

1793

LIVER TRANSPLANTATION IN THE WORLD: PRESENT CONDITIONS OF LIVER TRANSPLANTATION FROM CADAVER DONORS IN USA

Ignazio Roberto Marino, M.D., and Thomas E. Starzl, M.D., Ph.D.

Pittsburgh Transplantation Institute, University of Pittsburgh Medical Center and the Veterans Administration Medical Center, Pittsburgh, PA 15213.

INTRODUCTION

The potential usefulness of orthotopic liver transplantation (OLT_x) in the treatment of end-stage liver diseases was recognized in the 1950s, and the first clinical attempt was carried out at the University of Colorado in Denver, on March 1, 1963 [1,2]. It was unsuccessful: the 3 year old patient, affected by extrahepatic biliary atresia, exsanguinated on the operating table. Among the next 8 patients, transplanted in Denver (6 patients), Boston (1 patient), and Paris (1 patient), the longest survival was 23 days [2]. The first long-term survivor was a child transplanted for hepatoma on July 23, 1967, who died of carcinomatosis 400 days later [3].

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% [4]. By then, the technical steps of the standard procedure had already been precisely described (Figure 1), and the surgical technique that is currently used at the Pittsburgh Transplantation Institute, and in most of the world transplant centers, is essentially the one developed at the University of Colorado in the 1960's [1,2]. On the other hand, the indications for OLT_x 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, post-necrotic cirrhosis of any etiology is today the most common indication for OLT_x in most liver transplant centers, while only one patient in the original Denver series had post-necrotic cirrhosis [2]. The reason for the paucity of cirrhotic patients (other than biliary atresia) in the early trials was that, while the fate of patients 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 25 years ago), several major immunological advances [5-8], and the progress in donor surgery, and organ preservation, what led to an expansion of the indications for OLT_x. As a consequence, diseases that were not considered before are now successfully treated with OLT_x, 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 OLT_x was 15 per million population [9], but this 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 4,000 and 50,000 OLT_x may be needed in the United States every year, with a similar number in Europe. 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.

INDICATIONS FOR LIVER TRANSPLANTATION

The indications for OLTx were mostly defined at the National Institutes of Health (NIH) Consensus Development Conference on Liver Transplantation, held in June 1983. There are four main groups: parenchymal liver diseases, cholestatic liver disease, congenital errors of metabolism, and hepatic tumors (Table 1).

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.

Post Necrotic Cirrhosis — The most common indication for OLTx in adults is post necrotic 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 heterogeneous group in whom no defined etiology can be identified.

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.

At the Pittsburgh Transplantation Institute, 69 patients who underwent 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 the 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 OLTx in patients with HBV infection. At this time, we believe it is justified to transplant those patients that are at low risk for recurrent HBV infection (i.e., HBeAg and HBV DNA negative). As for those patients that are at high risk for recurrence, rather than simply declaring defeat we should study the effects of new and promising agents, such as 3-TC, thymosin, or famciclovir, 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 in the United States have a history of alcohol abuse, 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. 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 should evaluate the patient's familial and social support structures 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) [10]. However, when liver function has been seriously compromised, and quality of life is significantly affected, OLTx should be considered.

We should mention that recently we described a new approach 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) [7]. After 3 months of therapy the serum ALT level was reduced by 80%, and the AST by 70% [11]. 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 that was previously healthy. 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, or "subfulminant hepatic failure" by the French literature. The prognosis is very grim in both conditions, with a mortality greater than 70% when the patient progresses to grade 4 encephalopathy. 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, and fulminant non-A non-B viral hepatitis and other drug hepatotoxicity (i.e. halothane) having the worst outcome.

Before 1982, results with OLTx could not justify advocating it for this patient population, especially since recovery without liver replacement occurred in 5 to 20% of cases. However, the results with transplantation have steadily improved in the past decade, and in a recently reported series of more than 600 cases of OLTx for fulminant hepatic failure in the USA, the one-year survival rate was 63% [12].

Budd-Chiari Syndrome --- The Budd-Chiari syndrome, caused by 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.

The number of different surgical procedures that have been proposed to treat Budd-Chiari has been reported to be as high as 23 [13]. The procedures most commonly used in the United States are the side-to-side portacaval and mesocaval

shunts. Success rates with these procedures range from 30% to 92%, with the majority being in the 60% to 75% range. However, if there is progressive liver failure, and no concomitant neoplastic disease, Budd-Chiari syndrome can be successfully managed by OLTx. The first OLTx for this disorder was performed by our group on November 28, 1974. This patient is still alive and well 21 years after the procedure, and has had two children. Since that time, a number of patients with this condition have been treated with OLTx at many institutions.

Other Parenchymal Diseases — There are many other hepatic parenchymal diseases for which OLTx has been successfully performed, including, but not limited to, cystic fibrosis, 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. 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 a severe impairment of bile excretion and hepatocellular dysfunction. These events may ultimately lead to cirrhosis. OLTx 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, is a disorder that primarily affects middle-aged women, with a ratio of women to men of approximately 10:1. The 5-year survival of patients with PBC, not treated with OLTx, ranges from 30% to 70%.

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 OLTx. In one such investigation [14], the survival following OLTx was markedly better than that predicted (assuming no transplantation) using survival analysis.

However, we should note here that, while the 1-year survival rates after transplantation were 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 [15]. In fact, if we compare these survival rates with the ones predicted by the Mayo prognostic model for PBC, 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 [14,15]. These data should be kept in mind when establishing candidacy and OLTx priority for this category of patients.

Biliary Atresia — Biliary atresia is by far the most common indication for OLTx in children. 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). It is estimated that 75% of the patients suffering from biliary atresia will eventually require a liver transplant, regardless of any previous surgical treatment. 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 [16].

Sclerosing Cholangitis --- Primary sclerosing cholangitis [PSC] is a chronic cholestatic liver disease which is extremely difficult to define accurately. It is recognized by liver dysfunction and a characteristic radiologic appearance with multiple localized strictures and dilatation, in the absence of known causes of cholangitis, such as operative trauma, calculus disease, or congenital anomalies.

In contrast with 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, and should be abandoned.

Recently, the survival of 216 patients transplanted for PSC was compared to the predictions made by survival analysis (again, assuming no transplantation) [17]. 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 at 5 institutions from Europe and North America [18]. The 5-year Kaplan-Meier actuarial survival after OLTx was 73%, compared to 28% expected survival according to the above mentioned model. Similarly to what is observed with PBC patients, 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 [18], the gain in 1-year survival rate with OLTx is only 7% in the low-risk patients, and as high as 40% in the high-risk group. Again, this information should be seriously considered when formulating policies for candidate selection and OLTx 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, familial cholestasis, and Alagille's syndrome are the most important diseases in this group [19].

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 [2]. The resolution of gout, naturally present in Dalmatian dogs, after OLTx using mongrel canine donors conclusively proved this hypothesis. The fact that the graft maintained its phenotype resulted in the cure of congenital errors of metabolism in many patients treated by OLTx for end-stage liver diseases, and anatomically normal livers have also been replaced to correct congenital metabolic defects. At least 16 distinct inborn errors of metabolism have been treated with OLTx, including, α -1-antitrypsin deficiency, Wilson's disease, tyrosinemia, and hemochromatosis [20]. Many other cannot be cured by OLTx and might benefit from allogeneic bone marrow transplantation [21]. The guidelines for decision making in specific metabolic errors became increasingly clear in the past decade, allowing better care of these patients [21,22].

TUMORS

Primary hepatic malignancies were originally considered "the indication" for OLTx. 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. As a consequence of this concept, 11 out of the first 25 patients transplanted at University of Colorado [2] had a

hepatocellular carcinoma. However, the results with malignant tumors did not fulfill these expectations, with high mortality rates due to recurrence [2]. The prognosis proved to be different in small, incidental tumors. The longest survivor in this group is a patient who underwent OLTx for biliary atresia on January 22, 1970. The removed liver had a 3 cm hepatoma, and the patient is still alive and well, 25 years after the surgery.

Benign Tumors — The experience with OLTx 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 OLTx. 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 [23].

Primary Malignant Tumors — We believe that two points should be made clear when treating patients with liver malignancies. First, the uncertainty of the prognosis must be openly discussed. Secondly, possible metastases should be aggressively searched for before candidacy for OLTx 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 subtotal liver resection and 105 with OLTx, one and five year survival rates in the resection group were 71% and 33%, respectively, and in the transplant group 66% and 36%, respectively [24]. Today, we routinely combine the surgical treatment with adjuvant chemotherapy which, theoretically, should work better when administered regionally (through the hepatic artery branch feeding the tumor).

Certain types of malignant liver tumors have a better outcome than others. While Klatskin tumors have the poorest long-term survival (with no survivors at 4.5 years in a previous series of 10 patients), epithelioid hemangioendotheliomas have a 5-year actuarial survival rate of 67% [25].

Metastatic Tumors — Liver transplantation has been used in the treatment of a very limited number of tumors metastatic to the liver. We have recently updated (unpublished data) the follow-up of 5 patients who underwent OLTx at our institution, between 1981 and 1987, for a neuroendocrine tumor metastatic to the liver [26]. 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

We analyzed the outcome of 1,501 consecutive patients who underwent OLTx, at the Pittsburgh Transplantation Institute, 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 1. 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 76.2), and the mean follow-up was 2.15 years (range: 0 to 4.5 years). All recipients were treated with the same immunosuppressive protocol, based on tacrolimus (formerly FK506) [7], and prednisone. The overall actuarial patient survival rates were 81%, and 73%, at 1, and 4 years, respectively (Figure 2). The overall actuarial graft survival rates were 72%, and 64%, at 1, and 4 years, respectively (Figure 2). Traditionally, patient survival after OLTx 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%, and 80%, at 1, and 4 years, respectively (Figure 3), while the 1,286 adults (> 18 years) had overall actuarial survival of 81%, and 71%, at 1, and 4 years, respectively (Figure 3). This difference was 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 (Figure 4). The actuarial survival rates for cholestatic liver diseases were 90%, and 87%, at 1, and 4 years, respectively (Figure 4); for the alcoholic group they were 82%, and 70%, at 1, and 4 years respectively (Figure 4); for the parenchymal and metabolic disease group, which included all the other parenchymal diseases (excluding tumors), the survival rates were 78%, and 71%, at 1, and 4 years, respectively (Figure 4); and for the hepatitides they were 79%, and 70%, at 1, and 4 years, respectively (Figure 4). When compared with each other, patients undergoing OLTx 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 1 - had an incidental tumor; however, they are not included with the "tumor" patients because their prognosis has been found in the past to be similar to that of patients with benign disease). The actuarial survival rates for patients undergoing OLTx for cholangiocarcinoma were 70%, and 50%, at 1, and 4 years respectively (Figure 5 - only 1 patient at risk at 4 years). The actuarial survival rates for patients with a known hepatoma before OLTx were 74%, and 58%, at 1, and 4 years, respectively (Figure 5). The actuarial survival rates for patient undergoing OLTx as treatment for a tumor metastatic to the liver were 86%, and 68%, at 1, and 3 years, respectively (Figure 5 - 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%, and 75%, at 1, and 4 years, respectively (Figure 5). As expected, patients with no known tumor before OLTx 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).

SPECIAL CONSIDERATIONS

There are few other issues regarding candidacy to OLTx 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-year survival rates that are similar to that of younger groups.

Thrombosis of the portal vein, and/or the mesenteric and splenic vein, were in the past considered as contraindication to OLTx. These problems were almost completely eliminated by the use of cadaveric vein grafts. Also, previous abdominal surgery can seriously complicate the transplant operation, and it was once considered a contraindication to OLTx by many liver transplant centers. Nowadays, these technical issues are not considered an obstacle at any major transplant center.

The last issue we would like to address is related to the question of candidacy to OLTx 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. 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 [27]. 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 [28]. The survival of the 15 liver HIV⁺ patients was compared to a group of 1,303 HIV⁻ patients who underwent OLTx during the same years. Kaplan-Meier actuarial survival was identical at one year. Survival rates at 2, 4, and 5 years was lower in the HIV⁺ patients, although it never reached statistical significance. It is our belief that HIV⁺ patients should not be excluded *a priori* from candidacy to OLTx. However, in the present organ shortage crisis, it is obvious that HIV⁺ patients will not be considered as transplants candidates at many institutions, both in the United States and in Europe.

CONCLUSIONS

Indications for OLTx have been substantially expanded in the last 30 years. Many factors that were previously considered as contraindications, like an upper age limit of 50, alcoholic cirrhosis, multiple upper abdominal operations, and HIV antibody carrier status are not any longer preventing candidacy for OLTx. In patients suffering from any 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 OLTx have in the treatment of diseases with high recurrence rates, such as hepatitis B and most malignant tumors. However, OLTx should not arbitrarily be 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 or 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" [29]. This sentence had a tremendous impact on the expansion of OLTx as a routine surgical service. Long-term survival (> 10 years), which was uncommon until the beginning of the 1980s, increased tremendously with the introduction of new immunosuppressive agents [5-8].

Nevertheless, OLTx 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 fourth, respectively) [30]. We believe such notions are wrong, and not supported by the current 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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LEGENDS

- FIGURE 1:** **Top:** The recipient cirrhotic liver is excised. **Bottom:** The new donor liver is placed in the field by the second assistant, and the implantation is started with the end-to-end anastomosis of the suprahepatic vena cava. The right and left corner stitches have been already placed on the recipient suprahepatic caval cuff. (From: Marino IR, Doyle H.R., and Starzl T.E. *Surgical Technique Of Orthotopic Liver Transplantation*. In: *Diseases of the Biliary Tract and Pancreas*, Hess W, Cirenei A, Rohner A, Akovbiantz A (Eds), Piccin Publishing, Padua, 1995. Used by permission).
- FIGURE 2:** 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. (From: Marino IR, Doyle H.R., Rakela J., Fung J.J., and Starzl T.E. *Liver Transplantation: Indications and Results*. In: *Diseases of the Biliary Tract and Pancreas*, Hess W, Cirenei A, Rohner A, Akovbiantz A (Eds), Piccin Publishing, Padua, 1995. Used by permission).
- FIGURE 3:** Kaplan-Meier actuarial patient survival for children (≤ 18 years: 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 ($p=0.298$). (From: Marino IR, Doyle H.R., Rakela J., Fung J.J., and Starzl T.E. *Liver Transplantation: Indications and Results*. In: *Diseases of the Biliary Tract and Pancreas*, Hess W, Cirenei A, Rohner A, Akovbiantz A (Eds), Piccin Publishing, Padua, 1995. Used by permission).
- FIGURE 4:** 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), post necrotic cirrhosis related to any type of hepatitis, and cholestatic diseases. The latter showed a significantly better survival at any given interval. (From: Marino IR, Doyle H.R., Rakela J., Fung J.J., and Starzl T.E. *Liver Transplantation: Indications and Results*. In: *Diseases of the Biliary Tract and Pancreas*, Hess W, Cirenei A, Rohner A, Akovbiantz A (Eds), Piccin Publishing, Padua, 1995. Used by permission).
- FIGURE 5:** 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 preoperative evidence of a liver tumor. The curves show the overall survival rates of: 1) patients with no preoperative evidence of a tumor ("no tumor"); 2) patients with a tumor metastatic to the liver, diagnosed before OLTx; 3) patients with a known hepatoma before OLTx; and 4) patients with a cholangiocarcinoma diagnosed before OLTx. As expected, patients with no known tumor before OLTx had higher survival rates. (From: Marino IR, Doyle H.R., Rakela J., Fung J.J., and Starzl T.E. *Liver Transplantation: Indications and Results*. In: *Diseases of the Biliary Tract and Pancreas*, Hess W, Cirenei A, Rohner A, Akovbiantz A (Eds), Piccin Publishing, Padua, 1995. Used by permission).

Table I

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



FIGURE 1

Overall Patient and Graft Survival

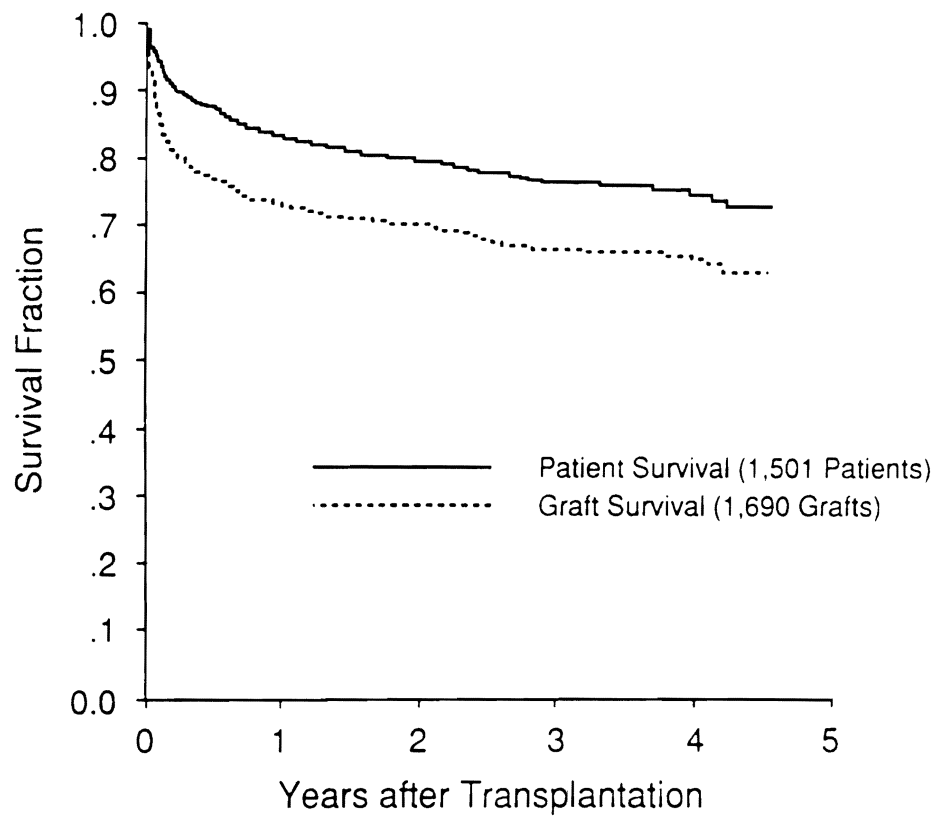


FIGURE 2

Patient Survival by Age Groups

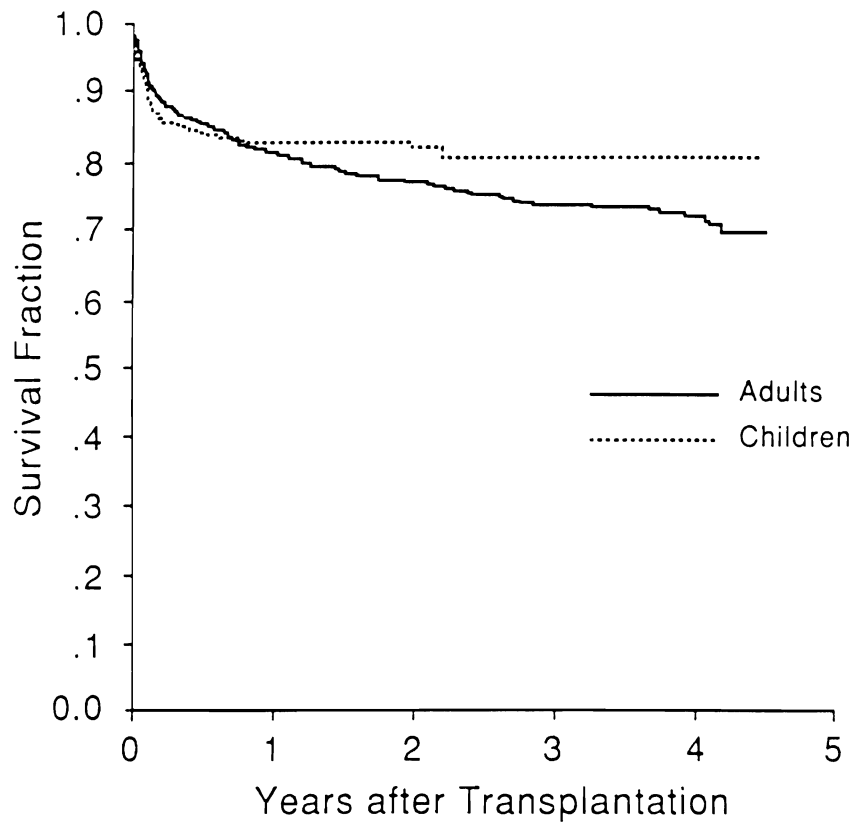


FIGURE 3

Patient Survival by Diagnosis

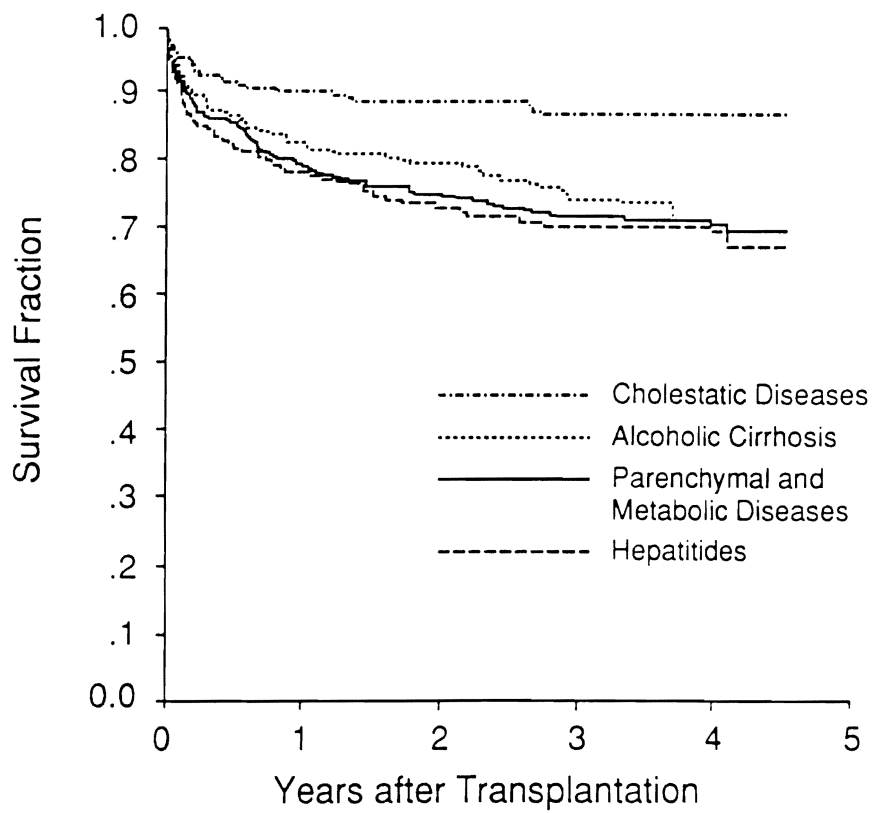


FIGURE 4

Patient Survival by Type of Tumor

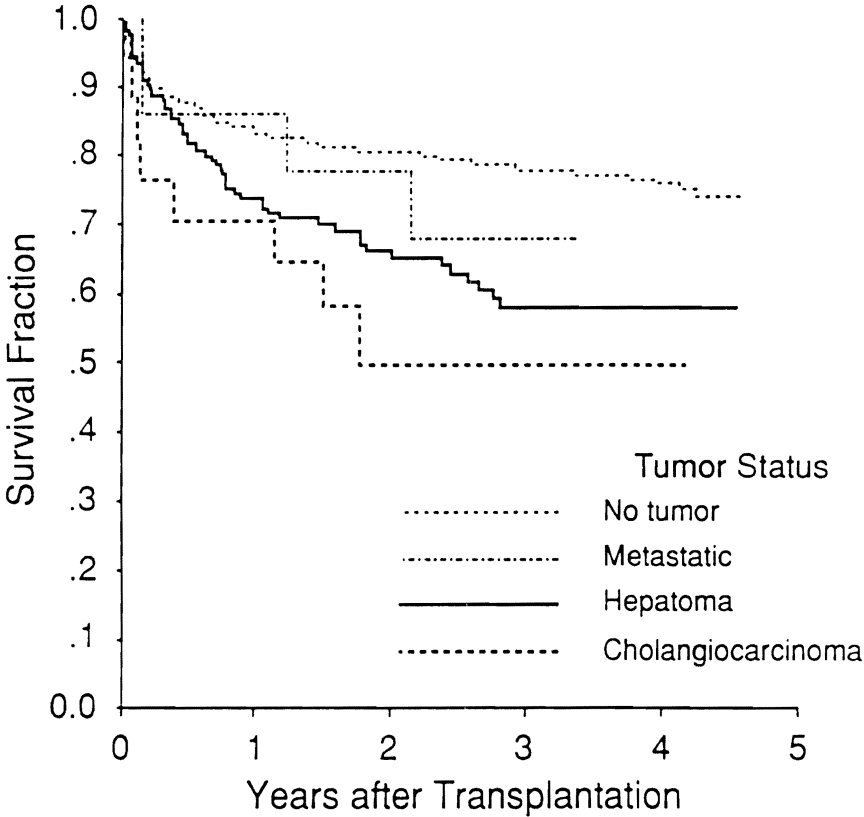


FIGURE 5