Leading article

Liver transplantation for hepatocellular carcinoma

As experience in orthotopic liver transplantation (OLT) has accumulated, it has become clear that frequent tumour recurrence has impaired overall survival figures for patients transplanted for hepatocellular carcinoma (HCC). In most series, two year survival has been 30% or less¹⁻⁵ and in the context of a limited supply of donor organs, the validity of continuing to transplant such cases has been called into question.^{3,6} Some HCC patients do achieve a cure with OLT, in particular those in whom the tumour is an incidental one, being found only on examination of the explant.^{4,6} These lesions are usually small, and tumour recurrence is less common – between 0%–13% compared with 37%–82% in cases where the diagnosis of HCC was established before operation.^{3,5,7,8} In general, the smaller the tumour the less likely it is to recur, but in a few patients even with large tumours cure is obtained, as in an early case in the Cambridge/King's College Hospital series when the tumour weighed 4 kg.⁹ Cases such as this add to the difficulty of decision making for the physician and patient who may feel that even the smallest chance of a cure is worth taking.

Patient selection and survival

The results of recent studies permit a more consistent approach to the selection of candidates for transplantation based on more precise knowledge of factors that influence the recurrence rate. The transplant group at Pittsburgh have reported good results with unifocal tumours smaller than 5 cm,⁴ with only 7% of such tumours recurring, compared with 62% for larger lesions. In our most recent series,¹⁰ recurrence was not seen in patients with unifocal tumours measuring less than 4 cm in diameter. Those with a unifocal tumour of between 4 and 8 cm diameter had a recurrence rate of 40%, and in cases with either unifocal lesions of more than 8 cm or when the tumour was multifocal, the recurrence rate was very high at 78%. Tumour infiltration of regional lymph nodes also has an important influence on recurrence. Pichlmayr reported one, two, and three year actuarial survival of 43%, 36%, and 24% in patients without nodal involvement, contrasting with 0% at one year in those with positive nodes,^{3,11} and the Pittsburgh group reported recurrence rates of 34% in node negative cases versus 75% in lymph node positive patients.^{12,13} The tumour, node, metastases (TNM) pathological classification of tumour stage of HCC¹⁴ also correlates with outcome after OLT. In 52 cases from Hanover,³ actuarial survival for the stage II tumour patients was 100% at five years; three year survival figures in those with stages III and IVa disease were about 25% and 9% respectively. Tumour invasion of blood vessels is another important prognostic factor. Patients without vascular invasion in a recent Pittsburgh series had a tumour free survival figure of 95.2% at five years. If microscopic vascular invasion was present, this figure fell to 49.8%, and with macroscopic vascular invasion, disease free survival was only 11.9% at 12 months, with no survivors at three years.¹⁵ Good prognostic indicators include the

presence of a pseudocapsule surrounding the tumour, circumscribed shape, and unilobar involvement.^{13,15}

Care is needed in the assessment of the influence of concomitant cirrhosis on prognosis. In pooled data analysed in 1988 from seven European centres,¹⁶ cirrhosis was an adverse risk factor: only 10.7% of patients in this group survived two years and 2.4% five years, compared with 24.7% and 9.6% respectively in non-cirrhotic cases. The Birmingham group¹⁷ recently reported seven deaths from surgical complications within the first month among 10 cirrhotic patients transplanted for HCC. Two others died within three months of recurrent tumour and recurrent hepatitis B, and the remaining case died of tumour recurrence at 12 months whereas their five non-cirrhotic patients had a median survival figure of 13 months. In Pichlmayr's experience,¹¹ however, operative mortality is higher in cirrhotic cases, but their subsequent survival is marginally better than non-cirrhotic patients, although the difference did not achieve statistical significance. In our own series, the presence of cirrhosis did not affect 90-day death rates,¹⁰ and the cirrhotic patients generally had smaller tumours than the non-cirrhotic group, with a lower frequency of multifocal involvement. Because of this factor, tumour recurrence in the cirrhotic patients was much less frequent. Patients with cirrhosis, if screened for HCC by regular serum α fetoprotein estimations and ultrasound, are more likely to have the diagnosis of HCC made when still presymptomatic with a small lesion, whereas the diagnosis in non-cirrhotic cases is made only when symptoms and signs appear.

Hepatitis B induced cirrhosis is an adverse factor. Interestingly, the poor survival is due not to a greater frequency of tumour recurrence, but to graft loss from viral reinfection.^{13,15} We have recently studied a cohort of 30-day OLT survivors with HBsAg positive liver disease.¹⁸ The graft reinfection rate at 12 months was 85.4% for those with HCC, and 65% for those without HCC, and graft loss was significantly more frequent in the tumour cases (56.3% versus 12.8%). The larger extrahepatic virus load may act as a reservoir for reinfection, the possible sites for this including mononuclear cells, and lymphoid tissue¹⁹⁻²¹ or extrahepatic micrometastases. Other possible factors include defects in the production of cytokines and cell mediated immunity in patients with HCC,²²⁻²⁴ and enhanced virus replication due to cytotoxic chemotherapy. The last factor is known to cause reactivation of HBV infection and fulminant hepatic failure in non-transplanted HBV carriers.²⁵⁻²⁷

Chemotherapy

The position is much clearer with regard to patient selection and the likelihood of tumour recurrence after transplantation, but the effectiveness of adjuvant peri-operative chemotherapy, so often recommended and given, has not been satisfactorily evaluated. A recent pilot study in Dallas²⁸ has shown that intravenous chemotherapy with doxorubicin 10 mg/m²/week preoperatively,

intraoperatively, and postoperatively to a cumulative dose of 200 mg/m² may improve survival. This dose was well tolerated and 17 of 20 patients completed the course; the main side effect seen was reversible leucopenia in 70%. Eleven cases had stage IVa disease. Actuarial three year survival was 59% and disease free survival 54%. In the cases with tumours larger than 5 cm, actuarial survival at three years was 63% compared with three year survival in previously published series of apparently comparable cases not receiving chemotherapy of 25% in Pittsburgh¹² and 15% in Hanover.²⁹ Carr *et al* have reported encouraging results using larger doses given intra-arterially and in a combined regimen for patients with advanced (stages III and IVa) HCC.³⁰ Doxorubicin and *cis*-platinum were given before transplant, together with subcutaneous α interferon, followed by intravenous chemotherapy after transplantation. Of cases treated in this way, 82% were disease free at one year, compared with 36% of a similar group who did not have chemotherapy. The value of hepatic arterial chemoembolisation, carried out before OLT, has not been proved. Its use is strongly supported by Bismuth, who reported 55 cases treated in this way, followed by OLT and conventional intravenous chemotherapy.³¹ Tumour free three year survival in this series was 59% for HCC smaller than 3 cm, and 26% for larger lesions, not significantly different from results in other series where such treatment was not given. Our own experience with adjuvant chemotherapy has shown that when it is used prophylactically there was no delay in the timing of tumour recurrence, but there was possibly some benefit when it is given after recurrence has occurred.¹⁰

Assessment of patients

In assessing patients with HCC for OLT, imaging techniques are essential to define the size and extent of tumour involvement. These include ultrasound, computed tomography of abdomen, thorax, and brain, as well as hepatic angiography. All have limitations: computed tomography and ultrasound may fail to show the true size or number of lesions, or both particularly if the liver is cirrhotic, and computed tomography techniques often fail to detect vascular invasion and affected hilar lymph nodes.³²⁻³³ One study of ultrasound in cirrhotic patients showed a detection rate for tumour nodules smaller than 3 cm of 84%.³⁴ The accuracy varies between centres, however, and others have reported only 50% sensitivity with ultrasound.³⁵ Ultrasound is of limited value in showing the extent of tumour involvement within the liver parenchyma. Vascular or lymph node involvement are also often missed. Computed tomography is more accurate in the detection of tumour deposits. Another recent study has shown that for tumours smaller than 5 cm, the detection rate is 44% for ultrasound, and 69% for computed tomography.³² Enhanced computed tomography with arteriography or lipiodol are even more reliable methods, with sensitivities of 93% for lesions smaller than 2 cm and 82% for those smaller than 1 cm.³³⁻³⁶ Computed tomography remains the best method for the detection of extrahepatic metastases in the abdomen, lungs or brain.³⁷ Magnetic resonance imaging is less sensitive for intrahepatic lesions, but accurately delineates tumour margins and detects 85% of cases with vascular invasion.³³ Bone scanning is essential as bony metastases can occur without symptoms. Fractures or degenerative bone disease can cause confusion, particularly in the lumbar spine and ribs and in such instances a bone biopsy is necessary.

Liver biopsy should be avoided if the evidence for HCC is certain, as there is a small risk of implantation metastases along the course of the needle track. We have reported one

such case.¹⁰ During the assessment of any patient, it must be emphasised that the histological appearance of some metastatic liver tumours (notably renal adenocarcinoma), can mimic HCC. If doubt remains, imaging of other intra-abdominal organs is required to exclude the possibility of secondary hepatic spread from an extrahepatic primary. It has been suggested that staging laparotomy should be carried out routinely before OLT for HCC. Because the surgical mortality of OLT is higher in patients who have undergone such a laparotomy,⁷ we recommend that it should only be carried out in the context of a transplant operation, with another patient with non-malignant liver disease in reserve. If extrahepatic tumour is found, the abdomen is closed, and the donor liver is transplanted into the reserve patient.

Finally, there is the question of subtotal hepatic resection versus transplantation, assuming that both treatment modalities are available in a particular centre. The surgical mortality of subtotal hepatic resection in cirrhosis exceeds 30%,¹³⁻³⁸ the risk of complications depending upon the severity of liver disease and the number of segments resected.³⁹ Moreover, cirrhotic patients are at risk of liver failure after resection, and HCC usually recurs in the remaining liver.⁴⁰ Survival in patients with cirrhosis is consistently and significantly better after OLT than with resection for any tumour stage.¹³ Uni or binodular tumours smaller than 3 cm have a three year tumour free survival of 83% with OLT compared with 10% after resection.³¹ Small tumours on the background of well compensated cirrhosis may be more suitably treated by resection if there is poor cardiac reserve or other adverse risk factors for transplantation.

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