

Liver Resection *Versus* Transplantation for Hepatocellular Carcinoma in Cirrhotic Patients

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Objective

Currently, there is considerable controversy about the place of transplantation in the treatment of hepatocellular carcinoma (HCC). This study compared resection to transplantation in cirrhotic patients with HCC in order to determine reasonable indications of each treatment.

Summary Background Data

The usual procedure is to resect when feasible and to transplant in other cases.

Methods

Three-year survival with and without recurrence was analyzed in 60 patients who underwent resection and 60 who underwent transplantation. Several prognostic factors, such as size, number of nodules, portal thrombus, and histologic form, were studied.

Results

In terms of overall survival rates, resection and transplantation yield the same results (50% vs. 47%, respectively, at 3 years). For transplantation, however, the rate for survival without recurrence is better than that for resection (46% vs. 27%, respectively; $p < 0.05$). In the case of small uninodular or binodular tumors (< 3 cm), transplantation has much better results than resection (survival without recurrence, 83% vs. 18%, respectively; $p < 0.001$). However, it seems that a group of patients with high risk of recurrence after transplantation can be determined (diffuse form, more than two nodules > 3 cm, or presence of portal thrombus).

Conclusions

The best indication for transplantation seems to be patients with small and uninodular or binodular tumors; until now, these patients were considered to be the best candidates for resection. Patients undergoing transplantation for unresectable, large, multinodular or diffuse tumors seem to represent bad indications for transplantation. These results could help define reasonable indications for transplantation in an era with a shortage of liver grafts.

Although until the late 1970s it was considered to be a tumor rarely diagnosed or treated and detected mainly at autopsy in cirrhotic patients, hepatocellular carcinoma (HCC) has been diagnosed and treated with increasing

frequency in recent years.^{1,2} Several treatment options are now available, including hepatic arterial chemoembolization, alcoholization, hepatic resection, and transplantation.¹⁻³ When the tumor has spread beyond the

liver, a cure is not possible and only palliative treatment may be offered. However, when there is no evidence of extrahepatic disease, an attempt at cure by complete surgical excision is applicable, although there is considerable controversy regarding the most appropriate treatment for each particular case.²⁻⁴ Indeed, results for hepatic resection, while initially promising, appear to have deteriorated with time² and in contrast liver transplantation, initially considered a poor treatment option, has recently been associated with improved results.⁴ Furthermore, several tumor characteristics, such as size, number of nodules, and portal venous involvement, have been identified as important prognostic indicators, but the exact significance of these in terms of deciding which therapeutic option is appropriate remains to be determined.⁵ In this study, recurrence and survival rates after hepatic resection or transplantation for HCC in cirrhotic patients were analyzed in an attempt to determine the exact importance of various tumor characteristics and whether these are reliable parameters that could identify the most appropriate surgical option in each particular case.

PATIENTS AND METHODS

Patients

From January 1980 to June 1991, 178 patients with HCC underwent liver resection or transplantation at Hôpital Paul Brousse, Villejuif, France. The tumor was present in a noncirrhotic liver in 52 cases (42 resections and 10 transplantations) and in a cirrhotic liver in 126 cases (60 resections and 66 transplantations). In six cases, an HCC was discovered in a cirrhotic liver after hepatectomy and liver transplantation for end-stage liver disease. These cases were excluded because the aim of the study was to compare resection and transplantation for known tumors and the prognosis for these tumors discovered after total hepatectomy and transplantation may be more favorable because they are usually less than 2 cm in diameter.⁶ Thus, 120 cases of HCC in a cirrhotic liver were available for study. The diagnosis of cirrhosis was confirmed histologically in each case, as was that of HCC. Other primary hepatic cancers such as hepatoblastoma, hemangio-epithelioma, or cholangiocarcinoma were excluded. There were no cases of fibrolamellar carcinoma.

Patient details including etiology of cirrhosis, severity of cirrhosis according to the Paul Brousse classification (which is a modification of the Child-Pugh scoring system),⁷ presence of symptoms and tumor characteristics

Table 1. CLINICAL DETAILS AND TUMOR CHARACTERISTICS

	Resection (N = 60)	Transplantation (N = 60)
Etiology		
Alcoholic	23 (38%)	6 (10%)
Posthepatic	34 (57%)	44 (73%)
Others	3 (5%)	10 (17%)
Classification of cirrhosis		
A	46 (77%)	19 (32%)
B	13 (21%)	21 (35%)
C	1 (2%)	20 (33%)
Tumor asymptomatic	45 (75%)	49 (82%)
Size (cm)		
< 3	25 (42%)	28 (47%)
3-5	21 (35%)	17 (28%)
5-10	14 (23%)	13 (22%)
> 10	—	2 (3%)
No. of nodules		
1	50 (83%)	24 (40%)
2	10 (17%)	6 (10%)
≥ 3	—	30 (50%)
Portal thrombosis—main branch	3 (5%)	10 (17%)

(including size and number of nodules [Nakashima classification⁸]), and presence or absence of portal thrombosis are given in Table 1. Most patients did not have symptoms attributable to their tumor (75% in the resection group and 82% in the transplantation group). In the resection group, 42% of the tumors were less than 3 cm; in the transplantation group, 47% of the tumors were less than 3 cm. The major differences between the two groups were the severity of the cirrhosis (77% grade A and 2% grade C in the resection group compared to 32% grade A and 33% grade C in the transplantation group) and the number of nodules (a single nodule in 83% of the resection group compared to 30% of the transplantation group).

Preoperative Investigation

Preoperative investigations included hepatic ultrasound, abdominal and thoracic computerized tomographic (CT) scans, bone scintigraphy, and sequential serum alpha-feto protein measurements. In the latter 2 years of the series, hepatic arterial chemoembolization was performed before resection or transplantation.³ In patients undergoing resection, this was performed both to reduce the tumor mass and to detect additional nodules (demonstrated during the procedure or on a computerized tomographic scan performed 3 weeks later by the persistence of lipiodol within the nodule). In patients undergoing transplantation, it was performed as adju-

vant therapy while waiting for a suitable graft (except in the case of severe liver insufficiency).

Resection Techniques

In each case, a standardized, systematic examination of the abdominal cavity was performed to exclude peritoneal metastases. Hepatic pedicle and celiac lymph nodes, if present, were removed for frozen section histologic examination. If this was positive, resection was not performed. Systematic, intraoperative hepatic ultrasonography was performed to detect additional nodules or portal thrombosis. If additional nodules were detected, ultrasound-guided needle biopsy was performed; if more than two histologically positive nodules were identified, liver resection was not performed.

The resection techniques principally involved ultrasound-guided segmentectomy or sub-segmentectomy.^{9,10} Assessment of liver function before surgery by measurement of routine liver function tests (including coagulation status) and indocyanine green clearance was used to indicate the extent of parenchymal resection that could be safely performed. After resection, adjuvant chemotherapy was not given because of underlying cirrhosis.

Transplantation Technique

A systematic examination of the abdominal cavity was performed in each case (including frozen section histology) to detect extrahepatic disease. In the event of a positive result, an alternative patient with nonmalignant disease was immediately prepared to receive the graft. The technique for transplantation was the standard one used in our unit,¹¹ with several modifications due to the presence of malignant disease. The use of a cell saver was avoided if tumor was present at the surface of the liver, and extracorporeal bypass was used only after clamping of the portal vein in order to avoid dislodging small intrahepatic portal thrombi during aspiration of the portal trunk. The presence of a portal thrombus invading the portal trunk (but not the bifurcation or primary and secondary branches) was considered a contraindication to transplantation. After transplantation, routine triple immunosuppression with azathioprine, cyclosporine, and steroids was used.¹² Postoperative chemotherapy consisting of doxorubicin (Adriamycin, Adria Laboratories, Columbus, OH) (50 mg/m² on day 1) and 5-fluorouracil (500 mg/m² on days 2 to 5) given for nine courses over 5 days each month for a total of 9 months was started as soon as the patient could tolerate it.

Histologic Study

In all cases, tumoral and nontumoral liver was examined. The size of the tumor, the number of nodules, and

the presence of capsule, satellites nodules, and vascular invasion were noted. The tumor was classified according to the Nakashima classification.⁸ In the resection group, all tumors except one (a diffuse type that was transplanted 6 months later) were expansive type (one or two nodules). In the transplantation group, there were 51 expansive (uninodular or multinodular), 4 infiltrative, and 5 diffuse forms. The whole liver was systematically examined and dysplasia, carcinomatous foci were noted in cirrhotic nodules.

Follow-up

In all cases of resection or transplantation, patients were observed for detection of recurrence by alpha-feto protein dosage and ultrasound of the liver every 3 to 4 months, and periodic computerized tomography scan of the lungs and bone scintiscan.

Statistical Analysis

Comparison of survival and survival without recurrence rates in each group, in relation to the tumor size and number of nodules, was performed using the Kaplan-Meier method and the log-rank test.

RESULTS

Morbidity and Mortality

Postoperative complications occurred in 24 patients (40%) of the resection group. These included hemorrhage requiring repeat laparotomy,⁴ bile fistula that closed spontaneously,² ascites that regressed spontaneously,⁵ liver failure with ascites, and renal dysfunction.¹³ In the transplantation group, postoperative surgical complications occurred in nine patients (15%). These included postoperative hemorrhage,³ intestinal perforation,² thrombosis of the hepatic artery,¹ infected ascites,¹ biliary stricture,¹ and wound abscess.¹

In the resection group, there were six operative (within 2 months) deaths (10%). These were caused by hepatic failure,³ unexplained cardiac arrest,¹ sepsis,¹ and hemorrhage.¹ In the transplantation group, there were three deaths (5%), all caused by cardiac complications.

Survival

Results for overall survival and survival without recurrence are shown in Figures 1 and 2 and Table 2. In the resection group, the overall 3-year survival rate was 52%, but most of these patients had recurrent disease (survival without recurrence, 27%). In the transplantation group, the overall 3-year survival rate was 49%; however, in

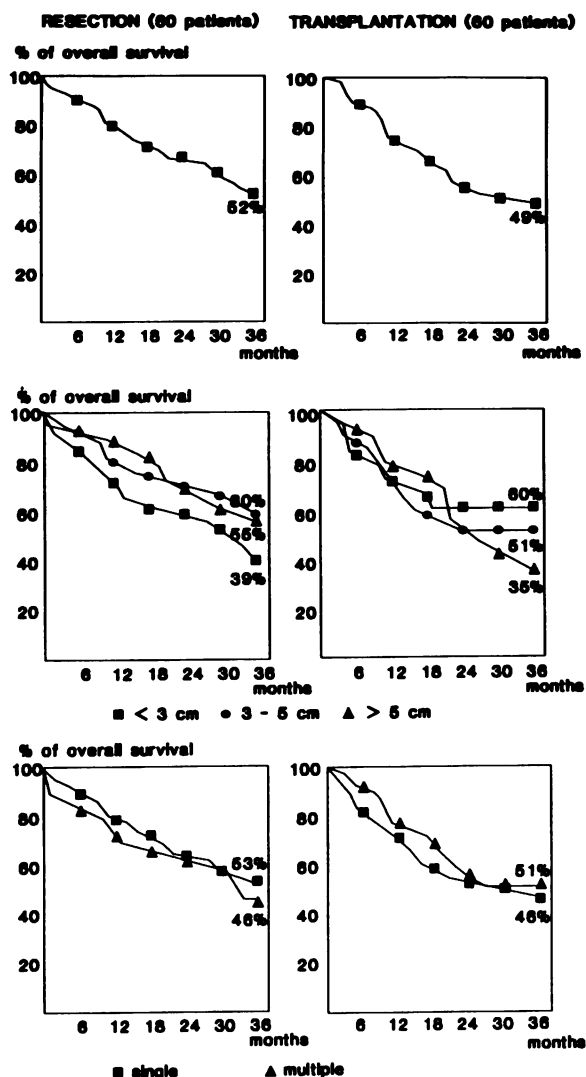


Figure 1. Overall survival in resection and transplantation groups. Upper curves—overall results. Middle curves—influence of the number of nodules (multiple—more than one). Lower curves—influence of tumor size.

contrast to the resection group, most of these patients were free from recurrence (survival without recurrence, 46%). Of 47 patients observed for more than 3 years after resection, 33 died (18 of the 28 known causes were attributed to recurrence), 5 are alive with recurrence, and 9 are alive without demonstrable disease (including 1 patient who underwent re-resection and 3 patients who later underwent transplantation). Of 22 patients in the transplantation group who have been observed for more than 3 years, 10 have died (5 of recurrence) and 12 are alive without recurrence.

Histology

In the transplantation group, all patients who had a diffuse HCC died of recurrence at 8 to 20 months (0%

survival rate at 2 years). In the other patients, carcinomatous foci in cirrhotic nodules or degenerated adenomatous hyperplasia was discovered in the parenchyma far from the tumor in 24% of the cases.

Tumor Size

The influence of tumor size on survival in each group is shown in Figure 1 and Table 2. In the resection group, the 3-year survival rate for patients with tumors less than 3 cm was 39% (survival without recurrence, 18%), while for those with lesions greater than 3 cm it was 56% (survival without recurrence, 32%). In the transplantation group, the 3-year survival rate for patients with tumors less than 3 cm was 60% (survival without recurrence,

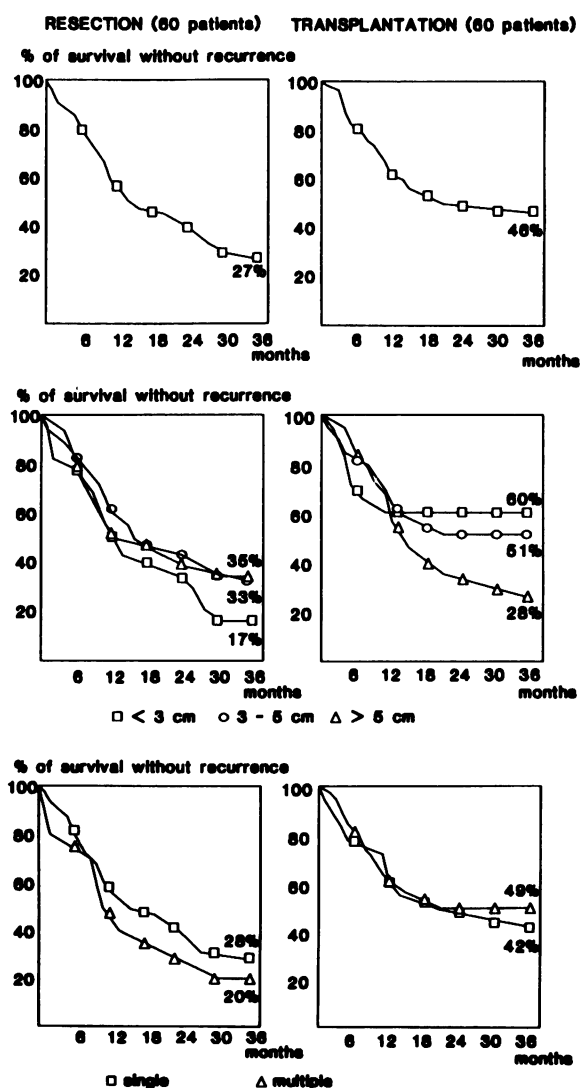


Figure 2. Survival without recurrence in resection and transplantation groups. Upper curves—overall results. Middle curves—influence of the number of nodules (multiple—more than one). Lower curves—influence of tumor size.

Table 2. THREE-YEAR SURVIVAL AND SURVIVAL WITHOUT RECURRENCE RATES (PARENTHESES) IN RELATION TO TUMOR SIZE AND NUMBER

	Resection (N = 60)		Transplantation (N = 60)	
Total series	52% (27%)	NS p < 0.05	49% (46%)	
Size (cm)				
< 3	39% (18%)	NS p < 0.05	60% (56%)	
≥ 3	56% (32%)	NS NS	43% (39%)	
No. of nodules				
Single	53% (28%)	NS	46% (20%)	
Multiple (> 1)	46% (20%)	NS p < 0.05	51% (49%)	
Size and number				
< 3 cm + 1 or 2 nodules	41% (18%)	p < 0.05 p < 0.001	83% (83%)	p < 0.01
≥ 3 cm + 3 or more nodules	—		46% (44%)	

56%; $p = 0.03$ compared to the resection group), while for those with tumors greater than 3 cm it was 43% (survival without recurrence, 39%).

Number of Nodules

The influence of the number of nodules on survival in each group is shown in Figure 1 and Table 2. In the resection group, the 3-year survival rate for patients with one nodule was 53% (survival without recurrence, 28%), while for those with multiple (more than one) nodules it was 46% (survival without recurrence, 20%). In the transplantation group, the 3-year survival rate for patients with a single nodule was 46% (survival without recurrence, 41%). For patients with multiple nodules, the 3-year survival rate after transplantation was 51% (survival without recurrence, 49%; $p = 0.04$ compared to the resection group).

Influence of Tumor Size and Number of Nodules (Table 2)

When tumor size and number of nodules were considered together, survival (83%) and survival without recurrence (83%) were better after transplantation than after resection in patients with tumors less than 3 cm and one or two nodules (3-year survival rate, 41%; $p = 0.05$; survival without recurrence, 18%; $p = 0.001$). The results of

transplantation in this group of small, uninodular or binodular tumors were better than those in patients with tumors more than 3 cm and three or more nodules (3-year survival rate, 49%; $p = 0.03$; survival without recurrence, 44%; $p < 0.01$).

Portal Thrombosis in a Main Branch

In the resection group, all 3 patients with a tumoral thrombus in a main branch had a recurrence at 9, 36, and 60 months; 2 died at 45 and 64 months and 1 is alive after liver transplantation.

In the transplantation group, the existence of a portal thrombosis in a main branch (ten patients) was significantly associated with a worse prognosis (survival rate at 3 years with portal thrombosis was 20% vs. 55% without portal thrombosis; $p = 0.001$).

DISCUSSION

The diagnosis and treatment of HCC has progressed remarkably in the last 10 to 15 years. These advances have been due largely to improved diagnostic imaging and the application of sophisticated surgical techniques, including liver transplantation.¹ Of the treatment options now available (alcoholization, chemoembolization, hepatic resection, and hepatic transplantation), only resection and transplantation, by theoretically removing all tumor tissue, can offer the chance of long-term survival or cure. While both of these have been applied with varying results in recent years, it is not yet possible to say which provides the better option in each individual case. This is further complicated by the fact that reported series generally concern all types of primary hepatic malignancy and both cirrhotic and non-cirrhotic patients.^{4,13,14} This may lead to confusing results because the natural history of the disease, the surgical management, and the outcome are different in each case.⁵ Thus, in this study, we have concentrated on resection and transplantation for HCC in cirrhotic patients only (in whom it is the most frequent type of primary hepatic malignancy) in order to reduce the number of variables and allow a more precise analysis and interpretation of results.

Clearly, when there is extrahepatic disease, neither resection nor transplantation will cure the patient. A recent autopsy study by Yuki et al.¹⁵ showed that the frequency of extrahepatic disease is high and increases with tumor size, histologic type, and number of nodules. The incidence of hematogenous extrahepatic metastasis ranged from 14% for single nodules to 82% for diffuse, multinodular disease. Experience with transplantation in our series would seem to confirm this because even when thorough preoperative and peroperative screening

is negative, there is a high rate of recurrence, which is often dramatic and early. This strongly supports the concept of microscopic extrahepatic spread and the contribution of the immunosuppressive effect of both major surgery and adjuvant immunosuppressive regimens.

If there is no extrahepatic spread, resection may cure the patient, providing the following criteria are fulfilled. First, a radical resection with at least a 1-cm clearance must be obtained.¹⁶ Second, it is essential that there are no coexistent undetected daughter nodules present in the liver (even the most thorough peroperative screening of the liver by ultrasound can miss nodules less than 1 cm). Third, there must be no new development of HCC in the remaining cirrhotic liver. Even in the absence of multinodular disease, new tumors, proved to be different from the original by DNA studies,¹⁷ may appear in the liver soon after resection. It seems that these criteria are rarely fulfilled in Western countries; this is reflected in our results for resection, with a 3-year survival rate of 50% and a 3-year survival without recurrence rate of only 23%. Although there was no significant difference in survival after resection between patients with one nodule and those with more than one nodule, the influence of lesion size was unexpected and puzzling. While it seems reasonable to expect results to be better for patients with small (< 3 cm) lesions, the opposite was found—better survival rates for patients with lesions greater than 5 cm. How can this apparent paradox be explained? One could postulate that when resection is performed in a patient with one or two small nodules discovered by repeated screening, other undetected nodules may be present. Our study of the parenchyma in cases of transplantation for expansive form seems to confirm the frequent existence of undetected carcinomatous foci in cirrhotic liver (24%).

In contrast, when resection of a single, large nodule is performed, the chance that the lesion is truly solitary may be higher, hence possibly explaining the better results after resection in these patients. This, together with differences in the biology of the disease and the underlying cirrhosis, may also help explain the different survival rates between our series and those from the Far East. For lesions less than 5 cm, 5-year survival rates of 43% in Japan and 75% in China have been reported, compared to the 3-year survival rate of 50% in our series.^{2,18} Furthermore, in contrast to the frequent early recurrence in our series, recurrence seems to be frequent but late in the Japanese series² and markedly low in the Chinese series.¹⁸

This concept may also explain why transplantation, when compared to resection in similar patients (tumors < 3 cm and one or two nodules), is associated with better results because by removing the liver completely the risk of synchronous nodules or metachronous nodules is re-

moved. In contrast, when performed for tumors more than 3 cm and three or more nodules, the tumor may have already spread outside the liver,¹⁵ explaining the poorer results after transplantation in this group.

Recently, the commonly adopted attitude has been to resect tumors that can be resected and to perform transplantation for those that could not.^{4,14,19} The generally poor results for transplantation in recent series reported by Ismail et al. (0% survival rate at 1 year)¹⁹ and Ringe et al. (17% survival rate at 5 years)¹⁴ can now possibly be explained by the findings of our study, which suggest that inclusion of large lesions, with the comparatively poorer results for these, adversely affects the overall results for transplantation. Therefore, it seems reasonable to suggest that, in Western countries, transplantation is particularly recommended for the group of patients in which it achieves the best results (*i.e.*, those with tumors less than 3 cm and one or two nodules).

Although transplantation still seems to be a better option than resection for large tumors, the results for transplantation are poor, with a 3-year survival rate of 31%. This is comparable to the figures for transplantation for secondary liver tumors or hilar cholangiocarcinoma.^{13,20} As in these latter groups, the general consensus is currently against transplantation, with the shortage of donor livers. Perhaps a similar attitude should be adopted for the unfavorable forms of HCC: tumors more than 3 cm and three or more nodules, tumors with portal thrombosis in a main branch, or diffuse tumors.

Should resection be abandoned completely in the treatment of HCC? It is certain that some cases of small HCC will be localized and will remain so, as seems to be the case in the series from China.¹⁸ These patients may be cured by hepatic resection. Efforts must, therefore, be made to identify these cases in Western countries so that resection is not withheld from suitable cases and transplantation is not performed unnecessarily. Resection still is probably indicated for tumors more than 3 cm, as a second stage procedure after tumor reduction by adjuvant therapy such as chemoembolization.³ In a few cases of large tumors, transplantation may be indicated if, after adjuvant therapy, there is a dramatic reduction in the size of the tumor and there is no evidence of extrahepatic spread.

We believe that hepatic transplantation for HCC should be avoided for large (> 3 cm) lesions with three or more nodules and should be restricted to small lesions (< 3 cm) with one or two nodules, the group which until now was thought to be the most suitable for resection. Resection may still be indicated for some small tumors that tend to remain localized (as in the series from the Far East), and further attempts must be made in Western countries to identify these types of lesions. Resection may be appropriate for patients with large lesions after

reduction of the tumor mass by chemoembolization or other adjuvant therapy. Transplantation may also be considered for these patients, depending on the degree of priority given to HCC as an indication (compared to other indications) for transplantation.

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