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Liver transplantation for hepatocellular carcinoma: clinical results and future aspects*

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Summary. The treatment of unresectable hepatocellular carcinoma (HCC) by liver transplantation remains controversial. In our series, the 5-year survival value for 87 patients who underwent transplantations between 1972 and 1990 was 19.6%. There was no difference in the long-term survival of patients who had underlying cirrhosis and those who did not. In patients with early-stage tumors the long-term prognosis was improved, the 5-year survival in stage II disease being 55.6% according to UICC criteria. Even in some cases of more advanced tumour stage, good long-term results were obtained. In a review of the recent literature, we evaluated prognostic factors to work out criteria for a more differentiated indication for liver transplantation. Resection of increased radicality – which will keep its place as the therapy of choice – and transplantation should be performed complementarily. Further developments will reveal the value of multimodal therapeutic strategies, including chemo-embolisation, chemotherapy and immunotherapy.

Introduction

At present, the treatment of choice for hepatocellular carcinoma (HCC) is surgical resection by partial hepatectomy. The long-term prognosis for resected cases is significantly better than that either for the natural course or following non-surgical therapy [10, 11]. Due to epidemiological differences, the incidence of underlying cirrhosis is much higher in Asia (70%–90%) than in Western populations (below 40%). For this reason, differences in perioperative mortality and in 5-year survival values amounting to 13%–28% and 15%–26%, respectively, in Asian groups [8, 9, 20, 23] and 9%–17% and 32%–37%, respectively, in Western series [1, 3, 16, 30] have been reported. In patients with subclinical or small cancers (below 5 or 2 cm), increases in resectability and reductions in operative mortality achieved by segmental resection or subsegmentectomy have led to an improvement in the 5-year survival to 48%–84.6% [19, 21, 36].

Despite recent developments in diagnostic imaging methods and surgical techniques, a majority of cases of HCC are unresectable due to anatomical or functional reasons caused by advanced tumours with bilateral or central localisation or underlying cirrhosis. In these patients, total hepatectomy with subsequent liver transplantation may be indicated [25], although its use in patients with hepatobiliary malignancy remains controversial. The arguments favouring this treatment include a lack of other efficient therapeutic options, a low operative risk and the achievement of significant palliation in many subjects and a possible cure of cancer in at least some patients. The arguments against such therapy are: most cases involve advanced tumours along with the problem of detecting micrometastases, inadequate knowledge about prognostic factors and specific biological behaviour under the influence of immunosuppression, early tumour recurrence in the majority of patients and the limited availability of donor organs. During recent years, this controversy has led to a general agreement about a more differentiated and restricted indication for transplantation in hepatobiliary malignancy. This overview reveals our present experience and strategy as well as the recent results of other study groups in liver transplantation as a treatment for HCC.

Review of the literature and our own results

In this survey of the literature (Table 1), 301 reported cases of liver transplantation in HCC were found [6, 12, 15, 18, 22, 24, 28, 38].

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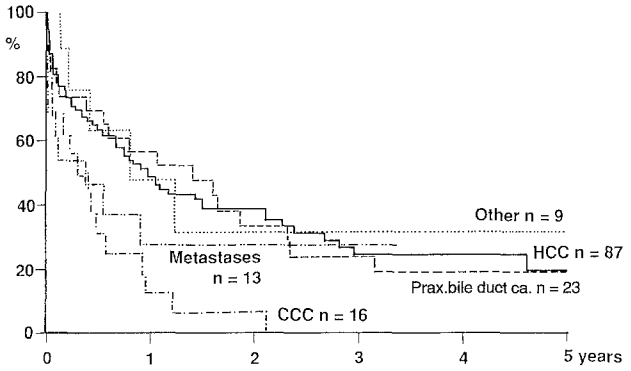

Fig. 1. Actuarial survival of 148 patients following liver transplantation for different hepatobiliary malignancies (1975–1990). *HCC*, Hepatocellular carcinoma; *CCC*, cholangiocellular carcinoma

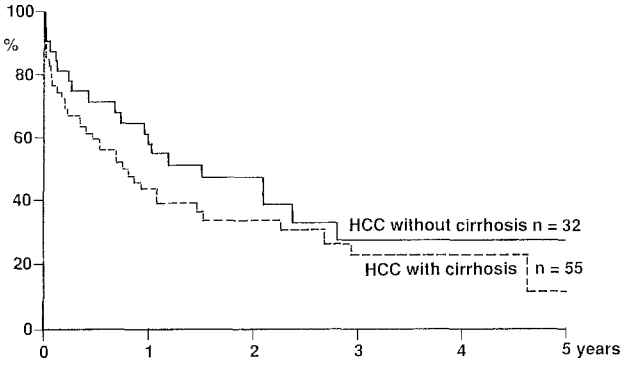

Fig. 2. Actuarial survival of 87 patients following liver transplantation for HCC (1975–1990)

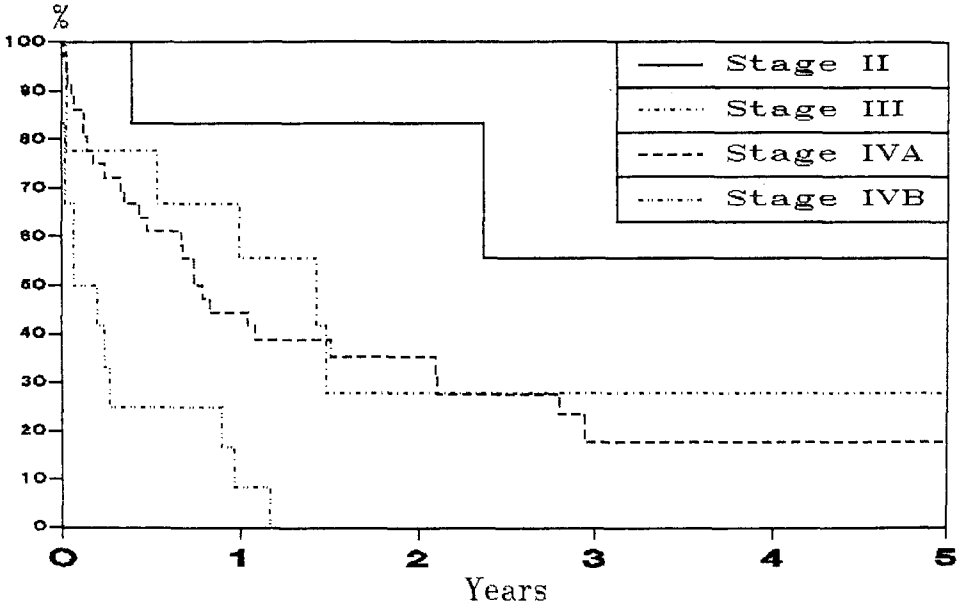

Fig. 3. Actuarial survival of 65 patients following liver transplantation for HCC as plotted according to tumor stage [28]. *Stage II*, $n = 6$; *stage III*, $n = 9$; *stage IVA*, $n = 36$; *stage IVB*, $n = 12$

Table 1. Liver transplantation for HCC: a review of the literature

Center, reference, period involved	Patients (*n*)	Overall survival			
		1-year	3-year	5-year	Median
Vienna, Funovics et al. [12], 1977–1986	26				2.96 months
Cambridge, O'Grady et al. [22], May 1968–April 1987	50				
Paris, Bismuth et al. [6], October 1985–March 1989	30	81%			
Boston, Jenkins et al. [18], July 1983–November 1987	88				
Hannover, Ringe et al. [28], November 1972–December 1988	65			22.8%	9.4 months
Pittsburgh, Yokoyama, et al. [38], January 1980–December 1988	80	64%	37%	37%	
Birmingham, Ismail et al. [15], January 1982–April 1989	21				11.5 months
Los Angeles, Olthoff et al. [24], January 1984–December 1989	16	40%			

From January 1975 to December 1990, 148 patients with hepatobiliary malignancy underwent liver transplantation in Hannover. The 5-year survival value was 18.6% (median survival, 9.7 months). The prognosis was worst in cholangiocellular carcinoma (CCC), with the median survival being 3.65 months, and in liver metastases (4.5 months; Fig. 1). 87 patients (58.8%) had HCC, 32 with no underlying cirrhosis (HCC–) – 6 with the fibrolamellar variant – and 55 with liver cirrhosis (HCC+). Whereas for ordinary HCC, particularly that associated with cirrhosis, the peak age of patients was found in the fifth and sixth decades, the fibrolamellar variant predominated in patients aged below 30 years. Six patients were transplanted due to intrahepatic tumour recurrence following partial hepatectomy.

The patients with HCC attained an overall 5-year survival value of 19.6%, with the median survival being 11.6 months. No significant difference was observed between HCC– and HCC+ patients (Fig. 2), with the 5-year survival values being 27.5% and 11.5%, respectively, and the median survival being 18.1 and 8.8 months, respectively. However, the 30-day mortality was higher in cir-

Table 2. Prognostic factors in HCC

Factor	Favourable	Unfavourable
Histological type	Fibrolamellar variant	
Differentiation	High-grade	Low-grade
Stage	Solitary Small No vascular invasion No regional lymph node metastases No distant metastases	Multiple-diffuse Large Vascular invasion/tumor thrombosis Regional lymph node metastases Intrahepatic metastases

rhotic patients (23.7% vs 12.5%). In the FLC variant, the best median survival was seen (28.4 months). In an earlier analysis [28], a comparison of subgroups according to the TNM classification (Fig. 3) revealed a significant improvement in outcome in stage II patients ($n = 6$), with the 5-year survival value being 55.6%. The majority of patients were transplanted in stage III ($n = 9$) and stage IVA ($n = 36$), with the median survival being 17.1 and 8.9 months, respectively. In stage IVB with distant metastases ($n = 12$), the median survival was only 0.9 months (maximum, 13.9 months). At present, three long-term survivors (9–15 years) have survived for more than 5 years. The longest survival was observed in a patient with a solitary stage II HCC, who was transplanted in 1975 and resected for pulmonary metastasis after 35 months and who is currently alive and shows no sign of tumour recurrence.

Neither the age nor the sex of the recipient nor the kind of immunosuppression alone had any significant influence on the outcome. The level of preoperative alpha-fetoprotein (AFP) did not correlate with the postoperative outcome. However, a decrease in AFP levels after transplantation and reappearance – generally within 3–4 months – was indicative of tumour recurrence.

Discussion

Liver transplantation has become an accepted treatment for end-stage liver disease. At present there is no doubt that chronic or acute hepatic failure due to benign disease has priority in most transplant programmes. This can be explained by the large number of potential recipients in this particular category as well as the usually good long-term prognosis for most of these patients [4]. However, the first successful liver transplantations were performed in patients with non-resectable malignant tumours [7, 32]. This success was in part related to the better survival values obtained during the early postoperative period, probably due to the more favourable general condition of patients with liver malignancy. In spite of the overall progress made in this field, the long-term results have generally been disappointing. Although a few long-term survivors have been observed, the majority of tumours recur within 1 or 2 years after transplantation. However, liver transplantation for the treatment of HCC should not be avoided but may be used with special indications. In advanced tumours, it can be stated that excellent individual palliation is an argument for transplantation in malignancy [25]. The limitation of donor organs has prompted the development of the technique of split-liver transplantation [26]. Therefore, criteria and prognostic factors (Table 2) for the selection of adequate recipients for liver transplantation are required.

The aim of our retrospective analysis was to determine the favourable and unfavourable prognostic factors, with special emphasis on tumour classification and staging according to the TNM system [14]. The results clearly point out the practicability and relevance of clinicopathological tumour staging. For this reason, the better outcome of patients whose tumours were diagnosed coincidentally during transplantation for other liver diseases [17] might be explained by an early tumour stage. In terms of tumour histology, the fibrolamellar variant of HCC may be associated with a more favourable prognosis as previously reported elsewhere [2, 33, 37]. A critical analysis of our data reveals that this may again be true only for early tumour stages. O'Grady et al. [22] showed that the interval between transplantation and death from recurrence was significantly longer in patients with a well-differentiated tumour than in those with a moderately or poorly differentiated lesion. In our series, no difference was seen between patients who had underlying cirrhosis and those who did not, in agreement with the results of Bismuth et al. [6] and O'Grady et al. [22]. Ismail et al. [15] found such a difference in 10 patients with cirrhosis among a total of 28 patients with HCC, which was due to the known higher mortality of these patients within 30 days of transplantation [6, 22, 28, 29]. Bismuth et al. [6] reported a reduced (no significance) 2-year survival for patients with plurinodular tumours as compared with tumours with one or two nodules or with lesions measuring more than 5 cm in diameter. Yokoyama et al. [38] found a significantly increased recurrence rate for tumours measuring more than 5 cm in diameter, for multiple as compared with single lesions and for cases of vascular invasion. For lymph node metastases, this was a non-significant trend. All of these results correlate well with our finding of a better prognosis for T2, N0 M0 stages II and III, respectively. However, controlled studies comparing partial hepatectomy and liver transplantation are needed to reveal whether liver transplantation in this tumour stage may provide a more radical approach along with a better long-term prognosis. In the small series of Olthoff et al. [24], which could not be evaluated statistically, the presence of cirrhosis, hepatitis B antigen, tumour size or number, vascular or serosal invasion or positive hilar lymph nodes had no significant effect on tumour recurrence or survival. O'Grady et al. [22] demonstrated the possible favourable influence of immunosuppression performed with cyclosporin as compared with the combination of prednisolone and azathioprine.

For these reasons, it is evident that exact staging of the tumour by thorough diagnostic imaging is a prerequisite before transplantation. The value of performing an explorative laparotomy in advanced HCC to rule out extrahepatic tumour spread is more doubtful. In our experience, which was confirmed by the results obtained by the Cambridge group [22], the procedure failed to predict the outcome of transplantation because the occurrence of an inter-

Table 3. Current possibilities of adjuvant therapy in combination with liver transplantation for the treatment of HCC

1. Preoperative chemo-embolisation (1–3 treatments)
2. Neoadjuvant chemotherapy with doxorubicin (Adriamycin) at a weekly dose of 20 mg/m^2 or combination treatment
3. Perioperative chemotherapy (low-dose) with weekly doses of 10 mg/m^2 doxorubicin or 20 mg/m^2 epirubicin for the prevention of micrometastases
4. Immunotherapy using antibodies (anti-tumour-mAb, [^{131}I]-anti-ferritin), cells (NK/LAK cells) and cytokines

val of several months between staging laparotomy and transplantation and the possibility of tumour progression in the meantime cannot always be avoided. Furthermore, micrometastases cannot be detected during laparotomy. If the indication for transplantation is shifted to earlier tumour stages, explorative laparotomy will probably obtain new importance for the determination of tumour resectability.

Future aspects

Because 50% of our resected and transplanted HCC patients showed tumour stages IVA and IVB as determined according to UICC criteria, the first requirement for early tumour detection is the systemic screening of high-risk groups, which has previously been realised in Asia [23, 36]. Of course, conventional resection will keep its place as the treatment of choice. Improvements in surgical techniques through the use of intraoperative ultrasound [5, 21] have enabled precise and limited resection. Systematic lymphadenectomy as practiced for gastrointestinal cancer should become a standard procedure. An increase in surgical radicality by preservation of the liver using prolonged ischemia during extended in situ and ex situ resections has become possible through the transfer of transplantation experience and technique in this field [27]. Another approach for the extension of radicality is cluster transplantation [34]. Whether advanced surgical techniques can improve the results from an oncological point of view will be demonstrated in the future.

Despite the rapid developments in surgical techniques and radicality, the long-term results remain disappointing. A few centers have attempted to increase the radical approach by the combination of liver transplantation and chemotherapy. Three major approaches are currently under investigation. First, preoperative chemotherapy and reduction of the tumour mass during the waiting period by repeated chemo-embolisation has been used by Bismuth et al. [6]. A report on the long-term effect of this pretreatment must be awaited. Another study by Stone et al. [35] involved perioperative adjuvant chemotherapy with a lowered dose of doxorubicin (Adriamycin, 10 mg/m^2 weekly). The rationale of this approach was to treat minimal residual disease (micrometastases) during hepatectomy and after radical surgery. The initial observations were quite promising, but the long-term results are pending. A third approach might involve aggressive neoadjuvant chemotherapy prior to liver transplantation [13]. This approach has been used only incidentally in our center and by other groups, but it may be investigated in more depth in the future. In this context, new possibilities of immunotherapy may be mentioned. It might be possible to use cytokine (IL-2, interferon) treatment, natural killer/lymphokine-activated killer cell or monoclonal ([^{131}I]-anti-ferritin) treatment [31] in a multimodal approach to the treatment of HCC before or after liver transplantation and extended surgical resection (Table 3). The therapy of HCC should include the entire spectrum of liver surgery, with partial and total hepatectomy being applied complementarily in a multimodal treatment. Such a concept would fulfill the present requirements of radical oncological surgery. At present, decision making should be attempted on the basis of the individual tumour stage.

The prognosis for individual patients and their risk of developing chronic hepatitis, however, cannot yet be calculated. Again, it should be mentioned that in our center, long-term survivors cured by liver transplantation were observed. In addition, some patients with advanced multimodular HCC have survived for several years without showing signs of recurrence. Thus, the individual situation and tumour biology cannot yet be exactly defined. Future developments in tumour biology and cancerogenesis by hepatitis are needed for the diagnosis of individual risk factors. Furthermore, diagnostic tools and experimental models have to be developed to study treatment possibilities for micrometastases and minimal residual disease. These may form an experimental background for multimodal treatment possibilities and may aid in the determination of the treatment of choice.

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