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Recurrence-free survival after liver transplantation for small hepatocellular carcinoma

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Abstract Recurrence-free survival (RFS) in patients with small hepatocellular carcinoma (HCC) after orthotopic liver transplantation (OLT) was analyzed. From 1988 until 1996, 725 OLTs were performed in 669 patients. In 52 adults, HCC was confirmed histologically. OLT was limited to patients with small (< 5 cm) HCC with a maximum number of three nodules. Actuarial survival for these 52 patients at 1 and 5 years is 88% and 71%. RFS was defined as time until death without recurrence, time until follow up with a diagnosis of recurrence, or, in patients without recurrence, time of last follow up. Overall, the 5-year RFS was 60%. Five-year RFS was less for bilobar compared to unilobar tumors (36% vs 70%), less for stage IVa tumors (UICC) compared to stage I–III tumors (17% vs 71%), and less for multiple compared to solitary tumors (54% vs 67%). In conclusion, potential cure may be achieved in more than 50% of all transplanted patients.

Key words Hepatocellular carcinoma · Liver transplantation · Recurrence

Introduction

Today, it is agreed that total hepatectomy and subsequent liver transplantation may be a suitable therapeutic strategy in the treatment of small hepatocellular carcinoma (HCC) in cirrhosis [3, 4, 7, 9]. This opinion is mostly derived from crude survival data while in oncology a more appropriate analysis should focus on recurrence-free survival (RFS). The purpose of this study was, therefore, to analyze determinants of RFS in patients with HCC who had undergone liver transplantation.

Materials and methods

From September 1988 until February 1996, 725 liver transplants were carried out in 669 patients. The retransplantation rate was thus 8.4%. Two patients from this series, both with benign liver disease had undergone their primary transplant at different institutions and had been referred for retransplantation. These latter were excluded from the further analysis. In cases of suspected HCC, candidacy for liver transplantation was limited to patients with small HCC with either a solitary tumor not exceeding 5 cm in diameter or up to three nodules with the largest tumor no greater than 4 cm. All patients underwent percutaneous ultrasound, contrast-enhanced CT scans, and angiography as part of their preoperative evaluation. Liver transplantation was carried out exclusively orthotopically according to standard techniques with routine use of venovenous bypass and side-to-side choledochocholedochostomy in the mayority of cases. In 52 adult cases HCC was histologically confirmed in the excised liver. These were 46 males and 6 females with a median age of 55 years ranging from 40 to 73 years. Underlying liver diseases were hepatitis C virus-related cirrhosis ($n = 22$), hepatitis B virus-related cirrhosis ($n = 14$), NANBNC cirrhosis ($n = 3$), alcoholic cirrhosis ($n = 7$), and others ($n = 6$). In 15 out of 52 cases (29%), the tumor was not diagnosed until the excised liver was examined histopathologically. Tumor staging was carried out according to the TNM staging system (UICC) [6].

Follow up in surviving patients was at least 18 months, the median follow up being 44 months and ranging up to 8.4 years. RFS was defined as time until death without recurrence, time until follow up with a diagnosis of recurrence, or, in patients without recurrence, time of last follow up. Recurrence was detected in alpha-fetoprotein (AFP)-positive cases by a rise in AFP and in all patients by imaging techniques appropriate to the suspected site of recurrence. Actuarial survival was analyzed according to the Kaplan-Meier life table method using the SPSS package. Differences between groups were compared using the Wilcoxon (Gehan) statistic.

Results

As of 25 August 1997, 36 out of 52 patients with small HCC after liver transplantation were still alive, yielding an actual survival of 69%. The actuarial 1- and 5-year survival of these 52 patients was 88% and 71%, respectively. This was significantly less than the 1- and 5-year survival of 615 patients without HCC transplanted during the same period being 91% and 84%, respectively ($P < 0.05$) (Fig.). The causes of death in the 16 out of 52 patients with HCC were tumor recurrence in eight cases (at 3, 6, 7, 11, 17, 56, 61, and 73 months), fatal HBV recurrence in two cases, de novo malignancy in three cases (pharyngeal cancer, esophageal cancer, and gastric cancer), and one each of multiple organ failure syndrome, hemorrhage, and sudden cardiac death. Currently, 3 patients are alive with tumor recurrence at 46, 80, and 85 months following their transplant. Initial sites of tumor recurrence were the liver graft (k = 4) and lung ($n = 4$), followed by bone ($n = 2$) and abdominal wall ($n = 1$). The total RFS in these 52 patients was 88% at 1 year and 60% at 5 years (Table 1). Five-year RFS was less in patients with incidental tumors compared to preoperatively known tumors (53% versus 64%) (Fig. 2), less for bilobar tumors compared to unilobar tumors (36% versus 70%), less for multiple compared to solitary tumors (54% versus 68%), and less for stage IVa tumors compared to stage I–III tumors (17% versus 71%) (Fig. 3). None of these differences were statistically significant in univariate analysis ($P > 0.05$) (Table 1).

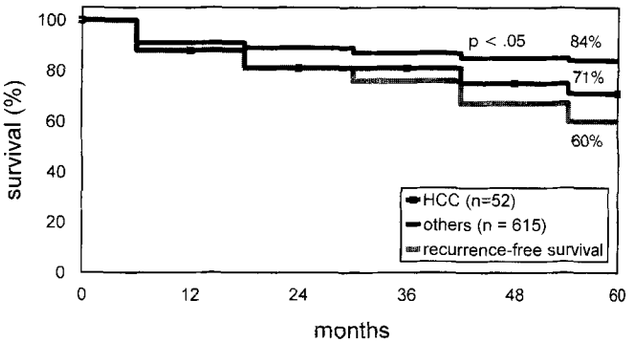

Fig. 1 Actuarial survival after liver transplantation: 5-year survival for 615 patients without hepatocellular carcinoma *(HCC)* and 52 patients with HCC ($P < 0.05$). The recurrence-free survival (RFS) of 52 patients with HCC is depicted by the *grey line*. Virchow Clinic Berlin, September 1988–February 1996; follow up August 1997

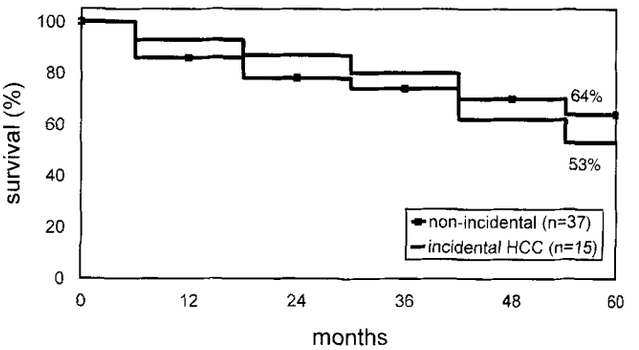

Fig. 2 RFS for 37 patients with preoperatively know HCC versus 15 patients with incidental HCC. Virchow Clinic Berlin, September 1988–February 1996; follow up August 1997

Discussion

In this series of patients we updated our previous experience with selection of small HCC for liver transplantation [1]. Perhaps surprisingly, crude survival and RFS

Table 1 Actuarial survival (S) and recurrence-free survival (RFS) in 52 patients with small hepatocellular carcinoma after liver transplantation

	One-year S	One-year RFS	Five-year S	Five-year RFS
Total series ($n = 52$)	88%	88%	71%	60%
Incidental tumor ($n = 15$)	93%	93%	60%	53%
Preoperatively known tumor ($n = 37$)	86%	86%	78%	64%
Unilobar tumor ($n = 35$)[a]	91%	91%	79%	70%
Bilobar tumor ($n = 13$)	85%	85%	38%	36%
Solitary tumor ($n = 23$)	87%	87%	76%	68%
Multiple tumor ($n = 29$)	90%	90%	67%	54%
Stage I–III tumor ($n = 35$)[b]	91%	91%	79%	71%
Stage IVa tumor ($n = 15$)	80%	80%	44%	17%

[a] In four cases, lobar involvement could not be adequately assessed

[b] In two cases, TNM staging could not be adequately assessed

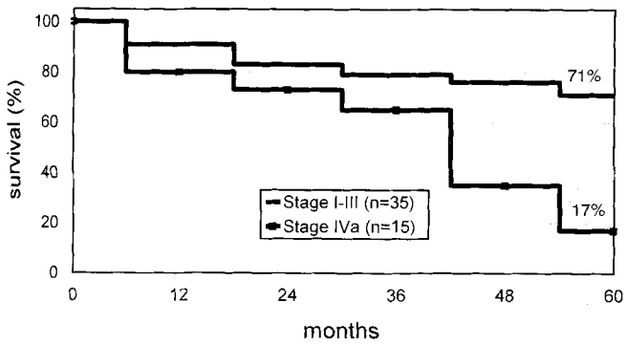

Fig. 3 RFS for 35 patients with UICC stage I–III tumors vs 15 patients with UICC stage IVa tumors. Virchow Clinic Berlin, September 1988–February 1996; follow up August 1997

during the 1st year after transplantation were virtually identical for the whole series and in analysis of subcategories as well. This may be explained by two factors. Firstly, selection of small HCC according to our criteria, listing only patients with a solitary tumor of no more than 5 cm diameter or a maximum of three nodules where the biggest tumor did not exceed 4 cm, helps to avoid early death due to tumor recurrence within the 1st year in the majority of cases. Even so, 4 out of 52 patients died within 1 year following the transplant due to tumor recurrence. Secondly, there were only two other fatal cases with multiple organ failure syndrome and hemorrhagic shock, both within the first 2 months following the transplant. Thus, the expected difference of the RFS being lower than the crude survival only becomes apparent in the whole series beyond the 2nd year. Also, perhaps surprisingly, was the fact that 3 patients died without evidence of recurrence, but with de novo solid tumors such as pharyngeal carcinoma, esophageal carcinoma, and gastric carcinoma. Two of these 3 patients had suffered previously from alcoholic liver disease so the development of these cancers is perhaps better explained as a consequence of their previous alcohol abuse than as a consequence of long-term immunosuppression. Overall, 8 of 16 patients died from causes other than recurrent tumor. In the total series of 52 patients, actuarial RFS of 60% at 5 years could be achieved. While the actuarial method often overestimates long-term results, it should be emphasized that 14 of these 52 patients have now been followed for longer than 5 years. The patterns of the initial site of tumor recurrence, with the predominant sites being the liver graft itself and the lung in our series, are in accordance with other reports in the literature [5].

As has been reported previously, survival and RFS after liver transplantation is related to tumor stage. Among the common determinants of long-term survival are the size of the tumor, number of tumor nodes, lobar distribution of tumor, and the stage according to the TNM system, with the importance of the latter three criteria being reflected in our own experience [1, 3, 4, 7, 9]. Surprisingly, patients with incidental tumors – and these accounted for 29% of our cases – showed a lower 5-year RFS than patients with preoperatively known tumors. This may be explained by the fact that 7 out of 15 patients with incidental tumor presented with stage IVa tumor because of small, bilobar, multicentric growth. Despite undeniable advances in hepatic imaging techniques, the rate of incidental tumors in excised cirrhotic livers in a liver transplant population is still high. Colleda et al. reported 13 out of 63 patients (21%) with incidental HCC in their series [4]. In another series of 80 consecutive liver explants, Mion et al. found a prevalence of 17.5% HCC with a mean size of 11.6 mm [8]. Furthermore, these HCC nodules were frequently found together with high-grade dysplastic nodules. While larger lesions nowadays seldom remain undetected even in cirrhotic livers, smaller lesions still escape sophisticated imaging techniques. In a series of 40 patients undergoing liver transplantation, Spreaficio et al. reported diagnostic sensitivity rates of 58% for iodized oil CT, 67% for digital subtraction angiography, and 85% for CTAP with regard to the number of nodules detected when compared with the explanted specimen [11]. Thus, even with CTAP, 15% of lesions went undetected. Using contrast-enhanced CT and percutaneous ultrasound alone, Shapiro et al. reported, in a series of 21 patients, a combined lesion detection sensitivity of 60% and patient detection sensitivity of 80% [10]. In other words, in their series 20% of patients and 40% of lesions went undetected before liver transplantation. While lipiodol injection may help to identify malignant lesions in the preoperative work-up, it may also help to detect malignant lesions in the explanted liver [2].

Using selection criteria similar to ours, Mazzaferro et al. reported a 92% survival and 85% RFS after 4 years in 35 patients whose pathological tumor staging did not exceed the predefined limits of one tumor up to 5 cm or three nodules up to 3 cm. However, in 13 out of 48 patients (27%) these predefined limits were found to be exceeded. In these latter patients, survival and RFS at 4 years was 59% and 50%, respectively [7].

Since liver cirrhosis is a precancerous condition, decision making for transplantation should take into account the possible development of HCC. Perhaps one has to accept the fact that small lesions will always go undetected to a certain extent. Since bilobar, multicentric growth will automatically put a patient into the UICC stage IVa group, the UICC staging is still of value for the postoperative classification, but has its limitations in the preoperative decision making. Certainly, larger detectable bilobar lesions and those with infiltration of major vessels, such as identifiable portal vein branches or hepatic veins, constituting a stage IVa lesion do not seem to be good indications for liver trans-

plantation. On the other hand, simple criteria such as ours or the ones proposed by Mazzaferro et al. help in decision making and may provide potential cure with a 5-year RFS of more than half the transplanted patients with HCC.

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