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Liver Cell Carcinoma

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Liver transplantation for hepatocellular carcinoma

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According to the U.S. National Cancer Institute, 13600 new cases of malignant tumours of the liver and biliary tree were expected to occur within the United States in calendar year 1986[1]. This incidence is rather low compared to many other more populous areas of the world such as Southeast Asia and Japan (Table 1) where the incidence of hepatitis B virus (HBV) infection and, as a result hepatocellular carcinoma (HCC), is more common. HBV is responsible for greater than 80% of the cases of HCC worldwide such that HBs Ag-positive carriers have a 200-fold greater risk of developing HCC than do Ag-negative controls and as many as 50% of all carriers may develop HCC. The risk of becoming a carrier for HBV is inversely related to the age at which the HBV infection occurs, being > 85% for infected newborns and < 10% for adults. Chronic hepatitis B viral infection with macronodular cirrhosis and integration of the hepatitis B virus DNA into the liver cell genome is not the only cause of hepatocellular carcinoma in the world, however. Hepatoma is a rather common consequence of a larger number of chronic liver diseases and occurs in such diseases at a variable rate between 1 and 100% depending upon the type of cirrhosis and the nature of the underlying liver disease (Table 2).

Table 1   Annual incidence of hepatocellular carcinoma

Rate	Incidence (per 100000)	Location
Very high	> 20	China, Southeast Asia, South Africa (Blacks)
High	10–20	Japan, Southern Europe, Switzerland, Bulgaria
Intermediate	5–9	East Europe, France, Germany, Yugoslavia
Low	5	Great Britain, United States, Australia, New Zealand, Latin America, India, Sri Lanka

Table 2 Rate of hepatocellular carcinoma as a consequence of cirrhosis

Disease	Rate
Macronodular cirrhosis	40-55%
Micronodular cirrhosis	3-10%
Alcoholic cirrhosis	15%
Haemochromatosis	17-25%
Alpha-1-antitrypsin deficiency	1%
Tyrosinaemia	100%
Wilson's disease	1%
Primary biliary cirrhosis	1%

Environmental factors other than viral infection also contribute importantly to the prevalence of hepatocellular carcinoma worldwide. These additional environmental factors include the therapeutic use of sex steroids, particularly oral contraceptives, nutritional deficiency states, fungal mycotoxin contamination of cereal products and of industrial exposures experienced in the workplace (Table 3).

The optimal treatment for hepatocellular carcinoma is partial or subtotal hepatectomy with preservation of as much normal residual hepatic tissue as is possible. This can be accomplished by experienced surgeons with a quite low mortality rate[2]. Mortality rates, however, vary considerably in various series and range between 5 and 30%[3]. The extent of the resection as well as the indication for the resection and the severity of the underlying liver disease present in a given patient importantly affect the mortality experienced with

Table 3 Environmental factors contributing to the development of hepatocellular carcinoma

- Oestrogens
  Especially oral contraceptive agents, with an estimated 500-fold increased risk after 85 months of use

- Available steroids

- Dietary restriction
  Protein
  Methionine
  Selenium
  Zinc
  Folic acid
  Vitamin B_{12}

- Aflatoxins

- Industrial Exposure
  Arsenic
  Vinyl chloride
  Other agents less well-characterized

Table 4 Types of hepatic resections

- Right on left hepatic lobectomy — gall bladder fossa and IVC
- Left lateral segment — falciform ligament
- . Right trisegmentectomy — all of true right lobe and medial segment of left lobe
- Left trisegmentectomy — all of true left lobe and the anterior segment of the right lobe
- Total hepatectomy with orthotopic transplantation
- Wedge resection — does not follow anatomic planes; usually reserved for benign lesions

such resections. The various types of hepatic resection possible are shown in Table 4 and Figure 1. Unfortunately, although hepatic resection is the only curative procedure for hepatocellular carcinoma, < 50% of cases explored are resectable either because of underlying cirrhosis or the size and/or location of the tumour and < 20% of explored cases are totally resectable despite the application of new surgical techniques such as intra-operative ultrasonic localization and dissection of the tumour, the hepatic vessels and the biliary tree.

Total hepatectomy followed by orthotopic liver transplantation is currently the only hope for cure in those patients with underlying cirrhosis or with extensive tumour burdens that preclude standard large hepatic resections (Table 4 and Figure 1). Liver transplantation has been applied to the problem of hepatic malignancy ever since the first clinical applications of the procedure[4-6]. Shown in Figure 2 is the accumulative survival rate for more than 800 adult transplant recipients operated upon at the University Health
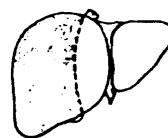

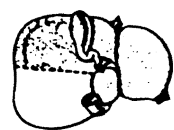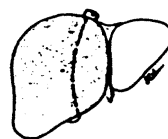LT. LATERAL SEGMENTECTOMY   NON-ANATOMICAL RESECTION
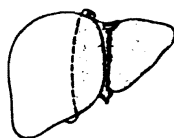
LEFT LOBECTOMY   RIGHT LOBECTOMY

LT. TRISEGMENTECTOMY   RT. TRISEGMENTECTOMY

Figure 1 Schematic representation of the types of major hepatic resections possible with good survival
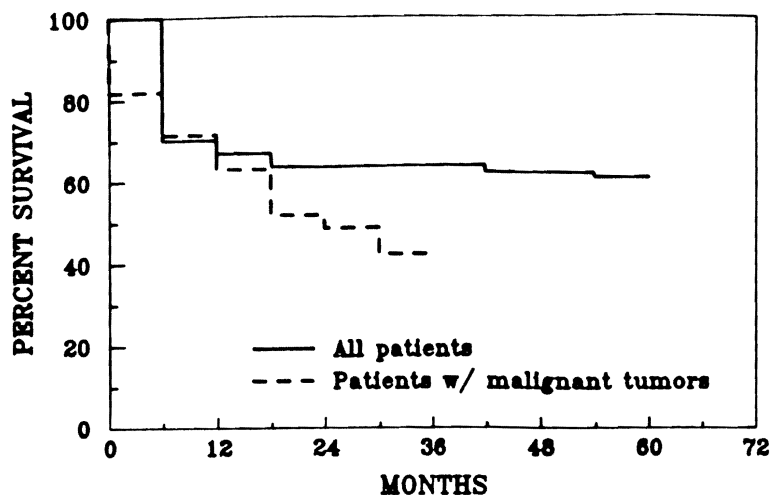
Figure 2 Kaplan–Meier survival curves for 800 adult liver transplant recipients (———) and a subset of 70 recipients transplanted because of a hepatic malignancy (- - - -)

Center of Pittsburgh for all indications except hepatic malignancy and the 70 patients transplanted for a malignant tumour of the liver at the same institution by the same surgeons, using the same immunosuppressive regimens[7].

The percentage of patients transplanted for hepatic malignancy at a given institution varies markedly depending upon a variety of factors including the longevity of the programme, the approach of the institution to patients with HBsAg positivity and cholangiolar carcinoma and the numbers of patients being referred for transplantation for other indications[6-9]. In the Denver–Pittsburgh experience during the pre-cyclosporine era, 13.5% of all recipients had hepatic malignancy as the indication for their procedure. In more recent times, following the introduction of cyclosporine and as a result of more cases being referred for indications other than hepatic malignancy, the percentage of cases transplanted for hepatic malignancy has fallen by 50% to 6.8%[10]. In contrast to the experience in the United States, the experience in Europe has included a larger percentage (29%) of cases with hepatic malignancy as the indication for transplantation. In some European centres, a full one-third of the patients transplanted have had a hepatic malignancy as the indication[9].

The experience with hepatic transplantation for malignancy at these various centres throughout the world has been very similar to that reported by the Pittsburgh group with long-term survival (> 3 years after transplantation) being between 20 and 30% (Figure 2). This survival figure is one-half to one-third that experienced for all other indications for which liver transplantation has been applied but is nonetheless considerably better than that experienced with any other type of therapy, particularly medical therapy where no survivors exist after one year[11].

Table 5 Co-existent liver disease in 21 patients with incidental primary liver neoplasms

Disease	Number of patients
Cirrhosis	5
Tyrosinaemia	4
Biliary atresia	4
Sclerosing cholangitis	4
Alpha-1-antitrypsin deficiency	2
Familiary cholestasis	1
Sea-blue histiocyte syndrome	1

The experience with liver transplantation applied for hepatocellular carcinoma is not entirely grave. Individuals who have been transplanted for other conditions in which a hepatic malignancy typically < 5cm in diameter was found (Table 5) have done very well and have had a survival rate similar to that experienced by those transplanted for the same condition not complicated with a hepatic cancer (Figure 3). Of the 14 such cases, all but one has survived without re-occurrence of their hepatocellular carcinoma with the duration of follow-up ranging from 3 to 73 months and with 6 of these 13 long-term survivors being free of recurrent disease beyond 3 years.

In contrast to the experience with hepatocellular carcinoma occurring 'incidentally' in a liver at the time of hepatic transplantation, the clinical course of those transplanted solely because of hepatocellular carcinoma has
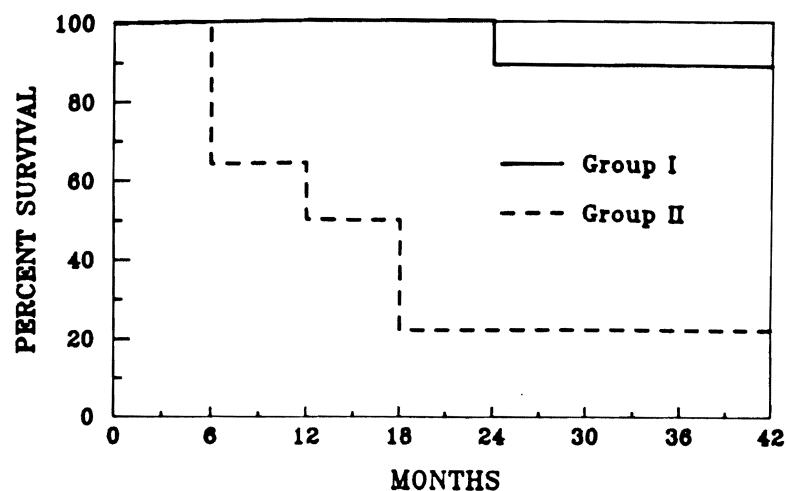
Figure 3 Kaplan-Meier survival curves for liver graft recipients to have an incidental hepatic neoplasm in a liver removed for another reason (———) and those transplanted for hepatic malignancy (- - - -)

been quite different. Among 20 such patients transplanted during the cyclosporine era, 5 (25%) died during the immediate post-operative period (within 2 months of transplantation); 8 of the remaining 15 (53%) developed recurrent disease at intervals of 4–12 months following transplantation. Recurrence of the hepatoma in the allograft was the first evidence of disease recurrence in 50% of the cases, in 38% of recurrent cases the recurrence occurred first in the lungs and 12% it occurred first in bone. Of the remaining 8, 2 have survived for only 1 and 8 months, respectively, while 6 have survived free of recurrent disease for intervals ranging from 6 to 54 months.

A recent report extracted from the European Liver Transplant Registry reported a 30% survival for patients transplanted for hepatocellular carcinoma at 2 years[8]. The data compiled by Pichlmayr[9] from 7 major European centres is quite similar to that experienced in Pittsburgh with 30% of the patients surviving for 1 year but only 17% surviving free of disease for > 2 years.

These results from Europe and the United States clearly document that despite the elimination of patients with extra-hepatic malignancy detected by a careful screening of each candidate for metastatic disease with computed-tomography scans of the chest, abdomen, and head as well as with bone scanning techniques, that microscopic metastasis, unrecognized either before surgery and at the time of the transplant procedure itself persists in such cases despite resection of the gastro-hepatic and hepato-duodenal ligaments, skeletalization of all vascular structures as well as the common bile duct and resection of the bile duct as it crosses behind the duodenum with the creation of a roux-en-Y choledochojejunostomy.

At this point in time, the results with the application of adjuvant chemotherapy after the hepatectomy during the anhepatic phase of the transplant procedure and in the first several months following liver transplantation for hepatoma are not yet available. The experiences with such modifications of current techniques are either being formulated now, or at least in some cases are only beginning to be accumulated.

The exception to the rule of a poor prognosis with hepatic transplantation for hepatocellular carcinoma is the experience with fibrolamellar carcinoma[14]. Typically, this tumour occurs in young adults and in the absence of any underlying liver disease. Moreover, it reportedly grows slowly, has a high resectability rate, and therefore, a longer survival rate than that experienced with other types of hepatocellular carcinoma[12-14]. A total of 9 patients with this variant of hepatocellular carcinoma have been treated by the Pittsburgh group during the cyclosporine era with orthotopic liver transplantation. None of them had distant metastasis at the time of transplantation although 2/9 had tumour infiltrating the diaphragm which necessitated excision of a part of the diaphragm with the liver and the tumour; 3 of the tumours (33%) showed some degree of vascular invasion of the resection specimen. One-third of these patients died early as a result of one or another non-tumour-related surgical problems. Of the remaining 6, 2 have died as a result of recurrent disease at 32 and 33 months post-transplant, while 4 are alive with only 1 having evidence of recurrent disease with a mean duration in survival of 30 months.

There has been no reported experience with the particular tumour variant in the data available from the European Liver Transplant Registry[8,9]. The available American experience however, suggests that a limited number of pulmonary metastases may not be a contraindication for liver transplantation in this sub-group and that an aggressive approach to recurrent disease with additional resectional surgery and chemotherapy may be possible[14].

Yet another unique type of hepatic malignancy that may be amenable to liver transplantation is the recently relatively recognized epithelioid haemangioendothelioma[15-17]. Characteristically, this tumour grows slowly like the fibrolamellar variant with a natural history that spans 5–10 years despite metastasis to bone, lungs, pleura and lymph nodes: 6 cases of this tumour have been transplanted in Pittsburgh; 2 had known distant metastatis (1 to the lung and 1 to a rib) prior to transplantation; 4 had extra-hepatic intra-abdominal disease recognized at surgery but not pre-operatively (3 in lymph nodes and 1 involving the diaphragm). All 6 have survived with follow-ups ranging from 10 to 49 months (mean 22 months). The 2 with distant metastasis have had their disease remain stable. Because the natural history of this disease is so unusual, it is not yet possible to make a definitive statement about the role of transplantation in such cases.

Bile-duct cancers comprise 16% of the tumours for which liver transplantation has been applied in the Pittsburgh experience. On average, these patients are older than the other tumour patients and 72% have had primary sclerosing cholangitis as the underlying chronic liver disease. Half have also had ulcerative colitis. In 55% of the cases, particularly those with sclerosing cholangitis, the tumour was not identified prior to hepatic resection despite an extensive pre-operative evaluation including brushing of the bile ducts for cytologic examination being obtained from the involved biliary tree whenever possible. Overall, 11% of the cases transplanted for sclerosing cholangitis had not been cholangiolar carcinoma[18]: 18% of these patients died early in the post-operative course; 78% of the survivors however, developed clinically-evident recurrent disease on mean at 8.5 months post-transplantation. Only 22% have survived > 15 months without recurrent disease. The experience of the Cambridge group with this tumour has been similar to that experienced in Pittsburgh[19]. The data of Pichlmayr suggest that those with nodal metastasis at the time of transplantation do very poorly, with only 13% being alive at 1 year and none at 2 years, while 100% of those without nodal metastasis are alive at 1 year and 83% are alive at 2 years following transplantation[9].

It is clearly evident from the above data that the results with total hepatectomy and orthotopic liver transplantation for the treatment of hepatic malignancy currently are less than ideal. Increasing surgical experience with the procedure and the use of cyclosporine has resulted in fewer immediate post-operative deaths such that the application of this mode of therapy can be more clearly evaluated. In general, particularly when compared to the results experienced with non-malignant diseases of the liver, the results have been poor, with only 20–30% of the patients surviving for periods > 1 year. Progress in this area awaits the development of new chemotherapeutic agents that are effective against hepatocellular carcinoma or the development of means of targeting and destroying microscopic metastatic foci of malignant

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disease once the bulk of the tumour load is removed as a result of the total hepatectomy.

Current recommendations are that liver transplantation be applied to those patients with hepatic malignancy such as the fibromellar variant and the more unusual epithelioid haemangioendothelioma and occasionally for those with other types of hepatocellular but not biliary epithelial tumours, who have extra-hepatic malignancy ruled out by means of computed tomography scanning of the chest, abdomen and head and a bone scan followed either by a careful staging laparotomy or with a back-up candidate available for the allograft should the potential recipient be found to have extra-hepatic disease at the time of operation.

Despite such caution, transplants are still likely to occur in patients with undetected extra-hepatic malignancy. The use of adjuvant chemotherapy may be effective in such cases. Currently, however no good data relative to this point exist.

Acknowledgement

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