of metastatic liver diseases such as colorectal carcinoma. There exist only two publications about mesohepatectomy in HB (19) (la Quaglia in New York and Gauthier in Paris).

The authors resected S IV, V and VIII in 11 children without metastases. In all cases an R_0 resection was achieved and all children survived. In three cases a biliary leakage occurred after surgery. This complication was managed with a percutaneous drainage. This technique is an excellent alternative for the trisegmentectomy in selected cases of HB. The main advantage is a higher percentage of healthy liver remnant with consecutively better clinical conditions of the children before postoperative chemotherapy.

3.3. Extended atypical left hepatectomy

Liver tumors that surround the three major hepatic veins traditionally have been considered unresectable. Superina described an extended atypical left hepatectomy technique for these tumors(40). These procedures are only possible in the presence of a back up liver transplantation facility. The liver is mobilized to the right and the accessory hepatic veins draining directly into the cava vein are preserved carefully. The three hepatic veins are clamped to judge the adequacy of the retrohepatic venous drainage. If the right side of the liver is soft, the resection can proceed.

The authors performed this procedure in three children. In one case there existed technical problems and a liver transplantation was necessary. All children survived.

3.4. Resection of HB with reconstruction of hepatic vessels

All above mentioned extended hepatic resections possibly include the reconstruction of major hepatic vessels. Pre-existing extrahepatic disease is a relative contraindication for liver transplantation. In a retrospective analysis Otte *et al* showed, that in cases of venous invasion before LTX only 54% of HB patients survived. The survival rate in cases without venous invasion was 78%(30). Analyses of liver transplantations in hepatocellular carcinoma in adults show a tumor recurrence within the liver or distant metastases in over 60%(36) because of immunosuppression. In such cases the only chance for survival is the complete tumor resection with conventional surgical approaches.

Based on the data in the literature it is not possible to judge the efficiency of the surgery in such constellations because of the low number of cases in all different international trials.

There exists a wide spectrum of surgical procedures to reconstruct the involved major hepatic vessels. It reaches from the simple resection of the main portal branches with re-anastomosis to the reconstruction of the retrohepatic cava vein with a prosthesis. Some authors prefer the usage of extracorporal bypass with deep hypothermia, others reconstruct the vessels under warm ischaemia.

3.5. Liver resection under extracorporal bypass

A radical approach of liver surgery is the resection under extracorporal blood circulation. This procedure was first described by Ein in 1981(6).The number of cases is the literature is very limited (Table 5). Our own experience covers 5 cases of which 3 have been published together with Oldhafer within the HB 94 study of the German Cooperative Liver Tumor Study. A complete surgical resection was realized in all cases without any complications. The 3 year overall survival rate was 3/5 (10;26).

Table 5. Resection and outcome of HB using cardiopulmonary bypass

Author	No. of patients	3 year overall survival
Ein(6)	4	50%
Chang(3)	5	60%
Mestres(22)	1	100%
Oldhafer(26)	3	66%
Towu(42)	1	0 %

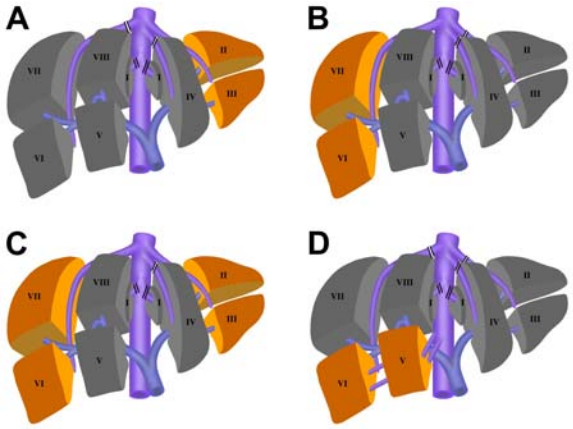

Figure 3. Different types of extended hepatic resections in HB (A- right TSE, B- left TSE, C- mesohepatectomy, D- extended atypical left hepatectomy).

The interdisciplinary surgical approach is based on a well defined flow chart and begins with the preparation of liver resection. Then follows the canulation of the atrium and ascending aorta via sternotomy, and the cardiopulmonary bypass is initiated. Now the surgeon completes the tumor resection followed by reconstruction of the involved vessels. The advantage of the extracorporal bypass is the controlled and bloodless reconstruction of the vessels with removal of large tumor thrombi. This is especially important for the inferior cava vein or hepatic veins and furthermore includes protection of the liver remnant from ischaemic damage during hypothermia. The low flow procedure allows a rest perfusion of parenchymal organs with approximately 30 % heart time volume and a deeper hypothermia (~30° C) with a consecutively lower risk of post perfusion syndrome in comparison to deep hypothermia and cardiac arrest. The disadvantage of the CPB is the complete antagonisation of coagulation and the patients' risk of developing a post-perfusion syndrome.

Haeberle published the preliminary results from the HB 99 study of the German Liver Tumor Study Group for high risk HB with and without involvement of major hepatic vessels (15). Due to the low number of cases a statistical analysis was impossible. On one hand a decreased 3 year overall survival and event free survival was observed for high risk tumors with vascular involvement (OFS 33%, EFS 33%) compared to high risk tumors without vascular involvement (OFS 72%, EFS 54%). On the other hand the data show that radical surgery with reconstruction of large vessels can lead to an improved long term survival in selected cases.

4. CONCLUSIONS

The international data analyses of liver transplantations by Otte *et al* underline the progress in local treatment of HB, especially in multifocal PRETEXT IV tumors. Extended hepatic resections are true alternatives in selected unifocal PRETEXT III and IV tumors. An essential point for survival in both treatment groups is an adaequate response to chemotherapy. Advantages for extended hepatic resections are the renunciation of immunosuppression with the risk of tumor recurrence and development of secondary non malignant and malignant diseases such as lymphoproliferative disorders(39). Otherwise the macroscopic complete tumor resection is a condition for excellent long term outcome in children after extended hepatic resection. Many questions remain open and can only be solved through prospective international studies because of relatively low numbers of cases. Positive aspects in these fields are the establishment of international treatment protocols for recurrent HB and the PLUTO registry. Another aspect is the foundation of national centers of excellence for the treatment of HB. These centers should have available experienced oncologists, pediatric surgeons, and transplant surgeons. The safety of children with advanced HB can only be improved, if major hepatic resections can performed with a back up of liver transplantation. The interdisciplinary collaboration is the way for better treatment results and a better future for children with advanced HB.

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