J Hep Bil Pancr Surg (1998) 5:18–23

Journal of HBP Surgery

Hepatocellular cancer: Resection or transplantation

Jan Dmitrewski, Galal El-Gazzaz, and Paul McMaster

The Liver and Hepatobiliary Unit, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH, UK

Abstract: Surgery remains the treatment of choice for hepatocellular carcinoma (HCC). For HCC without underlying cirrhosis resection remains the mainstay treatment option. Prognosis depends on the stage of the tumor. Survival appears to be better for small (less than 5 cm) solitary tumors with negative resection margins and absence of vascular invasion. At present, liver transplantation does not have an established role in the treatment of HCC in a non-cirrhotic liver. Because of the high recurrence rate, it should not be considered for more advanced disease which is not amenable to resection. The surgical approach in cirrhotics depends not only on the stage of the tumor but also on the liver functional reserve. Tumor size, presence of multifocal disease, and vascular invasion determine the risk of HCC recurrence after resection, and the functional stability of the liver determines both resectability and outcome. In societies in which transplantation is not available, small tumors will be treated with liver resection. The outcome in patients with well preserved liver function is relatively good, at least in the medium term. However, recurrent tumor and progressive hepatic decompensation have significant adverse effects on long-term survival. Poor functional reserve may be associated with significant perioperative mortality and lower survival due to progressive liver failure. In our opinion, for small cirrhosis-related HCCs, liver transplantation offers better long-term prospects than resection. Therefore, if liver transplantation is available as an option it should be considered as the treatment of choice, particularly for younger patients with otherwise good life expectancy.

Key words: hepatocellular carcinoma, liver resection, liver transplantation

Introduction

Worldwide, hepatocellular carcinoma (HCC) is one of the most common cancers and in areas with a high incidence it remains one of the leading causes of death from cancer. However, there is significant geographical variation in both incidence and etiology. Whereas its incidence in many parts of Africa and the Far East is extremely high and appears to correlate with the prevalence of hepatitis B virus (HBV) and C (HCV) infection, HCC is considerably less common in North America and Europe. In the United Kingdom, two-thirds of patients with HCC have long-standing alcoholic cirrhosis. The increased risk of HCC appears to be greater with alcohol-induced cirrhosis and hemochromatosis than with viral-induced cirrhosis (Table 1).[1,2]

The survival of patients with HCC not subjected to surgical intervention varies by stage at the time of presentation and the presence of an underlying liver disease, but is generally less than 6 months. Surgical removal of the tumor remains the treatment of choice for HCC. This option incorporates either hepatic resection or liver transplantation. As liver transplantation is not widely available in the communities with the highest incidence of HCC, resection is likely to remain the main treatment worldwide.

However, some transplant centers in Europe and North America have been offering liver replacement to selected patients with HCC. Both liver resection and transplantation for HCC are expertly reviewed in other papers included in this issue. In this article, we present our view of the role of these two treatment modalities in the surgical management of HCC.

Detection of HCC

Early detection of HCC improves the resectability rate and enhances option availability. Patients at high risk of

Offprint requests to: P. McMaster

Received for publication on June 9, 1997; accepted on July 3, 1997

Table 1. Liver disease and risk of hepatocellular carcinoma (HCC): Cross-sectional studies

Proportion of patients with HCC by Etiology of liver disease in Europe	
HCV	10%
HBV	16%
HCV + HBV	28%
Alcohol-induced	40%
Hepatitis + Alcohol	60%

From Colombo (1992)[1] and Curly et al. (1995)[2]
HCV, Hepatitis C virus; HBC, hepatitis B virus

Table 2. Treatment options for HCC

Hepatocellular carcinoma		
Operable (Exclude metastases)		Inoperable
Resection	Transplantation	Palliative (Alcohol injection, embolize, chemotherapy)

developing HCC, especially those with HBV and HCV infection, should undergo routine surveillance. This has been well established in Far East communities with the advances in non-invasive imaging techniques, and has resulted in an increasing number of "small tumors" being diagnosed.[3,4] At our institution, detection of a solid hepatic lesion on ultrasound (US) scanning in the presence of a high (above 1000) α-fetoprotein (AFP) level and established liver cirrhosis is regarded as diagnostic of HCC. However, it has to be acknowledged that in a number of HCC patients AFP is not elevated and in those with fibrolamellar tumors AFP is often normal. For screening of liver masses, US is well tolerated, easily available, and cost-effective. Morphological changes in the cirrhotic liver may, however, affect the accuracy of scanning. If US scanning is suggestive but not conclusive of HCC, a Lipiodol arteriogram should be considered. Supplementary imaging with computed tomography (CT) or magnetic resonance imaging (MRI) scanning may also be required. We do not routinely perform percutaneous biopsy, as this may result in tumor cells seeding, although laparoscopy and biopsy of the "normal" liver may be of value in assessing the degree of cirrhosis. In patients in whom the diagnosis of liver cirrhosis has not been previously established biopsy will determine the morphology of residual liver tissue.

Treatment of HCC

Treatment options for HCC are shown in Table 2.

Table 3. Hepatocellular carcinoma outcome

A: Stage of cancer	Size
	Number of lesions
	Vascular invasions
	Capsule
	L/N studies
B: Stage of liver disease	
C: Virology status	

L/N, Lymph nodes

Treatment in non-cirrhotic liver

Resection. For HCC in otherwise normal liver, i.e., without underlying cirrhosis, resection, if anatomically feasible, remains the mainstay treatment option. In such patients up to 75% of liver tissue can be removed with relatively low morbidity ensuring adequate tumor clearance.

Long-term results are generally good and 5-year survival rates of 45% with perioperative mortality of 3%–7% have been reported.[5,6] Factors influencing outcome are shown in Table 3.

Prognosis depends on the stage of the tumor. Minimal to moderate disease (stages 1 and 2) confined within the liver is associated with the best long-term outcome. Survival after liver resection appears to be better for small (less than 5 cm) solitary tumors with negative resection margins and absence of vascular invasion.[7]

Liver transplantation. At present, liver transplantation does not have an established role in the treatment of HCC in a non-cirrhotic liver. Curative resection of small HCCs (less than 5 cm) is associated with good long-term prognosis and also avoids the morbidity of long-term immunosuppression. (Historically, malignancy used to be a major indication for liver replacement). Our initial philosophy in the 1970s and 1980s was to resect tumors which could be resected and to transplant in patients with tumors not amenable to resection. The results of liver transplantation for such advanced HCCs were extremely poor, with only 25% of patients alive 2 years postoperatively and none alive at 5 years.[8] Equally disappointing results were reported by other centers.[5,9] It could be argued that transplantation for advanced HCCs should be regarded as a palliative treatment offering improved life quality and extended survival compared with the natural course of the disease. However, with uniformly poor results and donor organ shortage, such an approach does not seem to be justified at present. This may change if an effective adjuvant therapy becomes available.

Tumors developing in non-cirrhotic liver account for only a small proportion of HCCs.

Treatment of HCC in cirrhotic liver

Liver cirrhosis is present in up to 90% of patients with HCC.[10–12] The optimal surgical approach in cirrhotics is difficult to determine, as it depends not only on the stage of the tumor but also on a second critical factor, the liver functional reserve, and thirdly, on the patient's viral status.

Resection. In Southeast Asia, small (less than 5 cm) tumors are routinely resected in patients with compensated cirrhosis, with the reported 5-year survival rates between 25% and 67%, provided that adequate resection margins have been achieved.[13] Schwartz et al.[14] reported a 39% 3-year survival after liver resection for HCC in patients with Child's A cirrhosis.

The outcome appears to be determined by both the likelihood of recurrence and the functional stability of the cirrhotic liver. Size of the tumor (more than 5 cm), presence of multifocal disease, and vascular invasion increase the risk of HCC recurrence after liver resection.[15,16] However, as 10%–20% of patients with cirrhosis and a small HCC have multicentric disease not apparent on the preoperative imaging,[17] and vascular invasion is often present microscopically, even in most clinically localized HCCs,[18] it is unlikely that even more "radical" hepatectomy will prevent tumor recurrence. Furthermore, the underlying liver cirrhosis may be regarded as a "premalignant disease." Liver resection leaves behind the diseased organ in place, often with an element of hepatocytic dysplasia, and this may lead to the development of metachronous lesions.[19] In patients with chronic viral infection, HCC recurrence may be influenced by the histological activity of underlying hepatitis, resulting in multifocal carcinogenesis.[20] HCC developing after liver resection may therefore represent either progression of previously diagnosed disease or de-novo lesions.

In patients with cirrhosis, the residual liver function determines both resectability and outcome. Operative mortality in the presence of cirrhosis is significant (14%) even in Child's A patients.[7] Patients should be therefore selected according to their preoperative liver function. Criteria for inoperability include hepatic encephalopathy, refractory ascites, and gross impairment of synthetic function.[21] Whereas individuals with well compensated cirrhosis (Child's A) tolerate hepatectomy relatively well, in those with Child's B and C residual liver mass should be preserved by using segmental or non-anatomical resection. In such patients usually only peripherally situated tumors can be resected with adequate tumor clearance and acceptable mortality. Postoperatively, progression of liver disease has a significant adverse effect on long-term survival. High rates of death due to liver failure in patients free from recurrent tumor have been reported from both Japan and Europe.[22] Fewer than 25% of patients with Child's group B or C are expected to be alive 5 years postoperatively, with as many having succumbed to complications of cirrhosis as to tumor recurrence.[22]

Liver transplantation. It can therefore be argued that many cirrhotics would be best treated with liver transplantation, which removes not only the tumor but the diseased liver itself, thus preventing both late liver failure and recurred or de-novo HCC. Such an option would, however, be inappropriate in patients with active alcoholism, for example, and careful consideration is needed in patients with underlying viral disease which may lead to recurrent hepatitis, cirrhosis, and graft failure. Favorable prognostic factors for liver transplantation in HCC with cirrhotic liver are shown in Table 4.

The outcome of liver transplantation for HCC as the primary indication is difficult to determine (Table 5). Most reports include patients with HCC in non-cirrhotic livers as well as those with incidental tumors in cirrhotic livers. Tumor stage is the most important prognostic factor related to early recurrence. The results of liver transplantation for small (less than 5 cm) HCCs in cirrhotic patients are generally good; the 4-year survival rate is 66%.[14] Hospital mortality in patients with decompensated liver function (Child's group B and C) appears to be relatively high (11%).[23] However, both overall and recurrence-free survival rates are noticeably lower in patients with more advanced disease. Mazzaferro et al.[24] reported 85% actuarial and 92% recurrence-free 4-year survival after transplantation for patients with small HCCs, but only 50% and 59%, respectively, for those with larger or multifocal lesions. In the series reported by McPeake et al.,[25] 5-year actuarial survival for patients with single dominant lesions of less than 4 cm was 57%, whereas in those with tumors larger than 8 cm and multifocal lesions the 5-year actuarial survival was only

Table 4. Liver transplantation for HCC in cirrhotic livers

Favorable prognostic factors
1. Small tumor <5 cm
2. Unicentric tumors
3. No vascular invasion
4. Pseudocapsule
5. Low histology grade

Table 5. Liver transplantation

	HCC
Single HCC	<5 cm/<3 nodules <3 cm in size
4-Year survival	
Actuarial — 85%	
Recurrence-free	4-Year survival — 92%

From Mazzaferro et al. (1996)[24]

11%. Accurate staging, including tumor size, multifocality, vascular involvement, and extrahepatic disease, is essential to identify those patients who are most likely to benefit from long-term survival without tumor recurrence.

Some centers have been using adjuvant chemotherapy to improve the outcome of liver transplantation for more advanced HCC. Stone et al.[26] reported actuarial survival of 59% and tumor-free survival of 54% at 3 years in patients with large HCCs (more than 5 cm, multifocal disease, and vascular invasion) treated with doxorubicin. These results are encouraging, although the protocol has to be regarded as experimental and its long-term benefits remain to be fully evaluated.

Few comparative studies on the outcome of liver resection and transplantation for HCC have been published. Data reported by Bismuth et al.[27] suggest that although 3-year overall survival rates are similar (50% and 47%), disease-free survival may be better in patients who have been transplanted (46% versus 27%).

In patients with viral hepatitis, reinfection of the graft with HBV or HCV is a common problem. The possibility of subsequent liver failure may limit the application of transplantation in this group of patients.

Prophylaxis with high-dose hepatitis B immune globulin (HBIG) has been shown to decrease the post-transplant hepatitis B surface antigen HBsAg recurrence rate from 70%–100% to between 23% and 48%.[28] However, levels of antibody must remain high. Problems associated with the use of HBIG for post-transplant prophylaxis include the risk of allergic reaction; drug clearance after transplantation, and high maintenance cost. As HBIG is produced from pooled human blood there is a risk of virus transmission.[29]

HBIG prophylaxis in patients positive for HBV DNA is associated with a high reinfection rate. Enantiomer of 3-thiocytidine, Q2′ 3′-dideoxy-nucleoside, (Lamivudine, Glaxo-wellcome British Company, Uxbridge, Middx, UK) a new nucleoside analog with potent antiviral effects against HBV, has been shown to clear HBV DNA both pretransplant and post-transplant.[29,30] Recipients with actively replicating HBV may achieve a good outcome after liver transplantation with Lamivudine, but viral resistance is likely to be a significant problem.[29,30] Until conclusive data are available, patients with hepatits B infection, particularly those who are HBV DNA-positive, should be offered transplantation on an experimental basis.

Hepatitis C virus is also a major long-term concern after transplantation. Reinfection of the donor liver occurs in virtually all patients with viremia prior to transplantation. No truly effective HCV-specific treatment has been available but limited success has been achieved with interferon therapy. However, recurrent hepatitis C progresses relatively slowly and clinical manifestation of liver impairment is uncommon during the first 5 years after transplantation.[31] Therefore, underlying HCV cirrhosis should not be considered as a contraindication to liver transplantation for HCC.

Conclusions

The outcome of surgical treatment for HCC is influenced by the stage of the tumor; stage of underlying liver disease; and, in patients with viral hepatitis, the stage of infection. Therefore, the choice of optimal treatment should be determined by careful evaluation of these three variables.

Stage 1 and 2 tumors in non-cirrhotic liver are best treated by formal resection. Resection for more advanced disease (large tumor, multifocal lesions, vascular involvement) with or without underlying cirrhosis has been associated with poor long-term results. Because of the high recurrence rate, liver transplantation cannot be considered as a curative treatment in such patients and, with the shortage of donor organs, it will rarely be recommended as a palliative measure. It remains to be determined whether the development of effective adjuvant chemotherapy could improve the outcome of liver resection and transplantation for advanced HCC.

In societies in which transplantation is not available, small tumors with underlying cirrhosis will be treated with liver resection. Hepatectomy in patients with well preserved liver function (Child's group A) has been associated with a relatively good outcome, at least in the medium term. However, recurrent tumor and progressive decompensation of liver function have significant adverse effects on long-term survival. Liver resection in patients with poor functional reserve (Child's group B and C) may be associated with significant mortality and lower survival due to progressive liver failure. In our opinion, for small cirrhosis-related HCCs, liver transplantation offers better long-term prospects than resection, as transplantation removes the entire diseased and potentially carcinogenic organ, restores normal liver function, and with centrally situated lesions, allows removal of tumors not amenable to resection. Therefore, if liver transplantation is available as an option it should be considered as the treatment of choice, particularly for younger patients with otherwise good life expectancy. It could be argued that long-term immunosuppression would accelerate tumor recurrence. However, to data, experience suggests better disease-free survival after transplantation than after liver resection.[27]

Patients with active virus-induced cirrhosis are at risk of recurrent hepatitis, leading to graft cirrhosis and failure. No effective treatment for hepatitis C is as yet available. However, the progress of recurrent HCV

Table 6. Summary of treatment options and outcomes for HCC

1. Non-cirrhotic patients with HCC	5-Year survival
Treatment: Resection	45% (5-Year survival)
2. Cirrhotic patients with HCC — parenchymal failure (tumor <5 cm)	
Child's A: Resection	39% (3-Year survival)
Child's B/C: Transplantation	66% (4-Year survival)
3. Hepatitis C Transplantation	<80% (5-Year survival)
Hepatitis B (DNA +ve): ..... + Lamivudine/Immunoglobulin	?
4. "Large" HCC (tumor >5 cm)	
Outcome poor whether resected or transplanted	<20% (3-Year survival)

Conclusion: 1. Stages III and IV, palliative treatment
2. Stages I and II: Non-cirrhotic — resection; cirrhotic — transplantation

hepatitis is relatively slow with late clinical manifestation of the disease in our series of 50 patients, there has been a 95% 5-year survival. Therefore HCV infection should not be considered a contraindication to liver transplantation. Recurrence of hepatitis B, particularly in HBV DNA-positive patients, is often aggressive, with progression to cirrhosis. The long-term efficacy of Lamivudine in the prevention of hepatitis B recurrence after liver transplantation is being investigated urgently, and hyperimmune globulin may be effective (Table 6).

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