



Role of Liver Transplantation in Management of Esophageal Variceal Hemorrhage

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Abstract: The management of esophageal variceal hemorrhage ranges from conservative to surgical modalities. Before introduction of liver transplantation as a potentially curative therapy of the underlying etiology, decompressive portosystemic shunt operations have been the mainstay of mostly palliative procedures. Our own experience with surgery for advanced hepatic disease and portal hypertension over 20 years includes 803 liver transplantations and 201 portosystemic shunts, emphasizing our primary objective of treatment. The results after shunt surgery were favorable in Child class A candidates when performed electively and with selective decompression. After liver replacement the clinical status of the patient, including hepatic function and extrahepatic complications, had a strong influence on postoperative outcome, with the chance of excellent long-term survival. The additional risk of previous shunt surgery for subsequent transplantation could be reduced over time. Based on this experience and reports from others there are enough reasonable arguments for shunt and transplantation. Instead of the choice being controversial, the two forms of therapy should supplement each other and be available in the same center that specializes in the treatment of patients with diseases that eventually lead to liver failure and portal hypertension. Selection of either approach must depend on etiology, stage of the disease, and proper timing. Shunt procedures may be indicated in stable patients with the risk of bleeding after sclerotherapy failure, in those with contraindications to transplantation, or as a bridge to transplantation. The role of liver transplantation has been clearly established in patients with progressive or endstage (otherwise intractable) hepatobiliary disease.

The clinical picture of portal hypertension is characterized by a variety of secondary complications. Among others (ascites, hypersplenism, hepatorenal-pulmonary syndrome, hepatic encephalopathy and coma), hemorrhage from esophageal varices is probably one of the most devastating sequelae. The overall risk of active variceal bleeding in patients with cirrhosis and varices is estimated to be 20% to 30%, and the mortality of each bleeding episode is in the range of 30% to 50%, emphasizing the clinical significance of this particular problem [1, 2].

The general prognosis of variceal hemorrhage is mainly determined by factors such as etiology of portal hypertension (especially the cause of cirrhosis as the most frequent underlying pathology), the severity of hepatic disease with regard to liver function, and the presence of extrahepatic complications characterizing the clinical status of the patient, features that are usually described by the traditional Child's criteria [3]. Other

important prognostic determinants are clinical urgency and the treatment applied.

The wide therapeutic spectrum available today is not only a reflection on the history of technical developments possible but a sign of the inefficiency of many of the treatments [4, 5]. One explanation for this disappointing perspective is the fact that most of the treatment modalities are directed only at palliation of variceal hemorrhage, with the major aim to prevent rebleeding. There is little doubt, though, that many conservative and surgical methods are well established, ranging from pharmacotherapy, balloon tamponade, or endoscopic sclerotherapy to devascularization-transection procedures and various types of portosystemic shunts for portal decompression. In some way or other they fulfill their purpose and are important tools in the therapeutic armamentarium [6, 7]. On the other hand, the ideal goal of therapy should be curative treatment of the underlying disease. In principle, this goal can only be reached by eliminating the cause of the portal hypertension (e.g., removal of a cirrhotic liver or relief of a postsinusoidal anatomic obstruction as in special situations of Budd-Chiari syndrome).

Two historical events are regarded as surgical landmarks. In 1877 Nicolai V. Eck created a fistula between the portal and caval veins, an operation that became the pathophysiologic basis for all decompressive procedures on the portal venous system [8]. The first human liver transplantation performed by Starzl et al. in 1963 was the beginning of a new era where it became a reality that patients with endstage hepatic disease had the chance not only to survive but also to live a normal life [9]. Those two pioneering but different operations emphasize the extreme therapeutic alternatives and highlight an essential controversy—to shunt or to transplant—which still exists and is discussed later in the paper.

The objective of the present article is not to review comprehensively this particular debate regarding variceal hemorrhage. We are well aware that personal bias toward a specific treatment modality has a strong influence on the decision for its application. Hence this article reflects the authors' point of view on the role of liver transplantation based on their own experience, discussed with selected data from the literature published on this subject. The final discussion is an attempt to

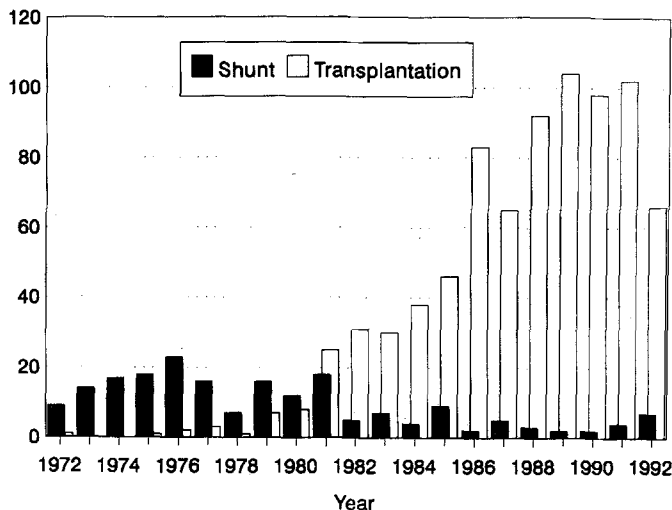


Fig. 1. Development of portosystemic shunt surgery and liver transplantation at the Medizinische Hochschule Hannover from 1972 to 1992.

focus on the most crucial question in this field: Who are the suitable candidates for liver transplantation instead of or subsequent to any other type of therapy?

Hannover Experience

Our experience with surgery for portal hypertension and its complications at the Medizinische Hochschule Hannover over the past 20 years was mainly influenced by the introduction and establishment of an active liver transplant program in 1972. Since that date our group has carried out 803 hepatic transplantations and 201 portosystemic shunt operations. Whereas until 1982 the shunt/transplantation ratio was 155:79, within the last 10 years only 46 shunts but 724 transplants have been performed (Fig. 1). This development clearly demonstrates that our major emphasis in the treatment of patients with diseases that eventually lead to endstage hepatic failure is to assess the potential indication for liver replacement. Especially in the most recent period, shunt operations have been restricted to few selected patients. This bias must be taken into consideration when analyzing frequency, indications, and results of those two treatment modalities at our own institution.

Portosystemic Shunts

Since 1983, during which time detailed evaluation and complete follow-up was available, 46 portosystemic shunts of various types were performed including 28 selective decompression operations: 23 end-to-side and 3 side-to-side distal splenorenal, 1 left gastric venocaval, and 1 makeshift anastomosis. There were 18 total diversions: 7 end-to-side and 6 side-to-side portocaval, 2 each proximal splenorenal and mesocaval interposition, and 1 cavomesoatrial shunt using a prosthetic jump graft.

The etiology of portal hypertension was as follows: postnecrotic cirrhosis due to viral hepatitis, alcohol, and other diseases ($n = 33$), Budd-Chiari syndrome ($n = 7$), portal vein thrombosis ($n = 4$), and hepatic fibrosis ($n = 2$). There were 32 patients in Child-Pugh stage A, 12 in stage B, and 2 in stage C.

The indication for shunt was acute or recurrent bleeding in most cases, with 11 procedures performed as an emergency and 35 electively. Thirteen patients were treated for ascites or splenomegaly with pancytopenia. Four patients of this consecutive series later received liver transplants.

Overall, 20 patients died, most from multiorgan and liver failure during the early postoperative period. Of the 46 patients, 26 (57%) are presently alive with a median follow-up of 65 months (range 11–122 months). The prognosis was strongly correlated to Child's stages (A versus B/C), urgency (elective versus emergency), and type of shunt (selective versus total) with significant differences in actuarial survival rates (Fig. 2). The only Child class B/C survivors (1–8 years) were those who underwent a subsequent liver transplant.

The data taken from our limited experience are in accordance with results from other groups and emphasize again that there is a selected group of patients who benefit from portosystemic shunt operation if it is performed in Child class A patients at an elective timing and preferably by selective decompression. The data also confirm that the clinical status and hepatic function of the patient are important selection criteria with regard to prognosis, and the indication for and timing of the liver replacement are especially influential.

Liver Transplantation

From 1972 to 1992 we performed primary liver transplantation on 680 patients (560 adults, 120 children) for a variety of diseases. Over this 20-year period numerous medical and non-medical improvements have contributed to the evolution of this operation. It progressed from an experimental procedure to standard therapy for patients doomed to die from endstage organ failure. This development and gain in experience is easily recognized from our own series, where the early high morbidity and mortality rates have been reduced significantly in recent years (Fig. 3).

The expectations following liver replacement focus on the long-term prognosis. This point is most apparent when comparing liver transplantation for benign versus malignant disease. Because most of the early deaths related to the transplant operation and its complications, we can study long-term survival by resetting the 1-year survival to 100% (Fig. 4). This change shows that the patients who were transplanted for benign disease and survived 1 year had only 5% mortality over the next 3 years, whereas 42% of tumor patients who made it to 1 year died during the next 3 years. The most striking result, however, was the complete physical and psychosocial rehabilitation seen in most long-term survivors. Our own longest surviving recipient is still in excellent health more than 17 years later.

Stratification of the various benign disease categories showed that postnecrotic liver cirrhosis after viral hepatitis, primary biliary cirrhosis, Budd-Chiari syndrome, and Byler's disease were the most frequent indications for liver transplantation; these diseases were well represented in the typical patients with endstage liver failure complicated by portal hypertension. Many of these patients had repeated, often life-threatening variceal bleeding episodes that necessitated chronic sclerotherapy over long periods before transplantation. The survival rates for patients with those diseases at 4 years were 67%, 76%, 80%,

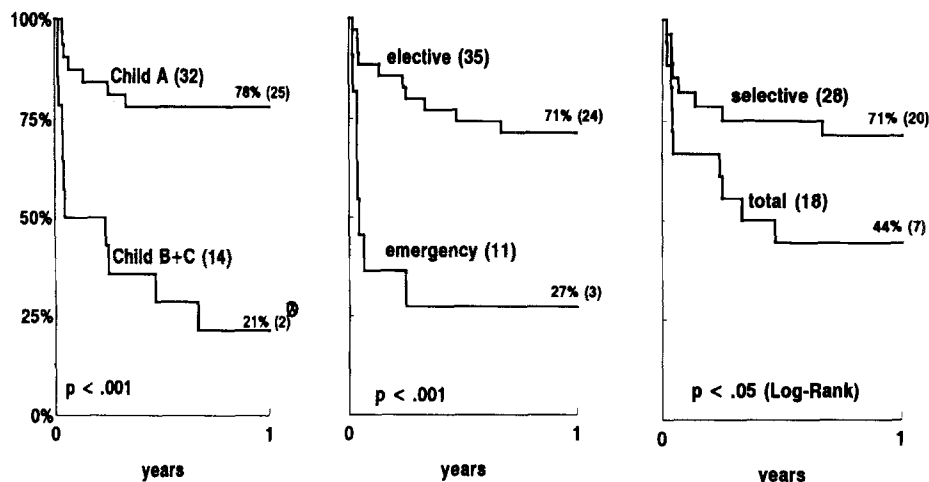


Fig. 2. Actuarial survival after portosystemic shunt operations in 46 patients according to various criteria: Child stage, urgency, and type of shunt (*after additional liver transplantation; 1983–1993).

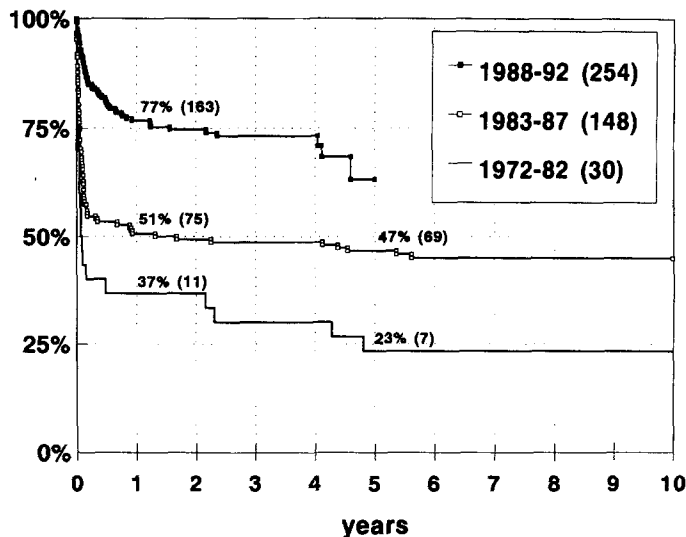


Fig. 3. Actuarial survival after liver transplantation in 432 patients with cirrhosis according to different eras: 1972–1982 versus 1983–1987 versus 1988–1992. (Benign diseases without cirrhosis and malignant tumors were excluded.)

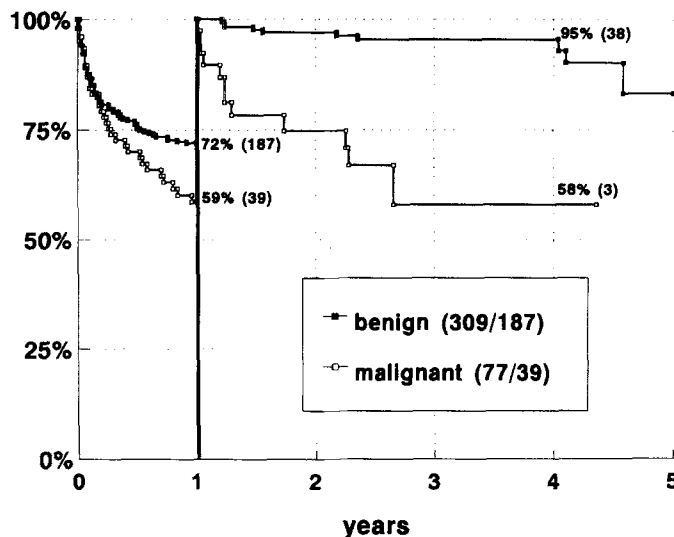


Fig. 4. Actuarial survival after liver transplantation in 386 patients according to indication: benign diseases versus malignant tumors, 1988–1992. (One-year survival was reset to 100%.)

and 100%, respectively (Fig. 5). These results not only reflect patient selection; they illustrate the potential for definitive long-term cure especially in patients with some cholestatic and metabolic disorders.

There were only a few patients who had an emergency transplant for acute bleeding. One of those patients was a 33-year-old woman with idiopathic Budd-Chiari syndrome who suffered from massive ascites and esophageal varices grade IV. She was evaluated for portocaval shunt when the second bleeding episode occurred that could not be controlled by sclerotherapy and balloon tamponade. She went into renal and respiratory failure, necessitating artificial ventilation. A Sengstaken-Blakemore tube was in place for 48 hours, when emergency liver transplantation was performed for ongoing hemorrhage. She was on artificial ventilation for 38 days. The patient was discharged after 75 days in good health and with normal liver function. This case report demonstrates that liver trans-

plantation can be successful even in such an exceptional situation but with significant risk.

Portosystemic Shunts and Subsequent Liver Transplantation

In 25 liver recipients other surgery for variceal bleeding had been performed previously. There were two cases of esophago-gastric devascularization with a difficult but successful subsequent transplant procedure; they are not discussed further here. A group of 23 patients (age 15–59 years) had various types of decompressive shunt operation: portocaval side-to-side ($n = 9$) or end-to-side ($n = 5$) shunts, mesocaval shunts with interposition grafts ($n = 4$), and distal ($n = 3$) or proximal ($n = 2$) splenorenal anastomosis. Underlying hepatic diseases were postnecrotic cirrhosis following viral hepatitis in 15 (4 with

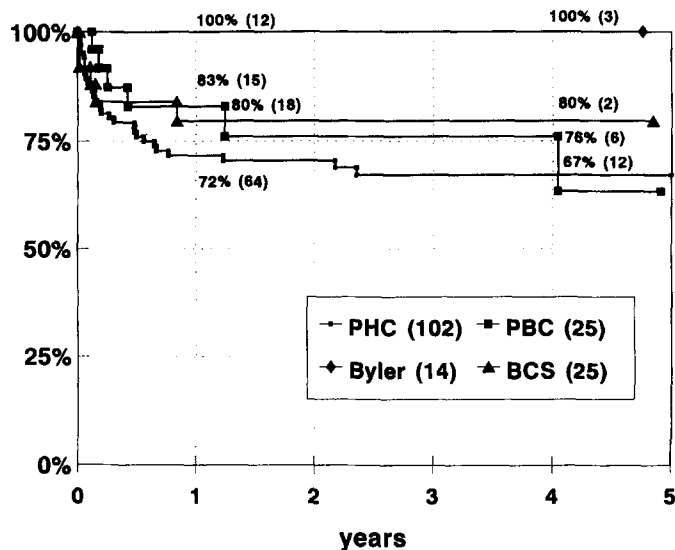


Fig. 5. Actuarial survival after liver transplantation in cirrhotic patients with the most frequent diseases: PHC (postnecrotic cirrhosis) versus PBC (primary biliary cirrhosis) versus BCS (Budd-Chiari syndrome) versus Byler (Byler's disease), 1988-1992.

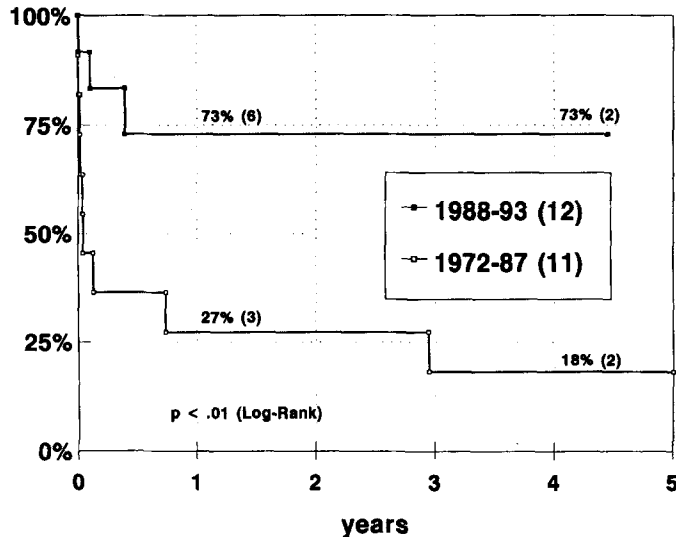


Fig. 6. Actuarial survival after portosystemic shunt operation and subsequent liver transplantation in 23 patients according to different eras: 1972-1987 versus 1988-1993.

additional hepatocellular carcinoma), Budd-Chiari syndrome in 4, and postalcoholic or primary biliary cirrhosis in 2 cases each.

Time intervals between shunt and transplantation ranged from 1.5 weeks to more than 13 years. Early shunt failures necessitating emergency liver replacement within 11 to 22 days—for thrombosis (n = 2), progressive liver failure (n = 1), or massive intractable ascites (n = 1)—were all seen in Budd-Chiari patients. Altogether, five anastomoses were occluded by thrombosis at the time of transplantation, including three of the four mesocaval prostheses. Whereas in the beginning no venous bypass was available during the anhepatic phase, more recently temporary partial femoroaxillary bypass has been used almost routinely. The portosystemic anastomoses were kept open as long as possible and taken down only immediately before or after portal vein reconstruction in all cases to sustain sufficient portal blood supply to the graft without steal effect.

During our early phase of liver transplantation, heavy bleeding from dense adhesions during the dissection—without adequate venous decompression—led to significant intra- and post-operative morbidity and mortality: 6 of 10 early deaths were related to those complications and thus to previous shunt surgery. Two additional patients died from recurrent hepatocellular carcinoma after 9 and 35 months, respectively. At present, 11 liver recipients are alive with a maximum follow-up of more than 11 years. The learning curve in our own experience is clearly visible in the actuarial survival analysis according to different eras: Before 1988 there were only 4 early survivors among 11 patients compared to the recent 5-year period with 9 long-term patient survivors among 12 operated on (73%) (Fig. 6).

As can be concluded from this consecutive series, the operative morbidity and the mortality among patients with previous portosystemic shunts is higher especially when liver transplantation is performed in centers with less than desirable personal experience. With this point in mind, the general risk is certainly acceptable, and a preexisting shunt is not considered to be a

contraindication to transplantation. In appropriate patients the performance of a selective shunt (e.g., distal splenorenal anastomosis) can even be encouraged in order to “buy time” for later liver transplantation.

Discussion

Endstage hepatic disease with portal hypertension complicated by upper gastrointestinal bleeding is a significant problem worldwide—regarding the large number of patients affected as well as the individual and often the fatal prognosis. The best available treatment is not always applied for a variety of medical, socioeconomic, and other reasons [10]. Thus palliation and prevention of just one symptom—variceal hemorrhage—has its place and is without doubt justified. On the other hand, the therapeutic principle to look for curative treatment whenever possible has paid off with truly convincing results. Therefore with regard to the therapeutic strategy for variceal bleeding in general, the controversy between palliation and cure cannot be totally avoided.

Instead of discussing all surgical approaches to portal hypertension, which are covered in other articles in this issue, we concentrate on liver transplantation, especially in comparison with portosystemic shunts as the two main cornerstones of surgery. There are a number of arguments for either approach, which are summarized briefly in order to elucidate the background for our own opinion. The operative risk of both procedures is comparable: high for emergency situations (30-50%) and low when performed in elective situations (< 10-15%). Although the costs are high after transplantation, the expenses cannot be neglected after shunt, taking into consideration the need for further hospitalization [11].

A patent shunt can effectively relieve portal hypertension, but late complications are observed frequently, depending on the type and site of decompression: rebleeding 10% to 20%, shunt thrombosis < 2% to 30%, and hepatic encephalopathy

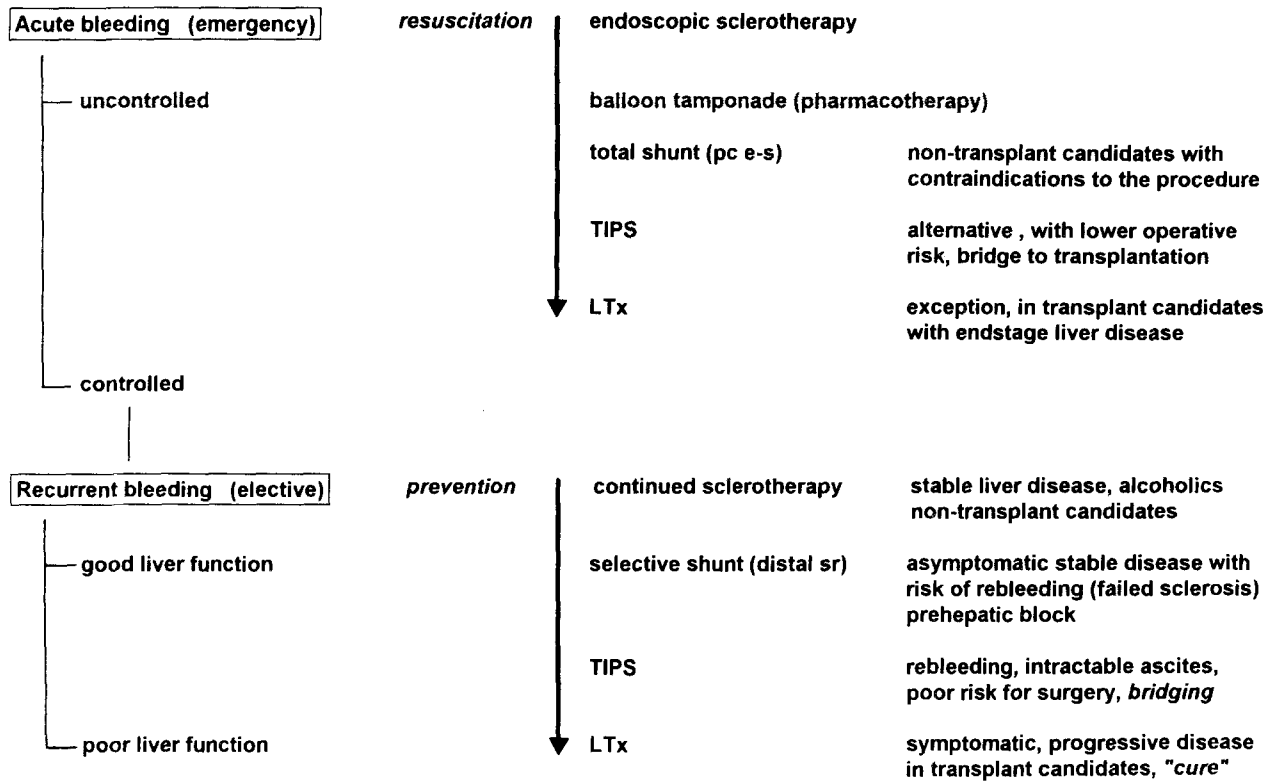


Fig. 7. Therapeutic options for management of esophageal variceal hemorrhage. TIPS: transjugular intrahepatic portosystemic shunt; LTx: liver transplantation.

10% to 40%. Because in most cases underlying liver cirrhosis remains unchanged, there is a continuous patient loss from liver failure and variceal bleeding, with 1-, 5-, and 10-year survival rates in the ranges of 70% to 90%, 40% to 60%, and 20% to 25%, respectively. Arguments in favor of shunts are widespread professional experience, few technical and organizational prerequisites, and almost no waiting time [12, 13].

In contrast, liver transplantation not only eliminates portal hypertension over time, and thus the risk of variceal bleeding completely, but (depending on the etiology) allows cure of the disease with normal graft function. Long-term prognosis can be influenced by recurrence of the original liver disease (e.g., hepatitis B infection), side effects of immunosuppression (nephrotoxicity, de novo malignancy), and chronic rejection. The 1- and 5-year survival rates are 80% to 90% and 60% to 70%, respectively, with good to excellent rehabilitation for most patients. Disadvantages are limitation of the procedure to specialized centers with a high degree of commitment and unforeseeable waiting time for donor organs [14, 15].

Although there are no data from randomized trials analyzing both forms of therapy, the role of liver transplantation as logical and ideal treatment for patients with advanced hepatic disease has been well acknowledged by a number of groups [10, 16–18]. The additional risk of previous sclerotherapy, and especially portosystemic shunts, on subsequent transplantation is recognized but usually not considered a contraindication [19–22]. Several authors recommend closure of all spontaneous and surgical portosystemic shunts at the time of transplantation in order to prevent any adverse effects on graft perfusion [23–25]. Recently, the complete reversal of pretransplant hyperkinetic

circulation has been questioned, but the mechanisms and consequences of this finding require further study [26].

Instead of the treatment modalities being in competition depending on the personal attitude and experience acquired at one specific institution, ideally portosystemic shunt surgery and liver transplantation should be available in the same center to complement each other. "The key is being able to select the right therapy for the right patient at the right time" [27]. In fact, there is much agreement now on common strategic concepts, combining ideas and expertise of both sides representing the "shunter" and the "transplanter" [4, 10, 17, 18, 28, 29]. Although several groups have developed algorithms of how to proceed, the various treatment options are outlined again here, describing our own perspective on the role of transplantation in the whole scenario (Fig. 7).

For emergency treatment of acute variceal bleeding the patient must be resuscitated and stabilized; then endoscopic sclerotherapy is carried out as first-line treatment, which controls the hemorrhage in most cases [1, 30]. If this treatment is unsuccessful, balloon tamponade with a Sengstaken-Blakemore or Linton-Nachlas tube is used for temporary control of bleeding. As next step if bleeding persists, portocaval shunt (preferably end-to-side) is considered, especially in nontransplant candidates and in those with contraindications to this procedure. The transjugular intrahepatic portosystemic shunt (TIPS), introduced as an innovative and promising technique, is an alternative with less operative risk and an attractive bridge to buy time for later transplantation. In patients with active variceal bleeding, liver replacement is technically feasible and has been performed successfully; it is not recommended as a

routine procedure, however, and should be restricted to exceptional situations and in potential transplant candidates with endstage liver disease only.

When the episode of acute hemorrhage is under control, recurrent bleeding must be prevented. Continued sclerotherapy is the preferred treatment of choice in transplant and nontransplant candidates, depending on liver function. Patients with sclerotherapy failure, good hepatic function, and asymptomatic stable disease or prehepatic block (e.g., portal vein thrombosis) are considered for distal splenorenal shunt [31]. TIPS may become the procedure of the future or be used as a bridge to transplantation; however, long-term results are still compromised by significant complications, so more experience is needed to estimate its true value [32]. The "ideal" transplant candidate is the patient for whom sclerosis or other therapies for complicated portal hypertension have failed, who has poor liver function, and who has symptomatic, progressive liver disease. Unless there are no contraindications, this operation should not be considered as desperation treatment but should be timed under elective conditions to give the patient a fair chance of long-term "cure."

In conclusion, liver transplantation plays an important role in the management of variceal hemorrhage as a complication of portal hypertension in patients with terminal hepatic disease. The indications and timing should be based on a full interdisciplinary assessment of the candidate, looking at the etiology of the disease, clinical status, liver function, and the presence of extrahepatic complications. Depending on those criteria, the spectrum of therapeutic possibilities must be considered with particular regard to selecting the most suitable form of therapy. Whether priority is given to palliative, symptomatic measures, bridging procedures, or definitive therapy with the potential of cure must be decided for each individual patient.

Résumé

La gamme thérapeutique de l'hémorragie par rupture de varices œsophagiennes comprend des mesures les unes conservatrices et les autres chirurgicales. Avant d'envisager la transplantation comme un moyen potentiellement curateur de l'étiologie sous-jacente, les interventions visant la décompression du système portocave restent l'essentiel de l'arsenal thérapeutique palliatif. Notre expérience dans le traitement des maladies hépatiques avancées et de l'hypertension portale sur ces 20 dernières années comporte 803 transplantations hépatiques et 201 anastomoses portocaves, mettant l'accent sur nos objectifs de traitement primaire des maladies hépatiques. Les résultats des anastomoses sont favorables lorsqu'il s'agit d'anastomose de décompression sélective, réalisée électivement, chez les patients du stade Child A. Après transplantation, hépatique, l'état clinique du patient, sa fonction hépatique, et la survenue de complications extrahépatiques ont fortement influencé l'évolution à court et à long terme. Avec l'expérience, le risque supplémentaire encouru par une chirurgie de décompression antérieure est réduite. D'après notre expérience et la littérature, il existe des arguments en faveur des deux formes de traitement, qui, en fait, sont complémentaires. Les deux modalités devraient être idéalement disponibles dans le même centre traitant des patients ayant une maladie susceptible d'évoluer soit vers une insuffisance hépatique ou une hypertension por-

tale. La sélection d'un ou de l'autre des procédés dépend de l'étiologie, du stade de la maladie, et du moment évolutif où la thérapeutique se discute. Les anastomoses portocaves sont indiquées plutôt chez le patient stable ayant un risque d'hémorragie après sclérothérapie, en cas de contreindication ou en attendant la transplantation. Le rôle de la transplantation est bien établi chez le patient ayant une maladie hépatique évolutive ou terminale, autrement incurable.

Resumen

El manejo de la hemorragia por várices esofágicas va desde una modalidad conservadora hasta la intervención quirúrgica. Antes de la introducción del trasplante de hígado como una forma de terapia potencialmente curativa de la causa etiológica primaria, las operaciones de descompresión porta-sistémicas eran la modalidad de preferencia entre los procedimientos quirúrgicos fundamentalmente paliativos.

Nuestra propia experiencia con la cirugía en pacientes con enfermedad hepática avanzada e hipertensión portal en más de 20 años, incluye 803 trasplantes hepáticos y 201 "shunts" porta-sistémicos. Los resultados de los "shunts" fueron favorables en pacientes Child A, cuando fueron realizados en forma electiva y fueron del tipo de la descompresión selectiva. Luego de trasplante hepático, el estado clínico del paciente, incluyendo la función hepática y las complicaciones extrahepáticas, demostró tener una fuerte influencia sobre el resultado post-operatorio, con excelente posibilidad de sobrevivida a largo plazo. Se ha logrado reducir el riesgo adicional que representa un "shunt" realizado con anterioridad al trasplante.

Nuestra experiencia y los informes de otros autores constituyen suficiente y razonable argumentación en favor de la cirugía derivativa ("shunts") y trasplante. En vez de plantear controversia, se considera que estas dos modalidades terapéuticas son complementarias.

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