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W. O. Bechstein
G. Blumhardt
H. Lobeck
H. Keck
H. P. Lemmens
M. Knoop
P. Neuhaus

Selection of small hepatocellular carcinoma improves long-term results of hepatic transplantation for malignancy

W. O. Bechstein (✉) · G. Blumhardt
H. Keck · H. P. Lemmens · M. Knoop
P. Neuhaus
Chirurgische Klinik und Poliklinik,
Universitätsklinikum Rudolf Virchow
der Freien Universität Berlin,
Augustenburger Platz 1,
D-13353 Berlin, Germany

H. Lobeck
Institut für Pathologie,
Universitätsklinikum Rudolf Virchow
der Freien Universität,
Augustenburger Platz 1,
D-13353 Berlin, Germany

Abstract Liver transplantation for advanced hepatocellular carcinoma is often followed by early tumour recurrence and death. At the beginning of the liver transplantation programme at Berlin Virchow we decided to offer liver transplantation only to patients with solitary tumours not exceeding a maximum diameter of 5 cm or to patients with two or three tumour nodes with a maximum diameter of 4 cm. From September 1988 to October 1993 435 liver transplants were performed in 403 patients. Of these, 32 patients (8%) had a histologically confirmed hepatocellular carcinoma (29 males, 3 females, median age 56 years). The overall actuarial survival according to Kaplan-Meier for the whole series of 32 patients with hepatocellular carcinoma was 82%, 78%, and 78% at 1, 2 and 3 years, respectively. Tumour size alone did not seem to be a relevant factor when comparing patients with tumours up to or larger than 3 cm in diameter. Patients with solitary tumours had a better prognosis than patients with multiple tumours. The largest difference was found between patients with stage I–III (UICC) tumours and those with stage IVA tumours: 1-, 2- and 3-year survival rates were 89% throughout in the former group, while the corresponding figures for patients with stage IVA tumours were 63%, 47% and 47%. Efforts should be made to identify stage IVA tumours preoperatively in order to use the precious resource of scarce donor livers in an optimal way.

Key words Hepatocellular carcinoma · Liver transplantation Oncology

Introduction

Results of liver transplantation for advanced hepatocellular carcinoma are generally poor with early recurrence and limited survival [4]. Since the beginning of our liver transplantation programme we have chosen to offer transplantation only to patients with preoperatively known solitary tumours of no more than 5 cm in maximum diameter or patients with up to three tumour nodules with the largest tumour not exceeding 4 cm in maximum diameter [5]. After more than 4 years of following this policy, we reviewed our experience with transplantation for small hepatocellular carcinoma.

Patients and methods

From September 1988 until October 1993 we performed 435 orthotopic liver transplantations in 403 patients. Of these, 32 pa-

tients (8%) had a histologically confirmed hepatocellular carcinoma. Only one of these appeared to be of the fibrolamellar type. There were 29 male and 3 female patients with a median age of 56 years (range 40–65 years). Liver transplantation was carried out according to standardized techniques with routine use of veno-venous bypass and side-to-side choledochocholedochostomy. Immunosuppression consisted of quadruple induction therapy with ATG (Fresenius, Oberursel, Germany), cyclosporine, azathioprine and prednisolone, which was carried on as triple therapy in 19 patients. In six patients immunosuppression was based on tacrolimus (FK 506, Fujisawa, Munich, Germany) and steroids, while a further seven patients received triple therapy supplemented with a monoclonal anti-interleukin-2 antibody (BT 563, Biotest, Dreieich, Germany), during induction. Follow-up was complete on all patients. The rules of the International Union against Cancer with regard to staging of hepatocellular carcinoma were followed according to the fourth edition of the TNM classification system [3].

Preoperatively, 20/32 patients were found to have an elevated alpha-fetoprotein (AFP) ($\geqq$ 10 ng/ml), the median AFP level was 175 ng/ml (range 10–16, 460 ng/ml). The distribution of associated liver disease was as follows: HCV cirrhosis 10, HBV cirrhosis 9, NANB cirrhosis 7, alcoholic cirrhosis 4, haemochromatosis 1, no cirrhosis 1.

Actuarial survivals were calculated according to Kaplan-Meier using SPSS.

Results

Histopathological examination of hepatectomy specimens revealed solitary tumours in 13 patients, two or three tumours in 15 patients and more than three tumour nodes in 4 patients. The maximum tumour diameter in all of these patients was 23 mm (range 5–70 mm). The TNM classification of the tumours (pT) was distributed as follows: pT1, 9 cases; pT2, 7 cases; pT3, 7 cases; pT4, 8 cases in the remaining case, the TNM classification by microscopic criteria is still pending). Since there were no patients with lymphnode or distant metastases at the time of operation, there were eight cases of TNM stage IVA tumours, while the other stages (I–III) were distributed according to the pT classification of the primary tumour (see above). Grading of the tumours revealed 13 well differentiated, 13 moderately differentiated, and 5 poorly differentiated hepatocellular carcinomas; in one case grading is still pending.

During follow-up, six patients died, four of them with recurrence at 5, 6, 11 and 17 months post-transplant, and two patients died without recurrence (autopsy-proven) at 3 and 15 months post-transplant. The overall actuarial survival according to Kaplan-Meier was 82%, 78% and 78% at 1, 2 and 3 years, respectively (Fig. 1).

Regarding tumour size alone as a potential prognostic factor, no significant differences were detected between patients with tumours of up to 3 cm in size and those patients with tumours greater than 3 cm in maximum diameter. For patients with tumours up to 3 cm 1-, 2- and 3-year actuarial survival rates were 82%, 75% and 75%, while the corresponding figures for patients with tumours greater than 3 cm were 82% throughout (Fig. 2).

A greater difference was observed when patients with solitary tumours were compared with those with more than one tumour. For patients with solitary tumours 1-, 2-

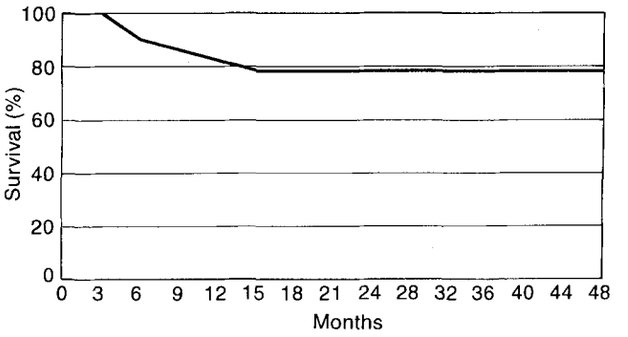

Fig. 1 Actuarial survival for 32 patients with hepatocellular carcinoma who underwent liver transplantation at Berlin Virchow between January 1989 and October 1993

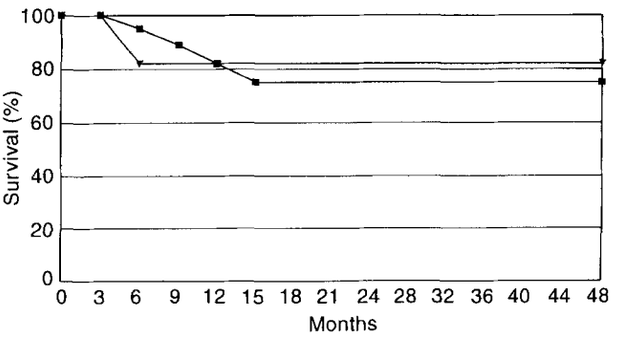

Fig. 2 Actuarial survival after liver transplantation according to size of hepatocellular carcinoma comparing patients with tumors up to 3 cm (■, $n = 21$) and those with tumors > 3 cm (▼, $n = 11$)

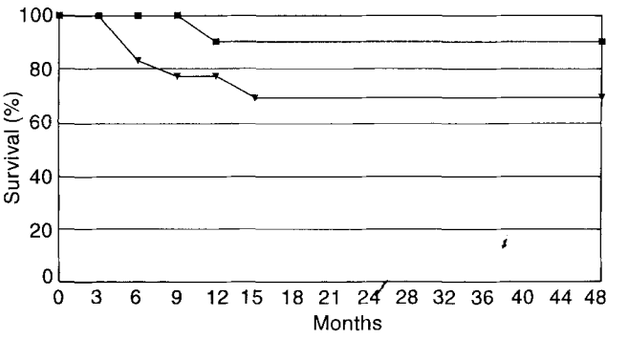

Fig. 3 Actuarial survival after liver transplantation according to the number of tumour nodes of hepatocellular carcinoma comparing patients with solitary tumors (■, $n = 13$) and those with multiple tumors (▼, $n = 19$)

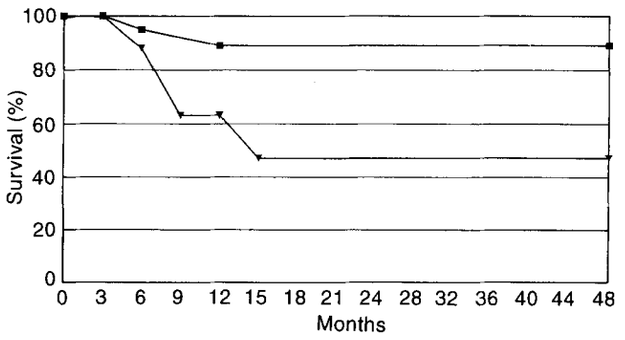

Fig. 4 Actuarial survival after liver transplantation according to TNM stage (UICC) comparing patients with tumour stage I–III hepatocellular carcinomas (■, $n = 23$) and those with tumour stage IVa (▼, $n = 8$) (one case of TNM staging pending)

and 3-year actuarial survival rates were 90% throughout, while the corresponding figures for patients with multiple tumours were 76%, 69% and 69% (Fig. 3).

The greatest difference was found between patients with tumour stage I–III and those with tumour stage IVA. For patients with stage I–III tumours 1-, 2- and 3-year actuarial survival rates were 89% throughout, whilst the corresponding figures for patients with stage IVa tumours were 63%, 47% and 47% (Fig. 4).

Discussion

Gennari et al. have stated recently that "the transplant surgeon's attitude toward a patient bearing an otherwise unresectable liver cancer has changed from an irrational optimism to an equally unwarranted mistrust in OLT as having a good potential for curing cancer" [2]. In their series of 22 transplants in patients with small hepatocellular carcinoma (the largest tumour diameter being 51 mm) they reported 82% of the patients alive without evidence of recurrence after a median follow-up of 11 months. Furthermore, as Bismuth et al. have pointed out, in their experience patients with uninodular or binodular hepatocellular carcinoma not exceeding 3 cm in maximum diameter have a better prognosis after transplantation when compared with a similar group of patients with identical tumour characteristics who had undergone resection [1]. In our series of patients selected for a preoperatively known tumour diameter not exceeding 5 cm we were unable to verify a significant difference between patients with tumours up to or larger than 3 cm.

The previous experience of the Pichlmayr group had drawn our attention to the importance of the TNM system in classifying patients with hepatocellular carcinoma [4]. Our own experience confirms that patients with stage IVA have the worst prognosis after liver transplantation. Stage IVA has already been reached in the presence of multiple tumours in more than one lobe or tumours involving a major branch of the portal or hepatic vein [3]. Thus, in our opinion, efforts should be made preoperatively to identify these patients before liver transplantation and offer them alternative treatments, e.g. lipiodol chemoembolization.

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