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ORTHOTOPIC LIVER TRANSPLANTATION: INDICATIONS AND RESULTS

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The potential usefulness of orthotopic liver transplantation (OLTx) in the treatment of end-stage liver diseases was recognized in the 1950's, and the first clinical attempt was carried out at the University of Colorado in Denver, on March 1, 1963[125]. It was unsuccessful: the three year old patient, affected by extrahepatic biliary atresia, exsanguinated on the operating table. Among the next eight patients, transplanted in Denver (6 patients[112]), Boston (1 patient[81]), and Paris (1 patient[23]), the longest survival was 23 days[112]. The first long-term survivor was a child transplanted for hepatoma on July 23, 1967, who died of carcinomatosis 400 days later[118]. The late 1960's and early 1970's saw very slow progress in this field, with patients suffering from frequent and disabling complications, and an overall one-year patient survival of only 35%[122]. By then, the technical steps of the standard procedure had already been precisely described, and the surgical technique that is currently used at the Pittsburgh Transplantation Institute (p. 1779), is essentially the one developed at the University of Colorado in the 1960's[111, 125]. On the other hand, the indications for OLTx were much more limited in those early days, and the list of the diseases being treated with this procedure has grown significantly in the past 30 years. For example, postnecrotic cirrhosis of any etiology is today the most common indication for OLTx in most liver transplant centers, while only one patient in the original Denver series had post-necrotic cirrhosis[110]. The reason for the paucity of cirrhotic patients (other than biliary atresia) in the early trials was that, while the fate of the patient with a liver malignancy or extrahepatic biliary atresia was easy to predict, the prognosis of a stable patient with cirrhosis could not be predicted as readily.

Therefore, given the uncertainty surrounding the operation, most candidates were first considered only when they were already moribund, usually as a consequence of recent or ongoing variceal hemorrhage, and most died while awaiting for a suitable donor. It was the routine achievement of long term survival (the longest surviving recipient was transplanted 26 years ago), several immunological advances[1, 11, 13, 14, 68, 115, 116, 117, 123, 124, 127, 135], and the progress in donor surgery[70, 120, 126], and organ preservation[50,51, 136], that led to an expansion of indications for OLTx. As a consequence, diseases that were not considered before are now successfully treated with OLTx, and the procedure could be used for virtually any patient suffering from a lethal hepatic disease.

In 1982 it was estimated that the annual need for OLTx was 15 per million population[123], but is probably now higher, as the advances of the past decade allow us to treat patients that not long ago would have been considered not transplantable. In fact, depending on the criteria used to determine what are appropriate indications, we can estimate that between 40,000 and 50,000 OLTx's may be needed in the United States every year, with a similar number in Europe[116]. But, while in the past, the appropriateness of the decision to proceed with transplantation was judged largely on the basis of technical and medical factors related to the recipient, nowadays it is the supply of organs that increasingly shapes these decisions. If substantial growth is to occur, there will have to be a re-evaluation of the poli-

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cies that surround organ donation[39,69,89]. In this chapter, we will outline the diseases that are presently considered as indications for OLTx , and we will report the results obtained in 1,501 consecutive patients who underwent OLTx at the Pittsburgh Transplantation Institute between January 1, 1990 and December 31, 1993.

INDICATIONS FOR LIVER TRANSPLANTATION

The indications for OLTx were mostly defined at the National Institute of Health (NIH) Consensus Development Conference on Liver Transplantation, held in June 1983[83]. There are four main groups: parenchymal liver diseases, cholestatic liver diseases,congenital errors of metabolism, and hepatic tumors. (Table 7.49).

PARENCHYMAL LIVER DISEASE

There are many causes of parenchymal liver injury that may lead to acute or chronic liver failure that grossly impairs the quality of life or poses an acute obstacle to survival. The choice of OLTx is predicated on the knowledge that other therapies are ineffective in decreasing morbidity, or in simply rescuing the patient's life.

Postnecrotic Cirrhosis

The most common indication for OLTx in adults is postnecrotic cirrhosis. The main etiology is chronic viral hepatitis, which may result from hepatitis B virus (HBV), with or without co-infection with hepatitis delta virus (HDV), from hepatitis C virus (HCV), or from other, not yet characterized viral agents. The other large group is formed by patients with cryptogenic disease, which is a heterogenous group in whom no defined etiology can be identified. There are no special features of this subset with regard to OLTx candidacy.

It should be noted that the true incidence of hepatitis C (and the risk for reinfection) in the population presented below is not known, because the test for the antibody against this agent was not routinely available until May, 1990. In many areas of the world, infection with HBV is endemic, and the most common cause of advanced liver disease and hepatocellular carcinoma.

Recurrence of infection after transplantation is high in HBsAg+ patients. In a previous report, the outcome of 59 patients with prior HBV infection was compared to that of 38 patients who had immunity to HVB. The mortality, rate of graft loss, and need for retransplantation were significantly higher in the group with prior HBV infection[134]. In the same study, an active immunization with HBsAg vaccine and passive administration with hepatitis B immune globulin led to clearance of HBsAg in 6 of 22 patients. Also, in this series none of the patients with HBeAg seroconverted. Efforts to reduce the incidence and severity of reinfection, with the use of α-interferon and active and passive immunization, have been done in many institutions. A large series of patients were analyzed in a retrospective multicenter study performed in Europe. Three hundred and seventy-two HBsAg positive patients underwent OLTx at 17 centers[106]. Patients were stratified as to the serologic markers for hepatitis B, acute fulminant versus chronic, coexistent HDV infection, and the length of hepatitis B immune globulin treatment. The mean three year actuarial risk of recurrence of HBV was 50%. Eighty-three percent of HBV DNA positive having recurrence; 66% of the HBeAg positive, DNA negative recurring; and 58% of HBV DNA negative, HBeAg negative recurring. Patients who have co-existent HDV infection in chronic phase, had a 32% incidence of recurrence, and those with fulminant hepatic failure related to hepatitis B virus had a 17% recurrence rate. Recurrence as related to hepatitis B immune globulin therapy revealed that no therapy was associated with 75% rate of recurrence, while those with short term therapy (less than 6 months of hepatitis B immune globulin) had a 74% recurrence rate. Those with more than 6 months of hepatitis B immune globulin had a 35% recurrence rate. At the Pittsburgh Transplantation Institute, 69 patients who under-

Table 7.49 - Native liver disease in 215 pediatric and 1,286 adult recipients who underwent orthotopic liver transplants at the Pittsburgh Transplantation Institute between January 1, 1990 and December 31, 1993

Disease	Number of cases
Parenchymal	
Postnecrotic cirrhosis	487*
Alcoholic cirrhosis	293**
Autoimmune hepatitis	53***
Fulminant and subfulminant hepatic failure	42+
Budd-Chiari syndrome	15++
Cystic fibrosis	10
Congenital hepatic fibrosis	9
Neonatal hepatitis	6
Cholestatic	
Primary biliary cirrhosis	116‡
Biliary atresia	103
Sclerosing cholangitis	99‡‡
Secondary biliary cirrhosis	21‡‡‡
Familial cholestasis	8°
Congenital errors of metabolism	58°°
Tumors	
Benign	2
Primary malignant	107
Metastatic	13
Miscellaneous	59°°°
TOTAL	1,501

* 43 patients also had HCC
** 13 patients also had HCC and 1 patient also had cholangiocarcinoma
*** 1 patient also had HCC
\+ 1 patient also had HCC
++ 1 patient also had HCC
‡ 6 patients also had HCC
‡‡ 1 patient also had HCC, 1 patient also had gallbladder cancer, and 1 patient also had metastatic cancer
‡‡‡ 2 patients also had HCC
° 1 patient also had HCC
°° 2 patients also had HCC
°°° 2 patients also had HCC

went OLTx between 1988 and 1992, were analyzed according to the HBeAg status, and the length of hepatitis B immune globulin treatment. The mean two year recurrence rate for this group of patients was 67%. Those who received long term hepatitis B immune globulin treatment had a recurrence rate of 60%, while those who had a treatment lasting for less than 6 months had a recurrence rate of 75%, and a small subset that did not receive any hepatitis B immune globulin treatment (9 patients) had a recurrence rate of 100%. Patients that were HBeAg positive had a three year recurrence rate of 80%, while those who were HBeAg negative had a three year recurrence rate of 46%.

Despite the high rate of recurrence, we do not believe that there should be an across the board ban on liver patients with HBV infection. Rather than simply declearing defeat, we should study the effects of new and promising agents, such as iamivudine, as we continue to strive to develop new strategies for the prevention or treatment of recurrent hepatitis B.

Alcoholic Cirrhosis

About 10% of the adult population of the United States have a history of alcohol abuse[96], and alcoholic liver disease is the most common cause of chronic liver disease in western society. Alcohol-induced liver injury is a prime example of a disease in which OLTx might have been precluded, or strongly discouraged, 10 years ago. With a multidisciplinary approach to substance abuse, properly selected cases of alcoholic cirrhosis have outcomes after transplantation that are comparable to those of other non-malignant diseases[129]. At our institution, the acceptance of these patients as candidates for transplantation usually requires a previous successful rehabilitation, with documented abstinence. However, we do not believe that patients should be allowed to die if they are too sick to meet an arbitrary period of sobriety, and in circumstances such as these we evaluate the patient's familial and social involvement before making a determination. This process requires an active involvement on the part of social workers, psychologists, psychiatrists and other professionals.

Autoimmune Hepatitis

Autoimmune hepatitis most commonly presents in women between the ages of 15 and 25, with a second peak in post-menopause. Corticosteroid therapy is effective in prolonging life (5-year survival of 85% in treated patients vs. 40% in the control group[57]). However, when liver function has been seriously compromised, and quality of life is significantly affected, OLTx represents the only therapeutic option. Attention should be paid to the possibility that the patient may harbor a resistant opportunistic infection (particularly fungal) related to the prolonged immunosuppressive treatment. If present, these infections obviously need to be treated prior to accepting the patient as a transplant candidate.

We should mention that, more recently, a new approach was tried for this group of patients, with encouraging preliminary results. A group of 21 patients with biopsy-proven autoimmune chronic active hepatitis were given the new immunosuppressive drug tacrolimus (formerly FK506)[127]. After three months of therapy, the serum ALT level was reduced by 80% and the AST by 70%[144]. These data suggest that tacrolimus should be compared to prednisolone in a randomized trial, to identify the best available medical treatment. If these preliminary results are confirmed, it is conceivable that the natural history of autoimmune hepatitis will be changed such that liver failure might be averted.

Fulminant Hepatic Failure

A diagnosis of fulminant hepatic failure can be made when jaundice and hepatic encephalopathy develop within 8 weeks of onset of the illness in a patient who was previously healthy[7, 137]. Some patients may develop encephalopathy after 8 weeks from the onset of symptoms, in the absence of pre-existing liver disease. This subset of patients has been described as *"late onset hepatic failure"* by the English literature[85], or *"subfulminant hepatic failure"* by the French literature[7]. The prognosis is very grim in both conditions, with a mortality greater than 70% when the patient progresses to grade 4 encephalopathy[87, 93, 100, 138, 147]. The leading causes are hepatitis viruses and drug hepatotoxicity caused by a variety of agents. The prognosis changes in relation to the etiology, with acetaminophen-induced liver injury having the best rate of recovery with medical treatment alone (approximately 50% survival in series of 32 cases[87]), and fulminant non-A non-B hepatitis and other drug hepatotoxicity (i.e. halothane) having the worst outcome.

Before 1982, results with OLTx were not good enough to justify advocating it for this patient population[123], since recovery without liver replacement occurred in 5 to 20% of cases[7, 137]. However, the results with transplantation have steadily improved in the past decade, and in a recently reported series of more than 600 OLTx for fulminant hepatic failure, the one year survival rate was 63%[24]. In light of this progress, OLTx has become widely accepted as therapy for this indication[9, 47, 87, 102].

The decision to replace an acutely failing liver is a most difficult one, and must often be made within a few hours. A systematic assessment can help establish whether the patient belongs to the subset that has a good chance of recovery, or identify those who have a high probability of dying without transplantation[18, 88]As mentioned before, the etiology is an important prognostic determinant[85], with fulminant hepatitis B and non-A non-B (most of which, later on, have shown to be cases of hepatitis C) having a much worse prognosis than fulminant hepatitis A. Other features that predict imminent death include relentless progression to grade 3 or 4 coma, severe coagulopathy, rapid liver necrosis, acidosis, renal failure and hemodynamic instability. The perioperative mortality is often related to brain-stem herniation during or just after the OLTx, sometimes despite the continuous monitoring of intracranial pressure. In general, referral to a liver transplant program should be done as early as possible, because it is the only treatment modality for a significant percentage of patients with fulminant hepatic failure[24].

Budd-Chiari Syndrome

The Budd-Chiari syndrome, caused by an

obstruction of the main hepatic veins, can be found in association with a wide variety of disorders, such as paroxysmal nocturnal hemoglobinuria, polycythemia vera and other myeloproliferative diseases, tumors of the adrenal glands or kidneys, hepatomas, amoebic abscesses, congenital vena cava webs, contraceptives, pregnancy, antithrombin III deficiencies and lupus anticoagulants[21, 27, 45, 56, 80, 91, 101, 142, 143, 149]. The number of different surgical procedures that have been proposed to treat Budd-Chiari has been reported to be as high as 23[3] and the results vary greatly[12]The procedures most commonly used in the United States are the side-to-side portocaval and mesocaval shunts, when the inferior vena cava and portal vein are patent, and the mesoatrial shunt when the inferior vena cava is stenosed or thrombosed and the portal vein is patent. Success rates with these procedures range from 30% to 92%, with the majority being in the 60% to 75% range[42]. However, when there is progressive liver failure, and no concomitant neoplastic disease, Budd-Chiari syndrome can be successfully managed by OLTx. The first liver transplant for this disorder was performed by our group on November 28, 1974. The patient is still alive and well 20 years after the procedure, and has had two children. Since that time, a number of patients with this condition have been treated with liver transplantation in many institutions[15, 42]. Based on our experience, and that of the Cambridge group[15], it is clear that liver transplantation is indicated for the Budd-Chiari syndrome once it has progressed to end-stage liver disease. Whether to transplant or shunt those patients with intermediate degrees of liver failure is currently uncertain. An interesting point is that the Budd-Chiari syndrome can recur after liver transplantation, as it happened to 3 of the patients we reported recently, all of whom died[42].

Other Parenchymal Diseases

There are many other hepatic parenchymal diseases for which liver transplantation has been successfully performed, including, but not limited to, cystic fibrosis[78], congenital hepatic fibrosis, and neonatal hepatitis. Liver transplantation once seemed so drastic a measure that it was used only as a last resort for "benign" hepatic disease[114]. Today, on the contrary, allowing a patient to deteriorate to the point that life-support devices are required before considering transplantation is unacceptable.

CHOLESTATIC LIVER DISEASES

Cholestatic liver diseases are a group of conditions characterized by bile duct injury which results in severe impairment of bile excretion and hepatocellular dysfunction. These events may ultimately lead to cirrhosis. Liver transplantation has provided patients with these disorders a chance for near-normal long-term survival.

Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC), or chronic nonsuppurative destructive cholangitis (p. 220), is a disorder that primarily affects middle-aged women, with a ratio of women to men of approximately 10:1[52]. The 5-year survival of patients with PBC, not treated with liver transplantation, ranges from 30% to 70%[19, 103]. The fact that the natural history of PBC is reasonably well characterized has allowed to study the influence of the stage of the disease on the outcome after liver transplantation[74, 84]. In one such investigation[74], the survival following liver transplantation was markedly better than that predicted (assuming no transplantation) using survival analysis[25]. It is clear that in PBC the timing of transplantation is critical, and it should be carried out before the stage of catastrophic deterioration is reached. The quality of life of individuals transplanted for PBC has been very good, with ninety percent of long-term survivors being fully rehabilitated[31].
We should note here that, while the 1-year survival rates after transplantation was 83%, 75% and 58%, according to the candidate risk category (low, medium, and high respectively), the actual gain in survival is particularly significant in the high-risk candidates[74]. In fact, if we compare

these survival rates with the ones predicted by the Mayo prognostic model for PBC[25], there is a 58% gain in survival at 1-year in the high-risk candidates, 55% in the medium-risk candidates, and only 14 % in the low-risk candidates[30]. These data should be kept in mind when establishing candidacy and liver transplantation priority for this category of patients.

Biliary Atresia

Biliary atresia is by far the most common indication for liver transplantation in children[4, 5]. The disease is already obvious in the neonate, characterized by increasingly severe cholestasis during the first 90 days of life and, unless treated, it is universally fatal. Children with this anomaly are often treated with a *portoenterostomy (Kasai operation)*[53] (p. 1727). However, only a small subset has been actually cured by this procedure, and most children die of liver failure that continues to progress after surgery. It is estimated that 75% of the patients suffering from biliary atresia will eventually require a liver transplant, regardless of any previous surgical treatment[96]. If a Kasai operation is performed, it should be done 60 to 90 days after birth to be successful. Also, it is important to avoid re-operation after an initial portoenterostomy, except to correct minor technical faults, or for relief of obstructions due to biliary stones. In fact, other re-operations are usually unsuccessful, and might seriously jeopardize a later transplant. Long-term survival after liver transplantation is excellent, ranging between 80% and 85% in most series, with an essentially flat survival curve after the first 6 months. The three principal causes of liver failure after liver transplantation for biliary atresia are thrombosis of the hepatic artery, primary allograft non function, and rejection[33, 37]. The quality of life of the long-term survivors is excellent, and the majority of these children have a very satisfactory growth and intellectual development[141].

Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) (p. 481) is a chronic cholestatic liver disease which is extremely difficult to define accurately[60, 76]. It is recognized by liver dysfunction and a characteristic radiological appearance (with multiple localized strictures and dilatation, in the absence of known causes of sclerosis, such as operative trauma, calculus disease or congenital anomalies), which is related to portal tract inflammation, bile duct proliferation, and periductal fibrosis involving small intrahepatic and large extrahepatic ducts. The introduction of endoscopic retrograde cholangiography in clinical practice has resulted in a marked development in the understanding of the clinical, radiological, and histlogical picture of PSC[43]. However, despite this progress, the etiology is still unknown, and no curative medical treatment has been identified.

In contrast to PBC, PSC affects mainly men (sex ratio 4:1) who are 30 to 50 years old. Until recently, patients with PSC often underwent different biliary operations for diagnostic or palliative purposes (such as surgical exploration of the biliary tree, T-tube placement, biliary stenting or reconstruction, or both). All these procedures failed to achieve long-term benefits[75] and just served to promote episodes of cholangitis and strong adhesions in the hepatic hilum. Liver transplantation offers the only prospect for cure and long term survival to patients with PSC in the terminal stage of the disease, and all other surgical approaches (with the exception of endoscopic retrograde cholangiography and percutaneous liver biopsy) should be abandoned.

Recently, the survival of 216 patients transplanted for PSC was compared with the predictions made by survival analysis (again, assuming no transplantation)[2]. The model incorporates physical findings, biochemical and histopathologic features of PSC, and was developed in a study of 426 patients affected by PSC and managed conservatively in five institutions from Europe and North America[26]. The 5-years Kaplan-Meier actuarial survival after liver transplantation was 73%, compared to 28% expected survival according to the above mentioned model. Similarly to what is observed with PBC patients[30], the most important gain in survival in patients with PSC corresponds to the high-risk group. If we compare the survival rates with the ones predicted by the Mayo prognostic model for

PSC[26], the gain in 1-year survival with liver transplantation is only 7% in the low-risk patients, and as high as 40% in the high-risk group[30]. Again, this information should be seriously considered when formulating policies for candidate selection and transplantation priority criteria.

Other Cholestatic Diseases

Liver transplantation is indicated as surgical treatment of a number of other cholestatic diseases. Secondary biliary cirrhosis, Caroli's disease (p. 521), familial cholestasis, and Alagille's syndrome (p. 515) are the most important diseases in this group.

In a series of 10 patients transplanted for Caroli's disease at the Pittsburgh Transplantation Institute, 7 patients were alive from 2.1 to 7.6 years after transplantation (mean = 4.8 years)[73]. The role of transplantation was also studied in a series of 15 children affected by familial cholestasis. Eleven children were alive and growing well from 1.8 to 6.2 years after transplantation[35]. Alagille's disease is an autosomic disorder characterized by intrahepatic cholestasis and peripheral pulmonary artery stenosis. Liver transplantation is indicated for a subset of these patients (usually about 12%) who develop cirrhosis, and in the ones with progressive portal fibrosis, severe and permanent cholestasis, progressive liver dysfunction and growth retardation. In a series of 13 patients transplanted for Alagille's syndrome, the 7-year survival rate was 52%. Of the 6 mortalities, 4 occurred within 11 days of transplant, and the other 2 before the eleventh postoperative months. All surviving children were growing well and participating in normal childhood activities[67].

CONGENITAL ERRORS OF METABOLISM

Several studies showed in the early 1960's that liver allografts retain their metabolic specificity after transfer to a new host[54, 55]It was obvious already at that time that a practical implication of this fact is that certain liver-based metabolic disorders can be cured by liver transplantation. The resolution of gout, naturally present in Dalmatian dogs, after liver transplantation using mongrel canine donors conclusively proved this hypothesis[58]. The fact that the graft maintained its phenotype resulted in the cure of congenital errors of metabolism in many patients treated by liver transplantation for end-stage liver diseases[40, 41, 44, 62, 65, 77, 78, 97, 105, 108, 113,130], and anatomically normal livers have also been replaced to correct congenital metabolic defects[8, 17, 20, 146, 148]. As the other side of the coin, there is at least one reported case where a coagulation defect of the donor was transferred to the recipient by liver transplantation[29].

α-1-Antitrypsin Deficiency

Patients affected by this condition can have progressive liver injury, eventually resulting in cirrhosis and hepatocellular carcinoma[34]. However, the natural history of the disease is quite variable. If cirrhosis occurs, liver transplantation is the treatment of choice. After successful transplant, the protease inhibitor status is reversed, and depressed serum α-1-antitrypsin levels return to normal[34, 44, 123].

Wilson's Disease

This is a genetic disorder of copper metabolism characterized by decreased biliary secretion of copper and its accumulation mainly in the liver and in the brain, and decreased serum ceruloplasmin. Recent linkage studies have assigned the Wilson's disease locus to chromosome 13, at q14-q21[6]. Its mode of presentation is variable. Traditionally, chelation with D-penicillamine is the treatment of choice. This has been shown to be extremely effective in most patients with Wilson's disease, and can frequently interdict the need for liver transplantation in patients manifesting with chronic hepatitis. Candidates for

liver transplantation are those patients presenting either with cirrhosis or a picture of fulminant liver failure, accompanied by hemolysis and renal failure. As in the case of α-1-antitrypsin deficiency, liver transplantation cures the underlying metabolic defect[34, 41]. A multicenter study published recently showed a 1-year survival of 79% in 55 patients who underwent liver transplantation in different institutions in the United States and Europe[107]. This study also indicated that neurological and psychiatric symptoms related to Wilson's disease can improve after liver transplantation.

Tyrosinemia

Hereditary tyrosinemia is characterized by fumaryl hydrolase deficiency, an enzyme responsible for the degradation of metabolic products of tyrosine metabolism. Liver dysfunction associated with this condition varies from acute hepatic failure to a slowly progressive liver disease that eventually results in cirrhosis and hepatocellular carcinoma[34, 36, 146]. OLTx is the treatment of choice in this situation.

Hemochromatosis

Hereditary hemochromatosis is a disorder of iron metabolism associated with an abnormal gene linked to the A locus of HLA complex on chromosome 6. Specifically, hereditary hemochromatosis is associated with the histocompatibility antigens HLA-A3, HLA-B14, and HLA-B7[133]. The syndrome is characterized by inappropriate increase in iron absorption and deposition, with functional impairment of the liver and many extrahepatic organs, including pancreas, heart, and pituitary. In symptomatic hemochromatosis, fibrosis or cirrhosis is present almost invariably. If the diagnosis is established early, cirrhosis can be prevented by treatment aimed at diminishing iron overload (e.g. depletion by phlebotomy). However, if cirrhosis is present, 10-years survival is 10% without removal of iron, and 32% with phlebotomy[10]. There is also an increased risk of hepatocellular carcinoma[95]. Liver transplantation is indicated when end-stage liver disease occurs, and the results justify the use of this procedure, both in classical hemochromatosis and in the fulminant pediatric variety[95, 116].

Other Congenital Errors of Metabolism

At least 16 distinct inborn errors of metabolism have been treated by liver transplantation[116]. Many other cannot be cured by liver transplantation and might benefit from allogenic bone marrow transplantation[92]. The guidelines for decision making in specific metabolic errors became increasingly clear in the past decade, allowing better care of these patients[92, 113].

TUMORS

Primary hepatic malignancies were originally considered "the indication" for liver transplantation. Removal of the diseased organ was seen as the best treatment for hepatic lesions that could not be treated with conventional techniques of subtotal liver resection[114]. As a consequence of this concept, 11 out of the first 25 patients transplanted at the University of Colorado[110] had hepatocellular carcinoma. However, the results with malignant tumors did not fulfill these expectations, with high mortality rates due to recurrence[112]. The prognosis proved to be different in small, incidental tumors. The longest survivor in this group is a patient who underwent liver transplantation for biliary atresia on January 22, 1970. The removed liver had a 3 cm hepatoma, and the patient is still alive and well, 26 years after the surgery.

Benign Tumors

The experience with liver transplatation for benign tumors of the liver is still limited, and has

yet to be defined. We have previously reported a small series of patients transplanted for *hepatocellular adenomatosis* and *focal nodular hyperplasia*, with 4 out of 5 patients alive from 4.1 to 9.6 years after liver transplantation. All of these patients were activated as transplant candidates because of progressive liver failure related to multiple lesions that occupied at least 80% of the liver parenchyma, and that were not resectable by subtotal hepatectomy[71]. In a case of hepatic lymphangiomatosis, the size of the lesion (the liver weighed 16.5 kg), the consequent disability (weight loss, pain, pedal edema and dyspnea), and the eventual development of significant deterioration of liver function, were the indications for transplantation[79].

Primary Malignant Tumors

In spite of disappointments due to poor long-term results, liver malignancies are still treated with transplantation in many centers. We believe that two points should be made clear when treating these patients. First, the uncertainty of the prognosis must be openly discussed with the patient. Secondly, possible metastases should be aggressively searched for before candidacy for transplantation is established.

Individuals with hepatic tumors and normal liver function can often be treated with liver resections. In a study that analyzed the outcome of patients with hepatoma, 76 treated by liver resection and 105 with liver transplantation, one and five year survival rates in the resection group were 71% and 33%, respectively, and in the transplant group 66% and 36% respectively[48]. In spite of aggressive preoperative evaluation to rule out extrahepatic disease, recurrence after liver transplantation for malignant tumors is invariably high[39, 49, 89, 94, 104, 112]. Today, we routinely combine the surgical treatment with adjuvant chemotherapy which, theoretically, should work better when administrated regionally (-through the hepatic artery branch feeding the tumor). The principle underlying this concept is that normal parenchyma has a dual blood supply, whereas hepatomas receive their blood supply mainly through the arterial neo-vasculature[16]. Whether these theoretical benefits will translate into reality remains to be seen.

Certain types of malignant liver tumors have a better outcome than others. While *Klatskin tumors* have the poorest long-term survival (no survivors at 4.5 years in a previous series of 10 patients[32]), *epitheloid hemangioendotheliomas* have a 5-year survival rate of 67%[63, 72].

Metastatic Tumors

Liver transplantation has been used in a very limited number of tumors metastatic to the liver[46, 49, 64, 66, 82, 89, 94]. We have recently updated (unpublished data) the follow-up of 5 patients who underwent liver transplantation for a neuroendocrine tumor metastatic to the liver[64]. Three out of these 5 patients died in less than 9 months. The other two, long term survivors, also had recurrence, with one patient dying 76 months after transplantation, and the other still alive (June, 1994) 9 years after the transplant.This last patient had only a liver transplant plus node dissection (possible primary tumor in the pancreas). This small experience makes it difficult to derive any guidelines.

RESULTS OF LIVER TRANSPLANTATION AT THE PITTSBURGH TRANSPLANTATION INSTITUTE

As mentioned before, we analyzed the outcome of 1,501 consecutive patients who underwent liver transplantation in a 4-year period (January 1, 1990 - December 31, 1993). Actuarial survival curves were estimated using the Kaplan-Meier method.Comparisons between groups were made using the Breslow test, with a Bonferroni adjustment for multiple comparisons.

The etiology of the liver disease in this population is shown in Table 7.49. There were 1,286 adults and 215 children at the time of their first liver transplant (there were 189 retransplants in this series), with 934 males and 567 females. The mean age was 43.3 ± 19.1 years (range 0.1 to

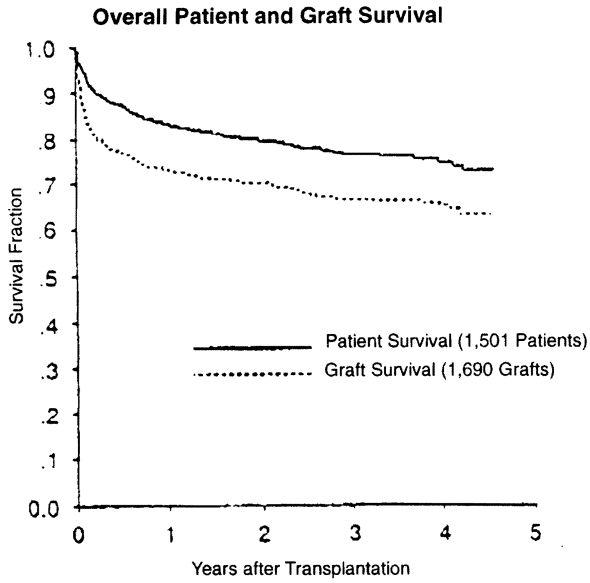

Figure 7.26. *Kaplan-Meier actuarial patient and allograft survival* for 1,501 patients who received 1,690 liver allografts at the Pittsburgh Transplantation Institute between January 1, 1990, and December 31, 1993.

76.2), and the mean follow-up was 2.15 years (range 0 to 4.5 years).

The *overall actuarial patient survival rates* were 81%, 77%, 74%, and 73%, at 1, 2, 3, and 4 years, respectively (Fig. 7.26). The overall actuarial graft survival rates were 72%, 68%, 65%, and 64%, at 1, 2, 3, and 4 years, respectively (Fig. 7.26). Traditionally, patient survival after liver transplantation is reported separately for adults and children, with the latter usually showing significantly better survival. The 215 children (< 18 years) had overall actuarial survivals of 82%, 81%, 80%, and 80%, at 1, 2, 3 and 4 years, respectively (Fig. 7.27), while the 1,286 adults (> 18 years had an overall actualial survival of 81%, 77%, 73%, and 71%, at 1, 2, 3 and 4 years, respectively (Fig. 7.27). The differrence, however, is not significant (p=0.298).

When the entire patient population is analyzed *according to the diagnosis*, after collapsing them into four broad categories (cholestatic, alcoholic, parenchymal and metabolic diseases, hepatitides), as expected, the *cholestatic diseases* showed superior results (Fig. 7.28). The actuarial survival rates for *cholestatic liver diseases* were 90%, 88%, 87%, and 87%, at 1, 2, 3 and 4 years, respectively (Fig. 7.28); for the alcoholic group, they were 82%, 80%, 75% and 70%, at 1, 2, 3 and 4 years, respectively (Fig. 7.28); for the *parenchymal and metabolic disease* group, which included all the other parenchymal diseases (excluding tumors), the survival rates were 78%, 75%, 72%, and 71%, at 1, 2, 3 and 4 years, respectively (Fig. 7.28); and for the *hepatitides* they were 79%, 73%, 70%, and 70%, at 1, 2, 3 and 4 years, respectively (Fig. 7.28). When compared with each other, patients undergoing liver transplantation for cholestatic diseases fared significantly better (cholestatic vs. hepatitides: $p < 0.0001$; cholestatic vs. alcoholic cirrhosis: $p < 0.0001$; cholestatic vs. parenchymal and metabolic diseases: $p < 0.001$).

The patients who underwent transplantation for a *malignant primary or secondary liver tumor* were also analyzed separately, and their survival compared with the rest of the patients (a number of these patients - see Table 7.49 - had an incidental tumor; however, they are not included with the "tumor" patients because their prognosis had been found in the past to be similar to

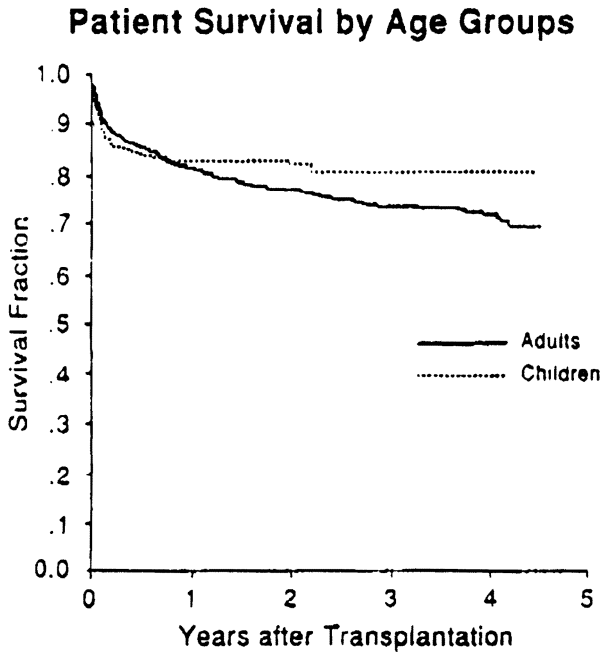

Figure 7.27. *Kaplan-Meier actuarial survival for children (< 18years: 215 patients) and adults (> 18 years: 1,286 patients)* who underwent liver transplantation at the Pittsburgh Transplantation Institute between January 1, 1990 and December 31, 1993 (p=0.298).

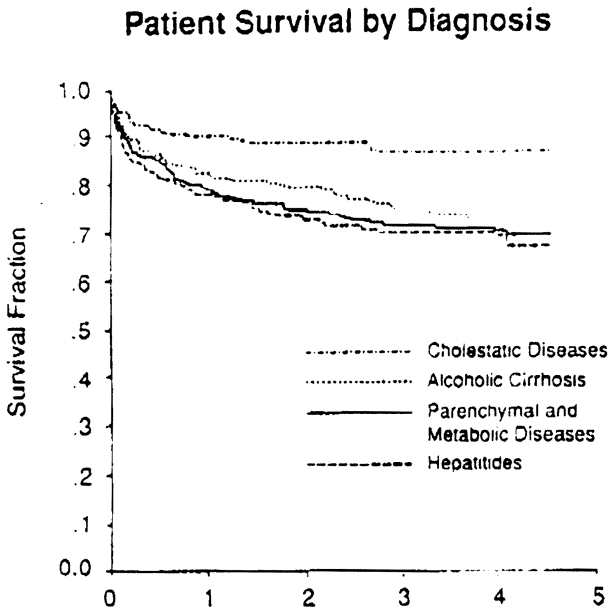

Figure 7.28. *Kaplan-Meier actuarial patient survival for 1,501 patients* who underwent liver transplantation at the Pittsburgh Transplantation Institute between January 1, 1990, and December 31, 1993. The patients were divided into four groups according to the liver disease: alcoholic cirrhosis, parenchymal and metabolic diseases (excluding tumors), postnecrotic cirrhosis related to any type of hepatitis, and cholestatic diseases. The latter show a significantly better survival at any given interval.

that of patients with benign disease). The actuarial survival rates for patients undergoing transplantation for *cholangiocarcinoma* were 70%, 50%, 50%, and 50%, at 1, 2, 3 and 4 years, respectively (Fig. 7.29: only one patient at risk at 4 years). The actuarial survival rates for patients with a *hepatoma* known before liver transplantation were 74%, 65%, 58%, and 58%, at 1, 2, 3 and 4 years, respectively (Fig. 7.37: only 7 patients at risk at 4 years). The actuarial survival rates for patients undergoing OLTx as treatment for a *tumor metastatic to the liver* were 86%, 68%, and 68% at 1, 2 and 3 years respectively (Fig. 7.29: only 2 patients at risk at 3 years). These surprisingly good results might just be related to the fact that most of the tumors listed as metastatic were neuroendocrine lesions, which have a peculiar biological behavior. Finally, actuarial survival rates for those patients with no preoperative evidence of a tumor were 82%, 79%, 77%, and 75%, at 1, 2, 3 and 4 years, respectively (Fig. 7.29: 159 patients at risk at 4 years). As expected, patients with no known tumor before transplantation had higher survival rates. These differences were significant when comparing their survival rates with those of patients with previously known hepatomas (p=0.0006) and cholangiocarcinomas (p=0.04). The difference in survival rate between patients with no known tumor and metastatic disease was not significant (most likely the result of the small sample size).

Outcome was also analyzed *according to the United Network for Organ Sharing (UNOS) classification.* UNOS is the organization managing organ allocation in the United States. When a patient is entered into the system as a trans-

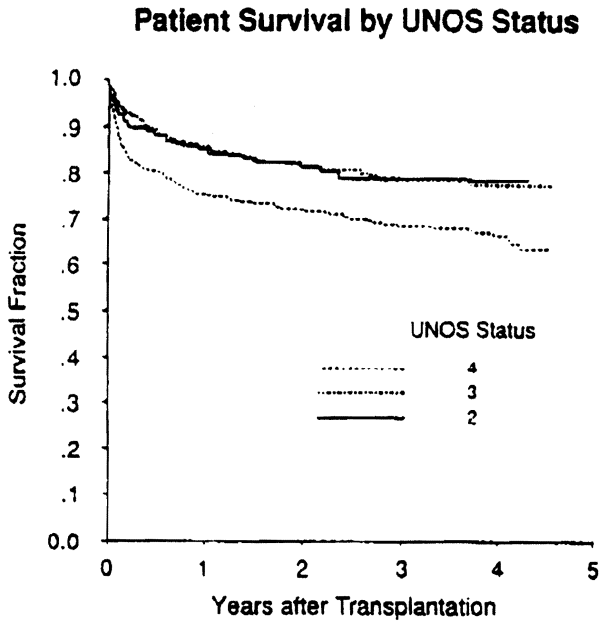

Figure. 7.29. *Kaplan-Meier actuarial survival for 1,501 patients* who underwent liver transplantation at the Pittsbrugh Transplantation Institute between January 1, 1990, and December 31, 1993. The patients are divided into four groups according to preoperative evidence of a liver tumor. The curves show the overall survival rates of: [1] patients with no preoperative of a tumor ("no tumor"); [2] patients with a tumor metastatic to the liver, diagnosed before OLTx; [3] patients with known hepatoma before OLTx; and [4]patients with a cholangiocarcinoma diagnosed before OLTx. As expected, patients with no known tumor before OLTx have higher survival rates.

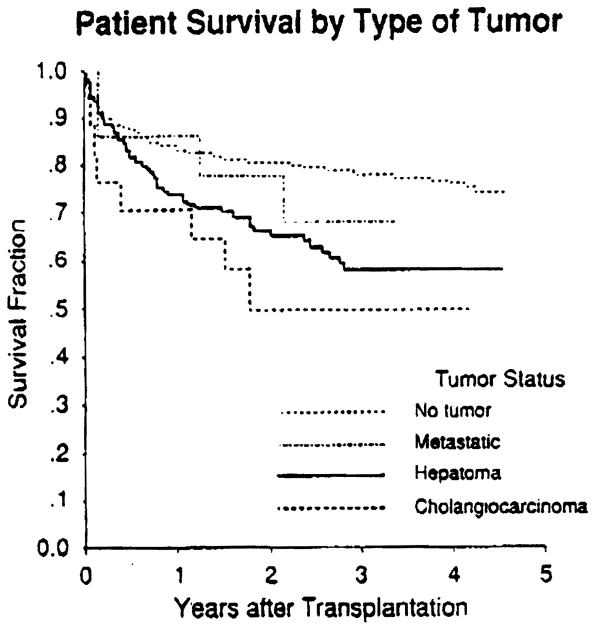

Figure. 7.30. *Kaplan-Meier actuarial patient survival for 1,501 patients* who underwent liver transplantation at the Pittsburgh Transplantation Institute between January 1, 1990, and December 31, 1993. The patients are divided into 3 groups, according to the United Network for Organ Sharing (UNOS) classification. UNOS is the organization managing organ allocation in the Untied States. UNOS 2 = stable patient who can wait for the transplant at home; UNOS 3 = unstable patient who needs to wait for the transplant in the hospital; UNOS 4 = critically ill patient who needs life support.

plant candidate he is given a score according to the severity to which the disease has progressed. UNOS 2 indicates that the patient is stable and can wait for the transplantation at home. UNOS 3 means that the patient is medically unstable and needs continuous hospitalization. UNOS 4 indicates that the patient's condition has deteriorated to the point at which life-support systems are required.

Actuarial survival rates for UNOS 2 patients were 85%, 82%, 79%, and 79%, at 1, 2, 3 and 4 years, respectively. For UNOS 3 patients they were: 86%, 82%, 78%, and 78%, at 1, 2, 3 and 4 years, respectively. Finally, for UNOS 4 patients they were 75%, 72%, 69%, and 67%, at 1, 2, 3 and 4 years, respectively (Figure 7.30). There was no statistical difference between UNOS 2 and UNOS 3 patients. However, both UNOS 2 and UNOS 3 patients had significantly better outcome than UNOS 4 patients (UNOS 2 vs. UNOS 4: p=0.005; UNOS 3 vs. UNOS 4: $p < 0.0001$).

SPECIAL CONSIDERATIONS

There are a few other issues regarding candidacy to liver transplantation that should be discussed. It is a policy in most centers in Europe, and in many in the United States, to limit candidacy based on the *age of the recipient.* A simple upper age limit is not used at our Institute, since it has been our experience that older patients have 5-years survival rates that are similar to that of younger groups[128, 131].

Thrombosis of the portal vein, and/or the mes-

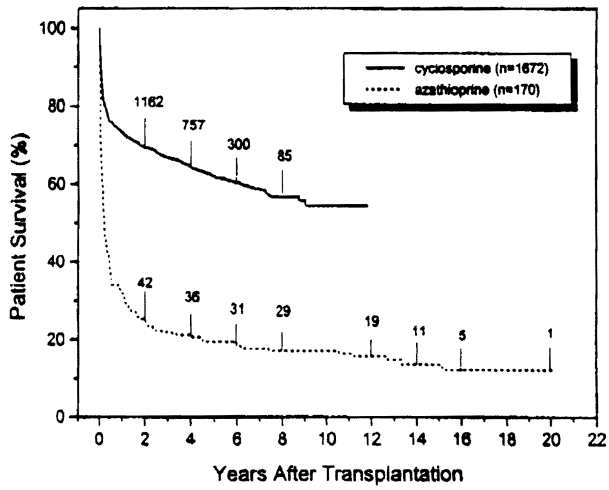

Figure 7.31. *Kaplan-Meier actuarial patient survival for orthotopic liver transplantation in the azothioprine and cyclosporine eras, in the single consecutive Denver-Pittsburgh series (1963-1988).* One hundred and seventy patients were transplanted between March1, 1963, and February 3, 1980, and were treated with azothioprine, while 1,672 patients were transplanted between March 9, 1980, and December 30, 1988, and were treated with cyclosporine. The numbers on the curves indicate the population at risk (From: Marino, I.R., Doyle, H.R.: Conventional immunosuppressive drugs. In: *Immunosuppressive Drugs. Developments in Anti-Rejection Therapy* A.W.Thompson and Th.E.Starzl, eds.], pp. 1-14. Edward Arnold, London 1994, used by permission).

enteric and splenic vein were in the past considered as contraindication to liver transplantation. These problems were almost completely eliminated by the use of cadaveric vein grafts[109, 121, 132, 140]. The vein graft is anastomosed end-to-side to a patent segment of the superior mesenteric vein, and then brought into the subhepatic area where it is used to revascularize the portal vein of the allograft. Also, *previous abdominal surgery* can seriously complicate the transplant operation, and it was once considered a contraindication to liver transplantation by many liver transplant centers. The greatest concerns were raised by previous operations on the porta hepatis and, in fact, the majority of technical complications involving the portal vein have been described in transplants performed after shunt surgeries[61]. Nowadays, these technical issues are not considered an obstacle at any major transplant center. Imaging techniques provide enormous help in defining the surgical strategy in advance.

The last issue we would like to address is related to the question of candidacy to liver transplantation for the *patients carrying antibodies to the human immunodeficiency virus (HIV)*. After the screening enzyme immunoassay for detecting HIV antibodies became available in March 1985, a number of positive kidney, heart, and liver recipients were quickly reported[59, 97]. However, the extent of the problem was clearly defined only after a large study was completed at the University of Pittsburgh. The stored sera of 1,043 transplanted patients were tested for HIV antibodies, and 1.7% were found to be positive[28]. Liver transplant patients showed a higher risk, with an incidence of 2.6%. One third of these liver patients were positive before the transplant. Fifteen liver patients were then followed, along with 5 heart and 5 kidney transplant recipients[139]. The survival of the 15 liver HIV+ patients was compared to a group of 1,303 HIV^- patients who underwent liver transplantation during the same years. Kaplan-Meier actuarial survival was identical at one year. Survival was shorter for the HIV^+ group at 2 or more years. Given the actual shortage in donor livers, it therefore seems justified that HIV^+ patients will not be considered as transplant candidates at many institutions, both in the United States and in Europe.

CONCLUSIONS

Indications for liver transplantation have been expanded substantially in the last 30 years. Many factors that were previously considered as contraindications, like an upper age limit of 50, alcoholic cirrhosis, multiple abdominal operations, and HIV antibody carrier status are not any longer preventing candidacy for liver transplantation. In patients suffering from an end-stage liver disease that is known not to recur in the transplanted allograft candidacy is no longer debatable. On the other hand, it is controversial what role should liver transplantation have in the treatment of diseases with high recurrence rates, such as hepatitis B and most malignant tumors. However, liver transplantation should not be arbitrarily refused to any of these patient groups. Patients at high risk for recurrent disease should be evaluated and entered into new protocols that may, eventually, improve their prognosis. Prime examples are the preoperative treatment of candidates carrying a primary hepatic malignancy with intra-arterial and/or systemic chemotherapy., and the use of novel antiviral agents for prevention of treatment of recurrent viral hepatitis B.

In June 1983, the Consensus Development Conference of the National Institutes of Health concluded that: "liver transplantation is a therapeutic modality for end-stage liver disease that deserves broader application". This sentence had a tremendous impact on the expansion of liver transplantation as a routine surgical service. Long-term survival (> 10 years), which was uncommon until the beginning of the 1980's, increased tremendously with the introduction of new immunosuppressive agents (Fig. 7.31), and technical refinements of the procedure[119]. Nevertheless, liver transplantation is still viewed as a high-technology procedure that society can do without. This view is surprisingly common in the United States and Europe. In 1991, 75 Directors of the British health system were interviewed about the priority of 12 given health care treatments. Liver transplantation ranked eleventh, and only the treatment for advanced lung cancer ranked lower. The treatment of AIDS and dialysis ranked significantly higher (seventh and forth, respectively)[22]. We believe such notions are wrong, and not supported by the cur-

rent long-term results. Liver transplantation is certainly a safe procedure and the only curative treatment for many people suffering from end-stage liver disease. The cost of the procedure and the organ shortage are the two main problems that should be addressed in the coming years.

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