Reprinted from: ANNALS OF SURGERY, Vol. 214, No. 3, September 1991

Hepatic Resection *Versus* Transplantation for Hepatocellular Carcinoma

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During the 10-year period (1980 to 1989), 76 patients with hepatocellular carcinoma (HCC) were treated by subtotal hepatic resection (HX) and 105 patients by orthotopic liver transplantation (TX) under cyclosporine-steroid therapy. Overall 1- to 5-year survival rates of the HX group were 71.1%, 55.0%, 47.2%, 37.2%, and 32.9%, respectively, and those of the TX group were 65.7%, 49.0%, 39.2%, 35.6%, and 35.6%, respectively. The survival rates after HX and after TX correlated well with pTNM stages and were similar in each stage between the two groups. However, when HCC was associated with cirrhosis of the liver, the survival rates after TX were significantly better than those after HX at each stage of pTNM classification. The tumor-recurrence rate was high both after HX (50%) and TX (43%), particularly in advanced stages of pTNM classification (60% or more). Twelve patients after HX and 13 patients after TX lived more than 5 years during this 10-year period. Fibrolamellar HCC and early stages of HCC were highly represented among the long-term survivors. Further improvement in survival rates depends on nonsurgical anti-cancer therapy before and/or after surgical removal of HCC.

LIVER TRANSPLANTATION HAS been widely accepted as a useful therapy for various advanced liver diseases.[1-3] However its role in the treatment of hepatobiliary malignancy still remains to be determined.[4-15] Our earlier reports[4-7] and those of others[8-11] have emphasized the high recurrence rate of hepatocellular carcinoma (HCC) in patients treated with liver transplantation, but they also recognized a handful of patients who were apparently cured of their malignancy by hepatic replacement. The same is true with conventional subtotal hepatic resection.[16-30]

In this study we compared the results obtained by liver transplantation to those achieved by subtotal hepatic resection among our own series of 181 patients with HCC according to the pTNM staging. The prognostic factors other than those included in pTNM staging were also examined for their significance.

Materials and Methods

During the 10-year period between 1980 and 1989, 76 patients with HCC were treated by subtotal hepatic resection (HX) and additional 105 patients by orthotopic liver transplantation (TX) under cyclosporine-steroid immunosuppressive therapy at the University of Colorado Health Sciences Center (1980), and at the University Health Center of Pittsburgh (1981 to 1989).

Liver transplantation was used if subtotal hepatic resection was not anatomically feasible due to extensive intrahepatic involvement of malignancy, or if the underlying liver disease and/or hepatic failure precluded this possibility. One third of the patients in the transplant group had anatomically unresectable HCC in the normal liver, one third had functionally unresectable HCC in the cirrhotic liver, and one third had misdiagnosed HCC in the failing liver. The extent of HCC was staged using the pTNM classification proposed by the International Union Against Cancer and the American Joint Committee on Cancer (Table 1).[31,32]

Presented at the 111th Annual Meeting of the American Surgical Association, April 11–13, 1991, Boca Raton, Florida.

Supported by research grants from the Veterans Administration and Project Grant DK 29961 from the National Institutes of Health, Bethesda, Maryland.

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Accepted for publication April 22, 1991.

TABLE 1. *pTNM Pathologic Classifications*

	Classification		
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N0, N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

T1: Solitary, ≤2 cm, without vascular invasion.
T2: Solitary, ≤2 cm, with vascular invasion.
Multiple, one lobe, ≤2 cm, without vascular invasion.
Solitary, >2 cm, without vascular invasion.
T3: Solitary, >2 cm, with vascular invasion.
Multiple, one lobe, >2 cm, with or without vascular invasion.
T4: Multiple, > one lobe.
Invasion of major branch of portal or hepatic veins,
N1: Regional
M1: Distant metastasis.

Subtotal Hepatic Resection Group (HX Group)

There were 76 patients in this group; 53 were male and 23 were female. The ages ranged from 9 to 86 years with a mean ± standard deviation (SD) of 51.4 ± 17.4 years. Seventeen of seventy-six patients had associated cirrhosis of the liver. Eight patients were chronic carriers of hepatitis B surface antigen (HBsAg), and three others had hepatitis B surface antibody and/or core antibody (HBsAb and/or HBcAb).

These 76 patients with HCC were stratified according to the pTNM classification and are shown in Table 2. Twelve of seventy-six HCCs were those of fibrolamellar variant (FL-HCC).

The follow-up periods of this group of patients ranged from 16 to 131 months, with a median follow-up of 53 months as of February 1, 1991.

Liver Transplantation Group (TX Group)

There were 105 patients in this group; 70 were male and 35 were female. The ages ranged from 3 to 69 years, with a mean ± SD of 43.5 ± 18.2 years. Seventy-one of one hundred five patients had associated cirrhosis of the liver. Twenty-three patients were chronic carriers of HBsAg and 11 others had HBsAb and/or HBcAb.

These 105 patients with HCC were stratified according to the pTNM classification and are shown in Table 3. Ten of one hundred five patients had FL-HCC.

The follow-up periods of this group of patients ranged from 16 to 131 months, with a median follow-up of 37 months as of February 1, 1991.

Prognostic Factors

The variables included in pTNM classification (Table 1) were examined individually for their influence on survival rates before grouping into the stages. Other variables examined were (1) associated cirrhosis, (2) HBsAg, (3) microscopic tumor margin, (4) shape of the tumor(s) (circumscribed *versus* infiltrative), and (5) fibrolamellar variant. All variables examined are listed in Table 7.

Statistical Analysis

Actuarial survival rates were calculated by the life-table method using the BMDP statistical software (University of California Press, Berkeley, CA). Statistical comparisons across different groups were made by the method of Mantel-Cox for univariate analysis. The Cox proportional hazards regression model was used to assess the relative prognostic importance of factors in predicting survival (multivariate analysis). Differences were considered significant if the probability value was less than 0.05.

Results

Survival Rates

Overall survival rates of the subtotal hepatic resection group (HX group) and those of the liver transplantation group (TX group) are shown in Figure 1 and Tables 4 and 5. There was no difference in the survival rates between the two groups.

In the HX group the survival rates of patients with FL-HCC were significantly ($p = 0.016$) higher than those of

TABLE 2. *pTNM Stages of 76 Patients with Hepatocellular Carcinoma Treated by Subtotal Hepatic Resection*

pTNM Stage	Number of Patients	Number of Patients	
	Total HCC	Non-FL	FL
I	0	0	0
II	19	16	3
III	25	18	7
IV-A	32	30	2
Total	76	64	12

HCC, hepatocellular carcinoma; FL, fibrolamellar HCC.

TABLE 3. *pTNM Stages of 105 Patients with Hepatocellular Carcinoma Treated by Liver Transplantation*

pTNM Stage	Number of Patients	Number of Patients	
	Total HCC	Non-FL	FL
I	4	4	0
II	19	17	2
III	23	23	0
IV-A	59	51	8
Total	105	95	10

HCC, hepatocellular carcinoma; FL, fibrolamellar HCC.

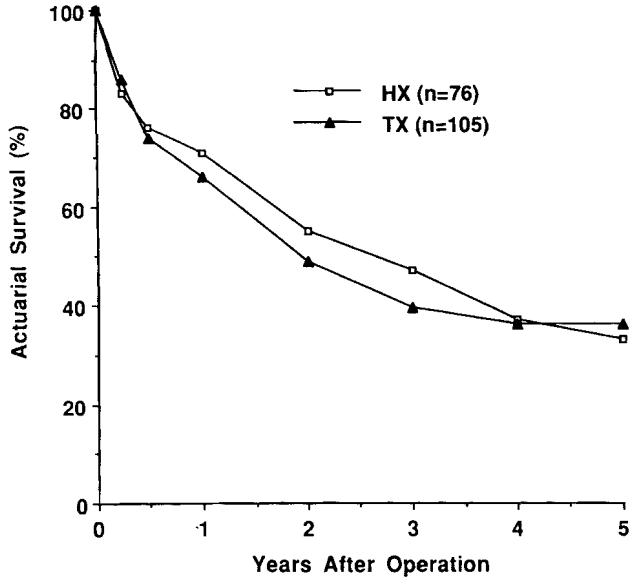

FIG. 1. Overall survival rates of patients with hepatocellular carcinoma. HX, subtotal hepatic resection; TX, liver transplantation.

patients with nonfibrolamellar hepatocellular carcinoma (non–FL-HCC) (Table 4). In the TX group, however, the survival rates were quite similar between them (Table 5) because 8 of the 10 patients were in stage IV-A (Table 3). The survival rates of patients with FL-HCC tended to be higher in the HX group than in the TX group, but the difference was not statistically significant (Tables 4 and 5).

When HCC was associated with cirrhosis of the liver, the survival rates were significantly ($p = 0.001$) lower than those without cirrhosis in the HX group (Table 4), but the survival rates were similar in the TX group (Table 5). The survival rates of the HX group were significantly ($p = 0.02$) lower than those of the TX group when HCC was associated with cirrhosis of the liver, but they were similar when HCC was not associated with cirrhosis (Tables 4 and 5). There was no 4-year survivor after subtotal hepatic resection (HX) among the patients with HCC in the cirrhotic liver, but the 5-year survival rate after transplantation (TX) was 40.7%.

The overall survival rates were stratified by the pTNM stages and are shown in Tables 4 and 5. Both in the HX group and in the TX group the pTNM stages correlated well with the survival rates. In both groups the survival rates of stage IV-A patients were significantly ($p < 0.05$) lower than those of other stages. There was no statistically significant difference in the survival rates when they were compared in the same pTNM stages between the HX group and the TX group (Table 4 and 5). However, when the survival rates of patients with HCC in the cirrhotic liver were compared in the same stages, the survival rates of the TX group were significantly ($p < 0.05$) better than those of the HX group (Table 6). The difference was most striking in stage III.

Prognostic Factors

Univariate analyses of five factors included in the pTNM classification and six others were performed by the Mantel-Cox test and the results were summarized in Table 7, with mean survival rates in months. The poor prognostic factors of statistical significance both in the

TABLE 4. *Survival Rates After Subtotal Hepatic Resection for Hepatocellular Carcinoma*

	3 months	6 months	1 year	2 years	3 years	4 years	5 years
Total HCC (n = 76)	82.9% (63)	77.6% (59)	71.1% (54)	55.0% (36)	47.2% (26)	37.2% (17)	32.9% (12)
FL-HCC (n = 12)	100% (12)	100% (12)	100% (12)	83.3% (9)	83.3% (9)	64.8% (6)	64.8% (5)
Non-FL-HCC (n = 64)	79.7% (51)	73.4% (47)	65.6% (42)	49.7% (27)	40.2% (17)	32.1% (11)	26.3% (7)
Cirrhosis (n = 17)	64.7% (11)	47.1% (8)	35.3% (6)	23.5% (4)	5.9% (1)	0 (0)	— —
Noncirrhosis (n = 59)	88.1% (52)	86.4% (51)	81.4% (48)	64.3% (32)	60.2% (25)	49.5% (17)	43.7% (12)
TNM Stage I (n = 0)							
TNM Stage II (n = 19)	100% (18)	100% (18)	100% (18)	84.2% (15)	78.6% (13)	58.2% (8)	43.7% (4)
TNM Stage III (n = 25)	80.0% (20)	80.0% (20)	76.0% (19)	68.0% (14)	53.4% (9)	46.8% (6)	46.8% (5)
TNM Stage IV-A (n = 32)	78.1% (25)	65.6% (21)	53.1% (17)	26.9% (7)	22.4% (4)	16.8% (3)	16.8% (3)

TABLE 5. *Survival Rates After Liver Transplantation for Hepatocellular Carcinoma*

	3 months	6 months	1 year	2 years	3 years	4 years	5 years
Total HCC (n = 105)	85.7% (90)	74.3% (78)	65.7% (69)	49.0% (45)	39.2% (26)	35.6% (16)	35.6% (13)
FL-HCC (n = 10)	90.0% (9)	90.0% (9)	80.0% (8)	70.0% (2)	50.0% (4)	37.5% (3)	37.5% (3)
Non-FL-HCC (n = 95)	85.3% (81)	72.6% (69)	64.2% (61)	46.8% (38)	38.3% (22)	36.5% (13)	36.5% (10)
Cirrhosis (n = 71)	84.5% (60)	71.8% (51)	63.4% (45)	48.6% (28)	42.9% (21)	40.7% (12)	40.7% (10)
Noncirrhosis (n = 34)	88.2% (30)	79.4% (27)	70.6% (24)	50.0% (16)	32.5% (6)	26.0% (4)	26.0% (3)
TNM Stage I (n = 4)	75.0% (3)	75.0% (3)	75.0% (3)	75.0% (3)	75.0% (2)	75.0% (2)	75.0% (2)
TNM Stage II (n = 19)	84.2% (16)	84.2% (16)	79.0% (15)	68.4% (12)	68.4% (12)	68.4% (8)	68.4% (5)
TNM STage III (n = 23)	87.0% (20)	78.3% (18)	78.3% (18)	59.8% (11)	59.8% (8)	52.3% (4)	52.3% (4)
TNM Stage IV-A (n = 59)	86.4% (51)	69.5% (41)	55.9% (33)	36.6% (15)	16.3% (4)	10.9% (2)	10.9% (2)

HX group and in the TX group were (1) multiple gross tumors, (2) vascular invasion, (3) advanced pTNM stages, (4) positive surgical margin, and (5) infiltrative shape of tumor.

The tumor size of more than 2 cm was a significantly poor prognostic factor in the TX group, but it could not be examined in the HX group because there was no tumor measuring 2 cm or less in this group. Bilobar involvement of tumor and lymph node metastasis were significantly poor prognostic factors in the TX group, but they were not significant in the HX group. Fibrolamellar histology was a significantly good prognostic factor in the HX group. The fibrolamellar patients had a higher survival rate in the TX group for the first 3 years, but this factor was not statistically significant because 8 of the 10 patients with this tumor were classified as stage IV-A. Associated cir-

TABLE 6. *Survival of Patients with Hepatocellular Carcinoma in the Cirrhotic Liver*

	3 months	6 months	1 year	2 years	3 years	4 years	5 years
HX Group							
Stage I (n = 0)							
Stage II (n = 2)	100% (2)	100% (2)	100% (2)	50.0% (1)	50.0% (1)	0% (0)	
Stage III (n = 5)	60.0% (3)	60.0% (3)	40.0% (2)	40.0% (2)	0% (0)		
Stage IV-A (n = 10)	60.0% (6)	30.0% (3)	20.0% (2)	0% (0)			
TX Group							
Stage I (n = 4)	75.0% (3)	75.0% (3)	75.0% (3)	75.0% (3)	75.0% (2)	75.0% (2)	75.0% (2)
Stage II (n = 16)	81.3% (13)	81.3% (13)	81.3% (13)	75.0% (11)	75.0% (11)	75.0% (7)	75.0% (5)
Stage III (n = 19)	89.5% (17)	79.0% (15)	79.0% (15)	56.1% (8)	56.1% (7)	48.1% (3)	48.1% (3)
Stage IV-A (n = 32)	84.4% (27)	62.5% (20)	43.8% (14)	26.2% (6)	0% (0)		

TABLE 7. *Univariate Analysis of Prognostic Factors (Mean Survival in Months [± SE])*

Factor	Subtotal Hepatic Resection		Liver Transplantation	
Size of Tumor			p = 0.0241	
≤2 cm		(n = 0)	76.4 ± 14.8	(n = 12)
>2 cm	51.7 ± 6.6	(n = 76)	40.4 ± 5.2	(n = 93)
Number of Gross Tumor	p = 0.0004		p = 0.0143	
Single	65.5 ± 8.5	(n = 46)	68.6 ± 10.3	(n = 29)
Multiple	25.1 ± 6.1	(n = 30)	37.9 ± 5.5	(n = 76)
Lobar Involvement	p = 0.2916		p = 0.0003	
Unilobar	41.3 ± 7.8	(n = 44)	66.1 ± 7.8	(n = 51)
Bilobar	60.2 ± 9.7	(n = 32)*	28.0 ± 5.2	(n = 54)
Vascular Invasion	p = 0.0000		p = 0.0002	
None (V0)	67.1 ± 11.6	(n = 24)	73.2 ± 10.1	(n = 30)
Microscopic (V1)	51.8 ± 9.7	(n = 30)	43.3 ± 7.1	(n = 37)
Macroscopic (V2)	28.1 ± 9.2	(n = 22)	21.6 ± 5.6	(n = 38)
Lymph Node Metastasis	p = 0.6188		p = 0.0054	
Absent (N0)	52.7 ± 6.8	(n = 72)	49.7 ± 5.4	(n = 96)
Present (N1)	28.0 ± 7.2	(n = 4)*	10.5 ± 3.7	(n = 9)
pTNM Stage	p = 0.0069		p = 0.0015	
I		(n = 0)	81.1 ± 23.2	(n = 4)
II	64.0 ± 12.6	(n = 19)	70.0 ± 13.2	(n = 19)
III	57.0 ± 10.6	(n = 25)	53.7 ± 9.6	(n = 23)
IV-A	34.0 ± 8.7	(n = 32)	26.5 ± 5.3	(n = 59)
Histological Type	p = 0.0277		p = 0.7023	
Fibrolamellar	84.9 ± 15.8	(n = 12)	51.4 ± 14.4	(n = 10)
Nonfibrolamellar	42.9 ± 6.5	(n = 64)	47.5 ± 5.5	(n = 95)
Associated Cirrhosis	p = 0.0000		p = 0.6450	
Present	11.4 ± 3.0	(n = 17)*	50.0 ± 6.4	(n = 71)
Absent	64.6 ± 7.9	(n = 59)	39.0 ± 7.6	(n = 34)
Microscopic Margin	p = 0.0293		p = 0.0042	
Positive	29.3 ± 11.2	(n = 14)*	10.7 ± 3.9	(n = 9)
Negative	57.7 ± 7.6	(n = 62)	49.9 ± 5.5	(n = 96)
HBsAg	p = 0.0097		p = 0.3183	
Positive	17.1 ± 6.8	(n = 8)	30.4 ± 6.3	(n = 23)
Negative	56.9 ± 7.2	(n = 68)	49.6 ± 5.9	(n = 82)
Size of Uninodular Tumor	p = 0.1423		p = 0.0034	
≤5 cm	26.0 ± 7.2	(n = 6)*	89.6 ± 12.4	(n = 18)
>5 cm	69.4 ± 9.1	(n = 40)*	28.1 ± 9.8	(n = 11)
Shape of Tumor	p = 0.0000		p = 0.0010	
Circumscribed	63.1 ± 8.0	(n = 58)	57.2 ± 6.4	(n = 70)
Infiltrative	17.3 ± 5.4	(n = 18)	21.8 ± 7.5	(n = 32)

* The difference between the HX group and the TX group is statistically significant ($p < 0.05$).

SE, standard error.

rhosis of the liver and chronic HBsAg carrier status were significantly poor prognostic factors in the HX group but they were not significant in the TX group.

Multivariate analysis of prognostic factors that reached statistical significance in univariate analysis ($p < 0.05$) revealed that associated cirrhosis and infiltrative shape of tumor were independently significant factors of poor survival in the HX group. In the TX group, bilobar involvement, microscopically positive tumor margin, lymph node metastasis, and vascular invasion were independently associated with poor survival rates.

Tumor Recurrence and Cause of Death

The recurrence of HCC was confirmed in 38 (50%) of the 76 patients in the HX group and in 45 (42.9%) of the 105 patients in the TX group during the follow-up period. Although overall incidence of tumor recurrence was similar for the HX group and the TX group, the HCCs of stages II and III recurred more frequently ($p = 0.003$) in the HX group than in the TX group (Table 8). The incidence of tumor recurrence in stage IV-A was extremely high: 59.4% in the HX group and 67.8% in the TX group.

Forty-eight (63.2%) of the 76 patients in the HX group and 67 (63.8%) of the 105 patients in the TX group died during the follow-up period. Approximately two thirds of deaths were directly or indirectly related to the tumor recurrence, both in the HX group and the TX group. It is worth noting that tumor-related death among patients with HCC of stages II and III was significantly ($p = 0.013$) more frequent in the HX group than in Tx group (Table 8). Tumor-related death was quite frequent among patients with stage IV-A tumor both in the HX group (53.1%) and the TX group (64.4%) (Table 8).

Approximately one fifth of the patients in the HX group and in the TX group died of various complications of hepatic resection or transplantation that were not related to tumor recurrence (Table 8).

Five-year Survivors

There were 25 patients who survived for 5 years: 12 in the HX group and 13 in the TX group (Table 9). None of the twelve 5-year survivors in the HX group had associated cirrhosis of the liver, but 10 of the 13 5-year survivors in the TX group had HCCs that developed in the cirrhotic liver. Five of the twelve patients in the HX group and 3 of the 13 patients in the TX group had FL-HCC, which was highly represented among the long-term survivors.

Of the 25 patients surviving 5 years, 2 patients had stage I tumors, 9 patients each had stage II or stage III tumors, and 5 patients had stage IV-A tumors. Three of the five patients with stage IV-A tumors had FL-HCC and the remaining two patients had nonfibrolamellar HCC, both of whom were in the HX group. There was no 5-year survivor in the TX group who had nonfibrolamellar HCC (non–FL-HCC) of stage IV-A disease.

Discussion

The results of various therapies for HCC have rarely been reported using a universal staging system such as the TNM classification.[11,14,33] Thus the sensible comparisons of results among various therapies and among different reports have been very difficult. To compare our results of subtotal hepatic resection for HCC to those of liver transplantation, our patients were stratified according to their pTNM stage.[31,32] As shown in Tables 4 to 7, the pTNM staging has proved useful in predicting the survival rates after hepatic resection ($p = 0.0069$) and liver transplantation ($p = 0.0015$). Although all of the variables included in the TNM staging are significant prognostic factors (Table 7), the multivariate analysis of these factors among our patients revealed that macroscopic vascular invasion, lymph node metastasis, and bilobar distribution of the tumor(s) were independently significant among them in predicting the survival rates.

The factors other than those included in the TNM classification were also valuable in predicting prognosis of HCC (Table 7) as reported by others.[18–30] Our study confirms that associated cirrhosis of the liver and infiltrative shape of the tumor were independently significant in predicting the poor survival rates after subtotal hepatic resection and liver transplantation. Although the survival rates of patients with HCC were significantly lower than those without malignancy after liver transplantation,[1–11] they were quite similar to those after subtotal hepatic resection in each stage of the pTNM classification (Tables 4 and 5). However, when the patients had HCC in the cirrhotic liver, the survival rates after liver transplantation were significantly higher than those after subtotal hepatic resection in each stage (Table 6).

Our overall survival rates after subtotal hepatic resection for HCC (67.1% at 1 year, 47.2% at 3 years, and 32.9%

TABLE 8. *Tumor Recurrence and Causes of Death*

	Number of Patients		
	Recurrence of Tumor	Death With Tumor	Death Without Tumor
HX Group			
Stage II (n = 19)	10 (52.6%)	8 (42.1%)	2 (10.5%)
Stage III (n = 25)	9 (36.0%)	7 (28.0%)	6 (24.0%)
Stage IV-A (n = 32)	19 (59.4%)	17 (53.1%)	7 (21.9%)
Total (n = 76)	38 (50.0%)	32 (42.1%)	15 (19.7%)
TX Group			
Stage I (n = 4)	0 (0%)	0 (0%)	1 (25.0%)
Stage II (n = 19)	1 (5.3%)	1 (5.3%)	6 (31.6%)
Stage III (n = 23)	4 (17.4%)	3 (13.0%)	8 (24.8%)
Stage IV-A (n = 59)	40 (67.8%)	38 (64.4%)	10 (16.9%)
Total (n = 105)	45 (42.9%)	42 (40%)	25 (23.8%)

TABLE 9. *List of 25 Five-Year Survivors (12 in HX group and 13 in TX group)*

	Age/Sex	Histology	Cirrhosis	TNM Stage	Recurrence	Survival
HX Group						
1	9/M	FL	NO	II	No	Alive after 11 years
2	63/M	NON-FL	NO	IV-A	No	Alive after 10 years
3	43/F	NON-FL	NO	III	No	Alive after 9 years
4	14/M	FL	NO	III	No	Alive after 8 years
5	40/F	NON-FL	NO	IV-A	Yes	Alive after 7 years
6	39/M	FL	NO	III	Yes	Died after 7 years
7	33/M	FL	NO	IV-A	No	Alive after 7 years
8	40/M	FL	NO	III	No	Alive after 7 years
9	41/F	NON-FL	NO	III	No	Alive after 6 years
10	65/F	NON-FL	NO	II	Yes	Died after 6 years
11	50/M	NON-FL	NO	II	No	Alive after 5 years
12	62/M	NON-FL	NO	II	No	Alive after 5 years
TX Group						
13	26/M	FL	NO	IV-A	No	Alive after 9 years
14	47/F	NON-FL	YES	II	No	Alive after 9 years
15	3/F	NON-FL	YES	II	No	Died after 7 years
16	7/F	NON-FL	YES	I	No	Alive after 8 years
17	22/F	NON-FL	YES	III	No	Alive after 8 years
18	23/F	FL	NO	IV-A	Yes	Died after 6 years
19	4/F	NON-FL	YES	I	No	Alive after 7 years
20	8/F	NON-FL	YES	II	No	Alive after 6 years
21	3/F	NON-FL	YES	III	No	Alive after 6 years
22	9/M	NON-FL	YES	II	No	Alive after 6 years
23	48/F	NON-FL	YES	III	No	Alive after 6 years
24	42/M	FL	YES	II	No	Alive after 5 years
25	33/F	NON-FL	NO	III	No	Died after 5 years

at 5 years) were similar to or even slightly better than those reported by others.[17–30] However our survival rates after hepatic resection for HCC in the cirrhotic liver were significantly lower than those reported from Asia, where early stages of HCC were removed from the cirrhotic liver by limited hepatic resection.[21–30] Our overall survival rates after liver transplantation for HCC in the cirrhotic liver (63.4% at 1 year, 42.9% at 3 years, and 40.7% at 5 years) were higher than those after hepatic resection for HCC in Asia.[21–30] Our survival rates after liver transplantation for HCC Of Stages I and II (early stages) in the cirrhotic liver were 80% at 1 year and 75% at 3 and 5 years (Table 6). A meaningful comparison could not be made in our own patients because there were only two patients with HCC of stage II in the cirrhotic liver who underwent subtotal hepatic resection. However these survival rates were similar to or even better than those after hepatic resection for most favorable lesions in Asia,[26–30] although the hepatic functions were worse in the liver transplantation group than in the resection group.

It is impractical and even fraudulent to recommend that all HCCs in the cirrhotic liver should be treated by liver transplantation. It is equally incorrect to exclude the patients with HCC from liver transplantation when the malignancy is confined to the liver. The treatment of choice for HCC confined to the liver is subtotal hepatic resection when it is anatomically and functionally feasible. Liver transplantation is the treatment of choice for HCC confined to the liver when the hepatic functions are poor and/or the HCC cannot be removed by subtotal hepatic resection.

The HCC recurred in one half of the patients after hepatic resection and liver transplantation (Table 8). In the HCCs of stages II and III, the tumor recurrence was significantly higher after hepatic resection than liver transplantation. The fact may indicate either that the staging was less accurate in the hepatic resection group because only a removed part of the liver could be examined pathologically or that new HCC developed in the retained portion of the liver after hepatic resection. Nevertheless a relatively low incidence of tumor recurrence after liver transplantation for HCC of stages II and III were encouraging. On the other hand, two thirds of HCCs in stage IV-A recurred after hepatic resection and liver transplantation (Table 8).

Further improvement in survival rates will be achieved in some degree by reducing the incidence of early death from surgical complications, but the major progress will depend on nonsurgical anti-cancer therapy. For this series of our patients, organized plans of anti-cancer therapy before and/or after surgery were not available. Because the introduction of a novel immunosuppressive drug, FK 506, to our liver transplantation in mid 1989,[34,35] we have been exploring the possible beneficial effects of neoadju-

vant and adjuvant therapy for primary hepatobiliary malignancy. The improvement may be expected with this approach, particularly in HCCs of stages II and III after hepatic resection and in HCCs of stage IV-A after hepatic resection and liver transplantation, in which the tumor recurrence is frequent.

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Discussion

Dr. Ronald W. Busuttil (Los Angeles, California): Dr. Iwatsuki and colleagues have presented a comparative analysis of subtotal hepatic resection *versus* liver transplantation for hepatocellular carcinoma according to the TNM (tumor, nodes, and metastases) classification. Additionally they have evaluated other prognostic factors that might influence the outcome of these patients.

These data strongly support the tenet that liver transplantation plays an important role in the treatment of selected patients with hepatocellular carcinoma that is confined to the liver and is not amenable to subtotal resection. Moreover transplantation is superior to resection in patients with cirrhosis, because in this condition the tumor is most often multifocal.

To put this paper into perspective, however, I believe it is important to view it *vis-a-vis* a collective series of 452 patients treated with liver transplantation for hepatocellular carcinoma that has been previously reported.

May I have that slide, please? As shown here, the 2- and 3-year survival in this large group of patients is approximately 30%, and the 5-year survival is between 20% and 25%. The data presented today by Dr. Iwatsuki represent a measurable improvement over this, with a 40% to 50% survival at 2 to 3 years and a 36% survival at 5 years.

What factors have accounted for this benefit? The first that comes to mind is that all of the cases reported today were done in a modern area of liver replacement in which cyclosporine was the mainstay of immunosuppression, and many of the technical and management refinements of liver transplantation have been codified. Patient selection also could play a role.

This report includes a series of tumors that may have a more favorable prognosis: namely, fibrolammelar variant, 10 cases, although as mentioned, several of these were of the stage 4A variety; and early lesions,

TNM1, stage 1, four cases; and TM stage 2, 19 cases. Although the former group, fibrolammellar, did not show a statistically improved survival, a trend in this direction certainly is apparent at 2 to 3 years. Moreover, stage 1 and stage 2 lesions behaved similarly to incidental hepatocellular tumors, which are known to have an exceptionally good prognosis after transplantation.

Notwithstanding the above, the results reported with TNM stage 3 clearly represent an improvement over previous reports. In fact, 5-year survival in this group was 47%, which contrasts with a recent paper by Ring et al that reports no patient survival beyond 1 year in the presence of lymph node involvement.

The reason for this difference is not apparent, and thus I would like to ask: How many of the stage 3 lesions in the Pittsburgh group were T3 N0; in other words, how many had no lymph node involvement?

Finally it is unlikely that we can achieve much better results from surgery alone. In our program all patients with tumors who are transplant candidates are enrolled in an adjuvant trial of continuous 5-fluorouracil, cisplatin, combination adriamycin therapy for 6 months. Other centers have similar protocols. Results up to 3 years have been encouraging. Hepatitis-B–infected patients, however, have a high incidence of tumor recurrence, which was not reported in the Pittsburgh series.

Dr. Iwatsuki, you alluded to the use of adjuvant therapy in your manuscript. Do you have any further information on this, and how it specifically impacts on stage 3 and stage 4A tumors?

DR. HENRI BISMUTH (Villejuif, France): I agree with the general conclusion of the paper, that is, the superiority of transplantation when compared with resection, but there are several points I would like to raise.

Over the last 10 years, we have treated 115 patients with cirrhosis and hepatocellular carcinoma (HCC), 60 by resection and 55 by orthotopic transplantation. We have excluded from this transplant group tumors that were incidentally discovered at subsequent histologic examination so as only to compare the two groups in which tumor was identified preoperatively.

With respect to the results, we obtained broadly similar figures to those of Dr. Iwatsuki and the Pittsburg group when we examined the resection or transplant group as a whole. That is the 3-year survival was slightly better for transplantation (61%) than for resection (50%), but was much better, 54% and 24% respectively, when comparing survival without recurrence.

I would like to focus on two further points. When we compared our results for transplantation and resection, differences became highly significant when looking at single lesions: 74% and 25% 3-year survival without, respectively; and also for lesions less than 3 cm in size: 65% and 12%, respectively, again recurrence free at 3 years.

These clear advantages for transplantation are considerably reduced when we looked at lesions that were multiple or more than 3 cm in size.

So the point may be made by looking at the best and worse cases in which transplantation was performed in patients with less than three nodules all less than 3 cm in size or more than three nodules where one or more was more than 3 cm in size. Here the 3-year survival without recurrence is 93% and 10%, respectively. Thus in the latter group, the survival is comparable for secondaries and for HCC, in which people question whether we should transplant at all.

Although it may be unwise to extrapolate results from European patients, with HCC mainly occurring against a background of posthepatitic (B or C) cirrhosis, to those in America, I would be interested in knowing if Dr. Iwatsuki's large experience has led him to notice anything similar, especially in view of the fact that our conclusion—that we should be transplanting patients that we *could* resect and not transplanting those we cannot resect—superficially seems rather different from his own.

DR. SHUNZABURO IWATSUKI (Closing discussion): Answering Dr. Busuttil's question first, we have only four patients with lymph node positive in stage 3. In Hanover group, I believe that they had only six patients in stage 3, and that their survival is lower than ours. There are heterogenous patients in stage 3; lymph node positive and lymph node negative. TNM stage is useful, but if you read the rules of staging, there are still a lot of defects in the staging.

But in the past, we always presented the data of liver transplantation or hepatic resection without using any common ground of classification. The incidental tumor in Japan may be less than 2 cm, but in the United States, even a 5-cm lesion can be missed.

And with regard to adjuvant chemotherapy, we have been using a new adjuvant chemotherapy for hepatomas. We lose some patients because of the complications of chemotherapy, but we may gain some in long-term survival. The results are not in yet.

Answering Dr. Bismuth's questions of single tumor of less than 5 cm. If you treat this with liver transplantation, the survival rate is good. But if one can do the resection safely, there is no reason to transplant. There is a shortage of organs, and I think first choice of treatment for hepatoma or any tumor of the liver is subtotal resection.

Of course if we do the liver transplantation for a small tumor, the results are better, but there is no reason to do that. Liver resection can achieve the same result if the patient can tolerate the resection. The patients with a small tumor and with poor liver function tests should have transplants, not for cancer, but for the hepatic insufficiency.