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Results of orthotopic liver transplantation for liver cirrhosis in the presence of incidental and/or undetected hepatocellular carcinoma and tumour characteristics

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Abstract Orthotopic liver transplantation (OLT) for liver cirrhosis in the presence of hepatocellular carcinoma (HCC) is based on tumour number and size. The high incidence of undetected HCC before OLT has been reported previously. The object of this work to report the results of OLT for liver cirrhosis in the presence of incidental and/or undetected HCC and tumour characteristics. From 1985 to 1996, 334 patients received OLT. Two groups of patients were studied; group 1 (G1) where HCC was diagnosed on radiological examination before OLT (n = 13, mean age 53.8 ± 8.1 years), and group 2 (G2), where HCC was diagnosed on pathological review (n = 13, mean age 53.3 ± 6.1 years). Indications for OLT were (G1/G2) hepatitis C = 6/8, hepatitis B = 5/2, alcoholic = 2/3. There was no statistically significant difference in α-foetoprotein levels between both groups. Pathological review showed 26 and 30 HCC with a mean size of 1.6 ± 0.8 and 1.6 ± 1.2 cm ($P > 0.05$) in G1 and G2, respectively. Tumour stagings were (G1/G2) stage I = 6/2, stage II = 4/6, stage III = 2/3, stage IVa = 1/2. We had two (G2) hospital and three (G1) later mortalities; none had HCC recurrence. The other patients are alive and recurrence free. Reinforced immunosuppression related to acute or chronic rejection treatment was not associated with HCC recurrence. The 5-year actuarial survival rates were 76% for G1 and 85% for G2 ($P > 0.05$). Our study revealed that long-term survival can be achieved with liver transplantation in the presence of HCC in carefully selected patients.

Key words Orthotopic liver transplantation · Hepatocellular carcinoma

Introduction

The treatment of hepatocellular carcinoma (HCC) is still controversial. Surgical treatment is often contraindicated due to poor liver function, tumour number and location and advanced tumour staging. Nonetheless, the surgical management debate continues over resection versus orthotopic liver transplantation (OLT). Most authors have based their indications on the degree of liver cell failure and tumour size and number. Nonetheless, actual imaging techniques fail to determine the exact number and size of HCC prior to OLT. The rationale for OLT under these conditions is debated. In this study we report the results of OLT for liver cirrhosis in the presence of incidentally discovered HCC before OLT or undetected HCC found on pathological review of explanted livers and tumour characteristics.

Materials and methods

From March 1985 to December 1996, 334 adult patients received 359 OLTs [4]. In 11 cases (3.3%), indication for OLT was the presence of unresectable HCC of large size. In 26 patients (7.8%),

Table 1 Patients' description and indications for orthotopic liver transplantation *(OLT)* in groups 1 and 2 (*M* male, *F* female, *α-FP* α-foetoprotein, *VHC* hepatitis C virus, *VHB* hepatitis B virus)

	Group 1 ($n = 13$)	Group 2 ($n = 13$)
Sex ratio (M/F)	12/1	12/1
Mean age (years)	53.8 ± 8.1	53.3 ± 6.1
α-FP (mean ± SD) ($P > 0.05$)	102 ± 198	7.1 ± 3.9
Indication for OLT		
VHC	6	8
VHB	5	2
Alcoholic	2	3

Table 2 Operative procedures

	Group 1 ($n = 13$)	Group 2 ($n = 13$)
TIPSS	2	3
Alcoholisation	7	0
Intraarterial chemoembolisation	2	0
OLT procedure		
Extracorporeal veno-venous shunt (Biomedicus)	1	3
Piggyback with temporary porto-caval shunt	10	9
Without venous bypass	2	1
Biliary reconstruction		
Choledococholedocostomy over T tube	12	11
Choledocojejunostomy (Roux en Y)	1	2
Associated procedures		
Splenectomy	1	1

24 men and 2 women of a mean age of 52.6 ± 7.2 years, OLT was carried out for liver cirrhosis in the presence of HCC (Table 1). Diagnosis of HCC was made either in the preoperative period by α-foetoprotein (α-FP) level analysis and radiological exploration with an abdominal CT scan (3 weeks after intraarterial lipiodol injection) and abdominal ultrasound, or after OLT on pathological review. This cohort of patients is thus divided into two groups according to the time of HCC diagnosis (pre- or postOLT).

In group 1 (G1, $n = 13$), the diagnosis of HCC was done before OLT; these HCC were not a contraindication for OLT according to their number and size. In ten cases in G1, the main indication for OLT was liver cirrhosis, and HCC could not be resected because of poor liver function. In the other three cases in G1, while the presence of cirrhosis did not contraindicate resection of HCC, OLT was done as a prophylactic treatment of HCC, which was considered a complication of cirrhosis. In such cases, the presence of HCC could be considered as an incidental discovery during the follow-up of the liver cirrhosis.

In group 2 (G2, $n = 13$), all patients were considered free from HCC on the preOLT investigations. HCC were thus undetected before OLT and were diagnosed on pathological review.

Fine-needle biopsy was done in seven cases in G1 before percutaneous transhepatic alcoholisation of their HCC, and two patients received intraarterial chemoembolisation as a bridge to OLT.

Operative OLT procedures were performed with an extracorporeal veno–venous shunt without preservation of the retrohepatic vena cava in our early transplants. Since 1991, the piggyback procedure, with temporary portocaval shunt, is our procedure of choice (Table 2).

Pathological review was done for all explanted livers. Serial sections were cut every 2–3 mm. Every macroscopically suspected nodule was isolated for histological examination. Every nodule was fixed in formalin, embedded in paraffin and stained with haematein–phloxin–safran, aniline blue and Perls iron. Only HCC are reported in this study; other lesions such as dysplasia or borderline lesions were excluded from our report.

All patients had cyclosporin-based immunosuppression associated with steroids starting at 500 mg perioperatively and rapidly tapering to 4 mg by postoperative day 30.

All patients were regularly followed for HCC recurrence by α-FP levels, chest X-ray, abdominal ultrasound and CT scan examinations.

Results are reported as mean ± SD, statistical analyses were done according to Student's-*t*-test and were considered significant for $P < 0.05$.

Results

Seven patients in G1 and all patients in G2 had normal α-FP levels (< 20 μg/l). The mean α-FP level was 102 ± 198 μg/L 2–658) in G1 and 7.1 ± 3.9 μg/l (3–17) in G2 ($P > 0.05$).

In G1, 11 patients were diagnosed with HCC by a lipiodol-positive CT scan, and in two cases diagnosis was made after pathological examination on fine-needle biopsies of suspected liver masses. The pathological review revealed the presence of 26 HCC with a mean tumour size of 1.6 ± 0.8 cm (0.2–3.5 cm). Eight patients had uninodular HCC, three patients had binodular HCC and in the other two patients there were four and eight HCC.

While no liver masses were recognised before OLT in G2, the pathological review revealed the presence of 30 tumours. Five patients had uninodular HCC, six patients had binodular HCC and in the other two patients there were three and ten HCC. The mean tumour size was 1.6 ± 1.2 cm (0.2–4.5 cm). The difference in tumour size in both groups was not statistically significant ($P > 0.05$).

Pathological review (Table 3) revealed totally encapsulated HCC in nine patients in G1 and five in G2. In two patients in each group there was a microvascular invasion. One patient in G1 and two patients in G2 had bilobar HCC. None had lymphatic or macrovascular HCC extension. In all cases, HCC was well differentiated. Pathological review revealed also that percutaneous transhepatic alcoholisation performed in seven patients in G1 allowed complete tumour destruction in four patients and partial tumour destruction in the other three patients. None of these patients developed tumour recurrence at the site of puncture. In two cases treated by intraarterial chemoembolisation there were one complete and one partial tumour destruction.

Table 3 Pathological criteria of patients in groups 1 and 2 (*HCC* hepatocellular carcinoma)

	Group 1 (n = 13)	Group 2 (n = 13)
Size (mean ± SD in cm)	1.6 ± 0.8	1.6 ± 1.2
Total numbers of HCC on pathological review	26	30
HCC numbers		
Patients with uninodular HCC	8	5
Patients with binodular HCC	3	6
Patients with three HCC	0	1
Patients with four HCC	1	0
Patients with eight HCC	1	0
Patients with ten HCC	0	1
Patients with encapsulated HCC	9	5
Patients with microvascular invasion	2	2
Patients with lymphatic invasion	0	0
Patients with bilobar HCC	1	2
HCC staging		
Stage I	6	2
Stage II	4	6
Stage III	2	3
Stage IVa	1	2

Table 4 Acute and chronic rejection episodes and fate of patients

	Group 1 (n = 13)	Group 2 (n = 13)
Acute rejection (number of patients)	5	6
Acute rejection (number of episodes)	5	6
Corticosteroid-resistant acute rejection (treated by OKT3)	4	0
Chronic rejection	1	0
Treatment of chronic rejection		
FK506 rescue (failure = 1)	1	0
Retransplantation	1	0

The pTNM stagings for HCC were in G1/G2: stage I = 6/2, stage II = 4/6, stage III = 2/3 and stage IVa = 1/2.

Reinforced immunosuppression was required for successful control of acute rejection episodes that occurred between postoperative days 8 and 180 and between 8, and 64 in G1 and G2, respectively. One patient from G1 had chronic rejection requiring FK506 rescue therapy, followed by liver retransplantation 5 months later (Table 4).

Two patients in G2 died in the postoperative period at 7 and 21 days from haemorrhagic and infectious complications. Three patients in G1 died within the first year postOLT (250–319 days), one from recurrent hepatitis B infection, one from infectious complications with liver abscess and one from Kaposi syndrome after liver retransplantation for chronic rejection. None of them had HCC recurrence. All the other patients are alive and recurrence free. The overall mean survival rate is 690 ± 547 days (7–1955). The mean survival rate was 751 ± 549 days and 629 ± 560 days in G1 and G2, respectively. Actuarial survival rates at 5 years were 76% in G1 and 85% in G2 (P = 0.57) (Fig. 1).

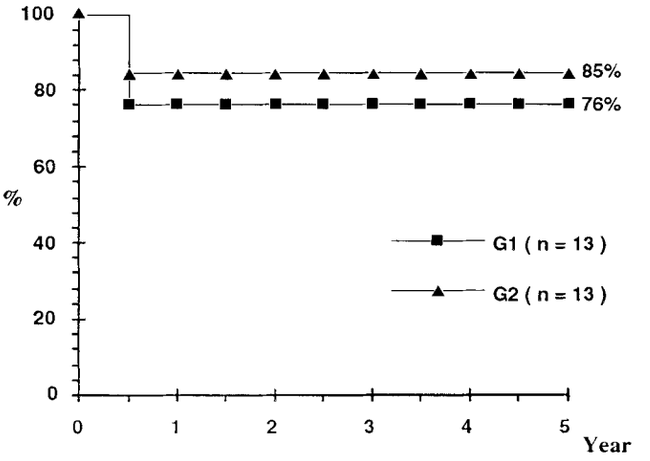

Fig. 1 Actuarial survival rate for group 1 (*G1*) and group 2 (*G2*)

Discussion

Curative treatment of HCC through liver resection or OLT is still controversial [13] . In early practice, OLT was considered as the appropriate treatment for HCC of large size and advanced stage. Nonetheless, due to high recurrence, there was a decline in the percentage of patients transplanted for HCC [14]. At present, OLT is usually proposed according to hepatic functional reserve. The presence of liver insufficiency usually contraindicates hepatic resection. OLT is also discussed in cases with favourable prognostic factors such as tumour number, location and staging [8, 11]. In practise, the organ shortage, recent management strategies and technical surgical advances make the decision between liver resection and OLT more than ever controversial [5, 10].

One of the main problems is the exact diagnosis of the number of HCC before OLT. In a previous study we reported the high incidence of undetected HCC on pathological review [1]. While these lesions were frequently of small size, they were usually numerous. The frequency of undetected HCC before OLT is widely discrepant, ranging from 7% to > 60% [6, 15] . In a recent study of adult cirrhotic liver explants, the prevelance of undetected HCC was 17.5% and, as in our series, with a higher incidence in men [12]. In our series, 13 patients (50%) were thought HCC free before OLT. Of the 56 liver masses diagnosed as HCC on pathological review, only 20 masses (35.7%) were truly identified as HCC on the preoperative examinations, the other 36 HCC (64.3%) were undetected. These findings confirm that

the exact number of HCC cannot be identified accurately in patients with liver cirrhosis who are candidates for OLT.

In other reports it was demonstrated that the best results of OLT for HCC are obtained for small uni- or binodular lesions [2, 7]. Nevertheless, diagnosis of HCC by preoperative diagnostic imaging is not easy. In our series, four patients had more than three HCC, two of them had eight and ten tumours; none had HCC recurrence.

Prognostic factors for HCC-related survival after OLT were recently reported, showing that vascular invasion is the most significant factor related to tumour recurrence [3]. Unsatisfactory results of OLT could also be explained by undetected extrahepatic extension [9]. In our series, only 15.4% had microvascular invasion and 11.5% had bilobar HCC. The absence of poor prognostic factors related to HCC and the small tumour size noted in both groups contributed to the good outcome. Reinforcement of the immunosuppression regimen by the use of steroids bolus, orthoclone or FK506 was not associated with HCC recurrence.

In conclusion, our study revealed that preoperative diagnostic tools did not allow accurate diagnosis of the exact number of HCC. These findings make the reliability of OLT according to the number of HCC detected on preoperative examination controversial. Good results can be achieved in carefully selected patients when HCC is not the main indication for OLT (uni- or binodular lesions, absence of bilobar localisation, absence of vascular invasion). In consequence, considering tumour and non-tumour risk factors, HCC with favourable tumour staging should not be considered a contraindication for OLT in patients with liver cirrhosis.

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