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Treatment of Fibrolamellar Hepatoma With Subtotal Hepatectomy or Transplantation

ANTONIO D. PINNA,[1] SHUNZABURO IWATSUKI,[1] RANDALL G. LEE,[2] SATORU TODO,[1] JUAN R. MADARIAGA,[1] J. WALLIS MARSH,[1] ADRIAN CASAVILLA,[1] IGOR DVORCHIK,[1] JOHN J. FUNG,[1] AND THOMAS E. STARZL[1]

Fibrolamellar hepatoma (FL-HCC) is an uncommon variant of hepatocellular carcinoma (HCC), distinguished by histopathological features suggesting greater differentiation than conventional HCC. However, the optimal treatment and the prognosis of FL-HCC have been controversial. Follow-up studies are available from 1 year to 27 years, after 41 patients with FL-HCC were treated with partial hepatectomy (PHx) (28 patients) or liver transplantation (13 patients). In this retrospective study, the effect on outcome was determined for the pTNM stage and other prognostic factors routinely recorded at the time of surgery. Cumulative survival at 1, 3, 5, and 10 years was 97.6%, 72.3%, 66.2%, and 47.4%. Tumor-free survival at these times was 80.3%, 49.4%, 33%, and 29.3%. The TNM stage was significantly associated with tumor-free survival. Patients with positive nodes had a shorter tumor-free survival than those with negative nodes ($P < .015$). Patient survival was most adversely affected by the presence of vascular invasion ($P < .05$). FL-HCC is an indolently growing tumor of the liver, which usually was diagnosed in our patients at a stage too advanced for effective surgical treatment of most conventional HCC. Nevertheless, long-term survival frequently was achieved with aggressive surgical treatment. When a subtotal hepatectomy could not be performed, total hepatectomy (THx) with liver transplantation was a valuable option. (HEPATOLOGY 1997;26:877-883.)

Fibrolamellar hepatoma (FL-HCC) was first described by Edmondson[1] as a rare histological variant of hepatocellular carcinoma (HCC). Although several reports have emphasized the indolent growth of this subtype as well as a higher survival than with surgical treatment of conventional HCC, the better postoperative prognosis has been questioned or denied.[2,3]

Resolution of this controversy has been hampered by the paucity of long-term follow-up data after surgical therapy for FL-HCC. Exclusive of the 41 patients described herein (some previously reported[4-6]), less than 100 such cases can be found in the literature.[2,3,7-17] In our series, we have compared the survival of patients with FL-HCC with that of patients with conventional HCC who were treated by the same team over a 27-year period.

PATIENTS AND METHODS

Case Material

Between 1968 and 1995, 477 patients with hepatoma underwent hepatic resection or orthotopic liver transplantation (OLT). Forty-one (8.9%) of the 477 patients had FL-HCC. Four were treated at the University of Colorado (before 1980), and the remaining 37 at the University of Pittsburgh Medical Center. There were 23 males and 18 females. The 41 patients were 29.5 ± 13.7 (SD) years old (range, 9-66; median, 25) (Fig. 1). The median follow-up was 58 ± 9.3 months.

Clinicopathological Characteristics

The pathology reports and operative findings were used to determine: the principal tumor size, number of lesions, lobar distribution, vascular and lymphatic tumor extension, surgical margins, distant metastases, and the presence or absence of associated cirrhosis. When available, the tumor markers were recorded as well as the virus markers (hepatitis C virus, hepatitis B virus).

Staging was with the pTNM classification proposed by the International Union Against Cancer and the American Joint Committee on Cancer.[18,19] Thirty-seven of the 41 patients had stage IV tumors at the time of surgery (Table 1).

Surgical Procedures

Partial hepatectomy (PHx) was the procedure of choice. Total hepatectomy (THx) and OLT were performed when tumor extension or the presence of underlying liver disease precluded PHx. Both PHx and THx were frequently performed under highly unfavorable conditions, such as lymph node involvement and/or direct invasion of tumor into the adjacent organs.[4]

Subtotal Hepatectomy (PHx). In 8 of the 28 patients, resection included one or more surrounding organs in an attempt to secure tumor-free margins. The types of PHx performed in this group are summarized in Table 2, using surgical techniques that have been described elsewhere.[20,21]

THx and OLT. In 6 of these 13 patients, the THx was extended to adjacent organs (Table 2). Two patients had upper abdominal exenteration and organ cluster transplantation.[22,23] In 1 patient, OLT was combined with pancreaticoduodenectomy (Whipple procedure). The surgical techniques for OLT and the immunosuppression used thereafter have been described elsewhere.[22-26] Immunosuppression was with cyclosporine and prednisone (n = 9), imuran and prednisone (n = 1), or tacrolimus and prednisone (n = 3).

Abbreviations: FL-HCC, fibrolamellar hepatoma; HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation; PHx, partial hepatectomy; THx, total hepatectomy.

From the Departments of [1]Surgery and [2]Pathology, The Thomas E. Starzl Transplantation Institute, University of Pittsburgh Medical Center, Pittsburgh, PA.

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Address reprint requests to: Shunzaburo Iwatsuki, M.D., 4th Floor Falk Clinic, 3601 Fifth Avenue, Pittsburgh, PA. 15213. Fax: (412) 648-3085.

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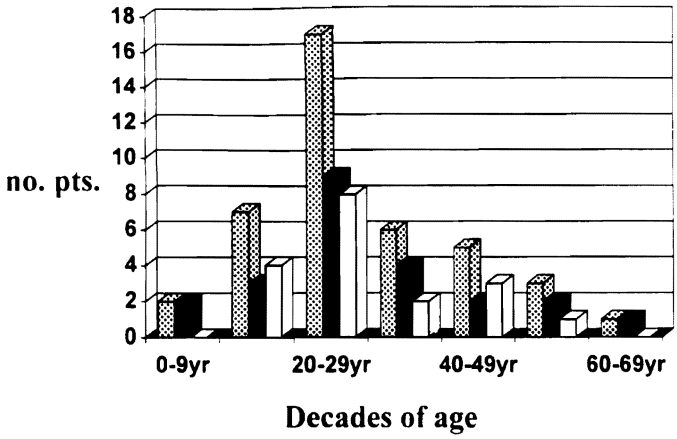

FIG. 1. HCC-FL: age and gender distribution by decades of age. (▨) All patients; (■) male patients; and (□) female patients.

Adjuvant Therapy

Sixteen patients received adjuvant radiotherapy or chemotherapy before and/or after surgery (Table 3). These regimens were highly variable in the long period of the study. Adriamycin ± Cis-Platinum were most commonly used.

Statistical Analysis

Cumulative overall survivals and tumor-free survivals were calculated by the method of Kaplan-Meier with adjustment for types of surgery (OLT vs. PHx).[27] Potential risk factors studied by univariate analysis were tumor size, number of lesions, lobar involvement, vascular invasion, lymph node invasion, distant metastases, pTNM stage, surgical margins, and adjuvant chemotherapy. $P < .05$ was considered significant. The small number of patients with different potential risk factors precluded multivariate analysis.

RESULTS

Pathological Characteristics

Tumor Size, Number, and Lobar Distribution. The principal tumors had a median diameter of 13 cm (mean ± SD = 12.4 ± 4.3 cm) with a range between 3 to 25 cm. Thirty patients (73%) had a single tumor. The remaining 11 patients (27%) had two or more lesions. The tumor(s) was bilobar in 30 patients (73%). The tumor(s) involved only the left lobe in 7 patients and the right lobe in 4 (Tables 4 and 5).

Vascular Invasion. Ten patients (24.4%) had no evidence of vascular invasion (V0), 21 (51.2%) had microvascular invasion (V1), and 10 (24.4%) had gross vascular invasion (V2) (Tables 4 and 5). The main branch of the portal vein or the portal vein trunk was involved in 7 of the 10 cases with V2. There was one example of inferior vena cava invasion, and two of the hepatic vein.

Margins. The margins of resection were free of tumor (R0) in 34 cases. The margins of resection were microscopically positive (R1) in 4 other patients and grossly positive (R2) in the remaining 3 (Tables 4 and 5).

Metastases. Thirteen patients (31.7%) had regional metastatic disease (M1) at the time of surgery (Tables 4 and 5), which was resected in continuity with the principal tumor (Table 6).

Cirrhosis, Tumor Markers, and Serology. Three patients in the OLT group had associated cirrhosis (7.3%). One of these patients is alive 120 months after OLT, 1 died with tumor recurrence at 25 months, and the third patient died at 66 months with tumor recurrence.

Nineteen patients were tested for α-fetoprotein, with only 2 (10.5%) elevations. However, all of the 10 patients tested for Des-γ-carboxy prothrombin[28] had elevated serum levels despite normal levels of α-fetoprotein.

Of the 30 patients tested for hepatitis B virus, none had a positive serology. The positive rate for hepatitis C virus was 1 of 17 tested.

TNM Stage. The pTNM stages of the 41 patients are summarized in Tables 1 and 4; 90.2% presented with pTMN stage IVA or IVB. One of the 2 patients with stage II was transplanted for decompensated cirrhosis; the FL-HCC was an incidental finding in the surgical specimens.

TABLE 1. Patient Distribution According to pTNM Stage

Stage	No. of Patients	Resection	Transplantation
II	2	1	1
III	2	2	—
IVA	24	15	9
IVB	13	10	3

TABLE 2. Surgical Treatment of FL-HCC

Hepatic Resection (n = 28)	No. of Patients
Right trisegmentectomy (n = 12)	
Adrenal + diaphragm resection	1
Diaphragm resection	2
Left trisegmentectomy (n = 7)	
Stomach + omentum + diaphragm resection	1
Diaphragm resection	1
Left hepatectomy (n = 4)	
Right hepatectomy (n = 1)	
Left lateral segmentectomy (n = 2)	
Celiac axis LN resection	2
Wedge resection (n = 2)	
Omentum + periaortic LN resection	1
Liver transplantation (n = 13)	
Standard OLT (n = 7)	
OLT + pylorus + omentum resect. (n = 1)	
OLT + diaphragm resect. (n = 1)	
OLT + adrenal + diaphragm resection (n = 1)	
OLT + Whipple procedure (n = 1)	
OLT + cluster resection (n = 2)	

NOTE. n = 41.

TABLE 3. Adjuvant Therapy in Patients with FL-HCC

Resection Group			Transplant Group		
Presurgery	Postsurgery	No. of Patients	Presurgery	Postsurgery	No. of Patients
NO	NO	17	NO	NO	7
NO	CT	7	NO	CT	4
CT	CT	1	CT	CT	1
CT + RT	NO	1	RT	RT	1
RT	NO	1			
CT	NO	1			

Abbreviations: CT, chemotherapy; RT, radiotherapy; NO, no therapy.

TABLE 4. Tumor-Free Survival

Risk Factor	PHx/OLT (n)	P	PHx/OLT (mean ± SE [mo])
Tumor size			
≤10 cm	10/2	>.2	112.1 ± 30.4/83.0 ± 26.2
>10 cm	18/11		73.9 ± 20.2/44.4 ± 15.0
Tumor			
Single	21/9	>.7	96.9 ± 22.0/58.5 ± 19.3
Multiple	7/4		59.7 ± 22.6/34.8 ± 10.6
Distribution			
Unilobar	8/3	>.8	47.9 ± 14.7/59.7 ± 25.8
Bilobar	20/10		100.9 ± 22.9/47.9 ± 16.3
Margins			
(−)	23/11	>.9	63.8 ± 27.6/62.8 ± 19.7
(+)	5/2		100.7 ± 22.7/30.3 ± 15.5
Lymph nodes			
(−)	19/8	<.015	119.1 ± 23.5/74.6 ± 24.1
(+)	9/5		23.4 ± 6.0/29.6 ± 9.2
Vascular invasion			
V0	9/1	>.16	109.9 ± 29.5/120.0 ± 0.0
V1	18/3		79.9 ± 21.8/33.0 ± 11.7
V2	1/9		5.0 ± 0.0/46.4 ± 16.9
Metastasis			
M0	18/10	<.003	135.2 ± 24.3/63.4 ± 19.5
M1	10/3		21.4 ± 6.7/28.0 ± 12.1
pTNM stage			
I, II, III, and IVA	18/10	<.003	135.2 ± 24.3/63.4 ± 19.5
IVB	10/3		21.4 ± 4.4/28.0 ± 4.9
Chemo/radiation			
No	20/7	<.013	100.5 ± 19.5/84.9 ± 25.9
Yes	8/6		43.9 ± 25.1/26.8 ± 8.0

TABLE 5. Patient Survival

Risk Factor	PHx/OLT (n)	P	PHx/OLT (mean ± SE [mo])
Tumor size			
≤10 cm	10/2	>.06	190.7 ± 23.4/93.0 ± 19.1
>10 cm	18/11		116.3 ± 22.7/53.1 ± 14.4
Tumor			
Single	21/9	>.6	166.1 ± 22.4/61.7 ± 18.0
Multiple	7/4		106.5 ± 23.0/45.0 ± 8.0
Distribution			
Unilobar	8/3	>.65	121.3 ± 23.2/70.3 ± 22.5
Bilobar	20/10		155.5 ± 23.0/55.9 ± 8.3
Margins			
(−)	23/11	>.48	146.8 ± 29.7/68.6 ± 17.8
(+)	5/2		153.3 ± 23.2/41.0 ± 12.7
Lymph nodes			
(−)	19/8	>.18	173.0 ± 20.0/61.8 ± 18.8
(+)	9/5		55.0 ± 11.7/55.6 ± 18.5
Vascular invasion			
V0	9/1	<.05	81.9 ± 20.8/120.0 ± 0.0
V1	18/3		130.2 ± 23.5/34.0 ± 7.8
V2	1/9		26.0 ± 0.0/56.1 ± 15.8
Metastasis			
M0	18/10	>.18	177.7 ± 21.1/60.3 ± 16.1
M1	10/3		69.1 ± 14.5/44.0 ± 16.2
pTNM stage			
I, II, III, and IVA	18/10	>.18	177.7 ± 21.1/60.3 ± 16.1
IVB	10/3		69.1 ± 14.5/44.0 ± 16.2
Chemo/radiation			
No	20/7	>.09	156.7 ± 17.6/67.0 ± 20.7
Yes	8/6		102.3 ± 36.1/50.5 ± 15.8

Survival Rate

There were no deaths within 6 months after either PHx or OLT. Thereafter, survival after PHx was consistently superior, and, at 5 years, the gap was 44% (Fig. 2). However, because the conditions dictating the use of THx and OLT were different than those for PHx, comparison of survival with these therapeutic modalities has little value. Of the 18 patients who died after the surgical treatment, 16 died from causes related to the tumor occurrences. Two patients, both in the OLT group, died from sepsis.

The cumulative survival and the tumor-free survival of the combined cohorts are shown in Fig. 3. The mean cumulative survival was 126.93 ± 16.34 (SE) months. The mean tumor-free survival was 86.93 ± 15.24 (SE) months. The cumulative survivals and the tumor-free survivals, stratified according to the pTNM stages, are shown in Table 7. The differences in the cumulative survivals and tumor-free survivals among the pTNM stages were statistically significant (Table 7).

Prognostic Factors

The influence of nine clinicopathological factors on tumor-free and overall survivals were examined by univariate analysis (Tables 4 and 5). The involvement of regional lymph nodes (N1), the presence of metastasis (M1), and advanced pTNM stage were statistically significant prognostic factors reducing tumor-free survivals. Although these factors did not individually influence the overall survival at a statistically significant level, survival of the patients with stage IVB was significantly lower than that of those with stages II and III combined ($P < .05$) (Table 7). The presence of macrovascular invasion of the tumor was a statistically significant prognostic factor reducing overall survival, but it did not influence tumor-free survival. Unexpectedly, adjuvant chemotherapy tended to decrease the tumor-free survival (Tables 4 and 5).

Tumor Recurrence and Treatment

Recurrence of FL-HCC was confirmed in 27 (65.8%) of the 41 patients during the study period: 18 (64.2%) of the

TABLE 6. Sites of Metastatic Lesions of FL-HCC at the Time of Surgery

Case No.	Locations	Survival (mo)	Tumor-Free Survival (mo)
Hx9	Abdominal fat + celiac lymph nodes	40, DWD	30
Hx10	Abdominal fat	110, AWD	30
Hx11	Omentum + celiac lymph nodes	17, DWD	0
Hx14	Stomach	82, AWD	30
Hx15	Stomach + diaphragm + paraaortic lymph nodes	15, DWD	8
Hx18	Celiac + mediastinal lymph nodes	37, AWD	23
Hx19	Paraaortic lymph nodes + lung	37, AWD	33
Hx22	SMA lymph nodes + retroperitoneum	19, AWD	13
Hx25	Paraaortic lymph nodes + peritoneum	11, AWD	5
Hx28	Diaphragm	88, DWD	42
OLT10	SMA lymph nodes	16, DWD	13
OLT11	Paraaortic lymph nodes + pancreas	38, DWD	19
OLT13	Paraaortic lymph nodes	38, AWD	32

Abbreviations: SMA, superior mesenteric artery; DWD, died with tumor; AWD, alive with tumor.

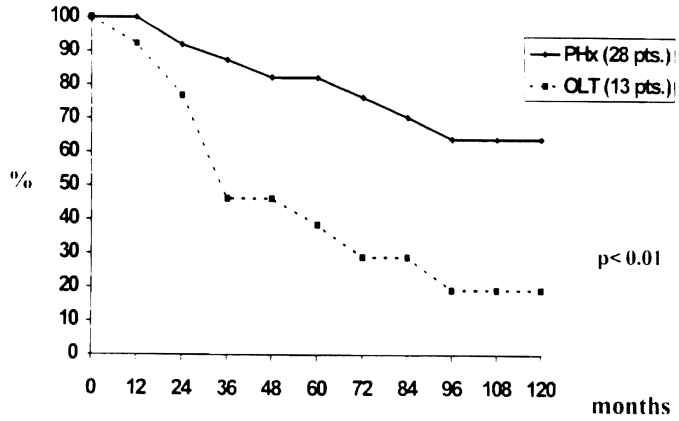

FIG. 2. FL-HCC: patient survival after PHx and THx with OLT.

28 treated with PHx and 9 (69.2%) of the 13 treated with THx and OLT. The time and site of tumor recurrence, treatment used for recurrence, and survival after diagnosis are summarized in Table 8. The liver was the organ most often involved, followed by the lungs and intra-abdominal lymph nodes.

Attempts at re-resection were made in 6 patients whose original surgery was PHx, and 3 who already had undergone THx and OLT. The secondary surgeries ranged from minor procedures to the drastic step of complete liver replacement in 3 cases, followed by survival of 2, 12, and 30 months (Table 8). After the diagnosis of tumor recurrence, the 18 patients initially treated with PHx lived for 1 to 80 months; the 9 first treated with OLT lived for 0 to 43 months. The overall actuarial postrecurrence survival in the combined group (n = 27) at 1, 3, and 5 years was 75%, 48%, and 28%, respectively (Fig. 4). The survival of the 9 patients whose recurrence was treated by surgical resection with or without combined chemotherapy was slightly better than that of the 13 patients who were treated with chemotherapy alone, but the difference was not statistically significant.

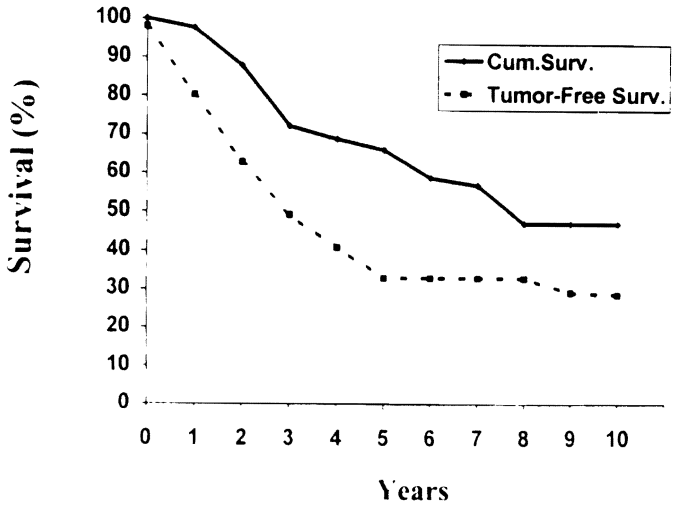

FIG. 3. FL-HCC: cumulative overall patient and tumor-free survival after surgery

Five-Year Survivors

Of the 31 patients treated more than 5 years ago, 19 (61.3%) achieved actual survival of at least 5 years; 15 (75%) of the 20 patients in the hepatic resection group and 4 (36.3%) of the 11 treated with OLT (Table 9 and Fig. 2). All 4 patients with tumor stage II or III survived for more than 5 years compared with 12 (63.1%) of the 19 with tumor stage IVA, and only 3 (37.5%) of 8 with tumor stage IVB. One of the 3 long survivors in the IVB group died after 7 years; the other 2 are alive with tumor after 7 and 9 years (PHx 10 and 14) (Table 9). The time of survival postrecurrence in these unusual cases has been 6.67 and 4.33 years.

DISCUSSION

FL-HCC was first identified by its unique histological features[1] and distinctive clinical behavior.[1,7] In our study (see Fig. 1), as well as in collected cases from the literature, FL-HCC showed a unimodal age distribution with the peak in the third decade. In contrast, common HCC has a bimodal age distribution when it occurs in the noncirrhotic liver with the peaks in the third and in the sixth decade,[29,30] and a unimodal peak in the fifth or sixth decade when cirrhosis is present.[30] The conventional HCC is more frequent in males than females, but the FL-HCC is found almost equally in females (44% in our series). FL-HCC is rarely found in the cirrhotic liver,[3,5,9] as was exemplified by only 3 (7.3%) of the 41 cases reported herein.

The tumor markers of FL-HCC have a characteristic pattern. In our series, only 10.5% of the patients tested had elevated serum α-fetoprotein levels, while the Des-γ-carboxy prothrombin serum level was elevated in all who were tested. The Des-γ-carboxy prothrombin level also identified tumor recurrence, whereas the AFP did not. High levels of neurotensin and vitamin B_{12} binding capacity also have been reported with FL-HCC,[11,13,31] but these were not determined in our cases.

The indolent growth of FL-HCC and an excellent long-term survival after surgery was first emphasized by Craig et al.[7] and by Berman et al.[8] in 1980, based largely on cases collected from the literature. Although Nagorney et al. were the first to question the prognostic significance of this diagnosis in 1985,[2] our report 1 year later[4] contained evidence that patients with FL-HCC were excellent candidates for aggressive surgery. Since then, the clinical significance of a histopathological diagnosis of FL-HCC has been debated among investigators, analyzing small numbers of their own cases in combination with reviews of the literature. Some

TABLE 7. Cumulative and Tumor-Free Survivals According to pTNM Stages

	Cumulative Survival			Tumor-Free Survival		
	II–III (n = 4)	IVA (n = 24)	IVB (n = 13)	II–III (n = 4)	IVA (n = 24)	IVB (n = 13)
1 yr	100%	95.8%	100%	75%	78.8%	76.9%
3 yr	100%	66.3%	75%	75%	60.9%	15.4%
5 yr	100%	66.3%	50%	75%	45.7%	0
10 yr	100%	44.2%	N/A	75%	39.2%	0

* $P < .05$.
† $P < .002$.

TABLE 8. Time and Site of Recurrence, Treatment of Recurrence, and Survival After the Diagnosis of Recurrence

Patient	Time of Recurrence (mo)	Site of Recurrence	Treatment of Recurrence	Survival After Recurrence (mo)	Status
Hx 6	110	Medistinum LN + chest wall	CT + RT	40	AWT
Hx 7	41	Liver	OLT	30	DWT
Hx 9	30	Lung	CT	10	DWT
Hx 10	30	Peritoneum + liver	CT	80	AWT
Hx 11	0	Abdominal LN + liver	CT	17	DWT
Hx 13	18	Stomach + peritoneum + liver	CT	9	DWT
Hx 14	30	Liver		52	AWT
Hx 15	8	Lung + abdominal LN	CT	7	DWT
Hx 16	5	Abdominal LN + bone + lung	CT	68	DWT
Hx 18	23	Lung	Sx.	14	AWT
Hx 19	33	Lung	CT + Sx.	4	AWT
Hx 20	5	Paraortic LN + liver	CT + Sx.	21	AWT
Hx 22	13	Paraortic LN + liver	CT	6	AWT
Hx 23	64	Liver	Sx.	2	AFT
Hx 24	10	Retroperit. LN		4	AWT
Hx 25	5	Paraaortic LN + adrenal Rt.	CT	7	AWT
Hx 26	7	Liver	CT	1	AWT
Hx 28	42	Chest wall + mediast. + paraaortic LN + liver + IVC	CT + Sx.	46	DWT
OLT 1	12	Liver + diaphragm + chest wall + lung + retroperit. LN	OLT	2	DWT
OLT 2	32	Pelvis + diaphragm		0	DWT
OLT 5	16	Lung	CT	16	DWT
OLT 8	13	Liver	OLT	12	DWT
OLT 9	52	Liver + pancreas + adrenal Rt		43	DWT
OLT 10	13	SMA LN	CT	3	DWT
OLT 11	19	Mediast. LN + bone + lung	CT + RT	39	DWT
OLT 12	46	Lung		20	DWT
OLT 13	52	Lung	Sx.	6	AWT

Abbreviations: CT, chemotherapy; RT, radiotherapy; Sx, surgery; SMA, superior mesenteric artery; LN, lymphnode; AFT, alive free of tumor; DWT, death with tumor; AWT, alive with tumor.

authors have not found the diagnosis of FL-HCC to confer a survival advantage,[3,14] but others confirmed the original claims.[11,12,17]

The 41 patients with FL-HCC reported herein of whom 31 were operated upon more than 5 years ago constitute the largest series with the longest follow-up known to exist. The cases were accrued over a 3-decade period by a single group of surgeons committed to aggressive treatment of these neoplasms. Despite the fact that 90% of tumors presented with pTNM stage IVA or IVB, our overall actuarial survival was

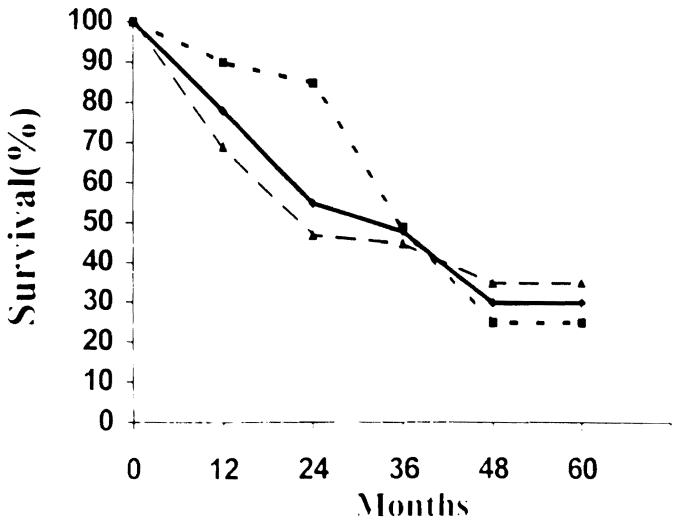

FIG. 4. Patient survival after recurrence. (—◆—) All patients (n = 28); (—■—) surgery (n = 9); and (—▲—) chemotherapy (n = 13).

TABLE 9. List of 19 Five-Year Survivors

Case No.	Age/Sex	Stage	Recurrence	Survival
Hx 1	9/M	IVA	No	Alive 19 yr
Hx 2	31/F	IVA	No	Alive 17 yr
Hx 3	9/M	IVA	No	Alive 16 yr
Hx 4	14/M	IVA	No	Alive 13 yr
Hx 5	33/M	IVA	No	Alive 13 yr
Hx 6	40/M	IVA	Yes	Alive 13 yr
Hx 7	23/M	IVA	Yes	Died 6 yr
Hx 8	19/M	II	No	Alive 10 yr
Hx 10	59/F	IVB	Yes	Alive 9 yr
Hx 12	23/M	IVA	No	Alive 8 yr
Hx 14	26/F	IVB	Yes	Alive 7 yr
Hx 16	19/F	IVA	Yes	Died 6 yr
Hx 23	45/F	III	No	Alive 6 yr
Hx 27	19/F	III	Yes	Died 12 yr
Hx 28	39/M	IVB	Yes	Died 7 yr
OLT 3	26/M	IVA	No	Alive 13 yr
OLT 7	43/M	II	No	Alive 10 yr
OLT 9	24/M	IVA	Yes	Died 8 yr
OLT 12	58/M	IVA	Yes	Died 6 yr

66.2% at 5 years and 47.4% at 10 years. The higher survival compared with that reported by others[2,3] could be explained in part by our wide use of extensive hepatic resection (including adjacent structures) at the original surgery, and an aggressive surgical approach to the recurrent tumors.

However, the most important factor obviously was the biological behavior of FL-HCC, the results with which can be compared with our contemporaneous experience with conventional HCC. In patients with HCC in noncirrhotic liver, 5-year global survival was 43.7% after hepatic resection and 26% after transplantation.[6] However, the 5-year survival when the HCC was stage IVA was only 16.8% after PHx and 10.9% after OLT,[6] similar to the experience of others.[32-38]

The indolent growth of FL-HCC was especially obvious when recurrences developed. Even after the diagnosis of tumor recurrence, survival was 75% at 1 year, 48% at 3 years, and 28% at 5 years (Fig. 4). Surgical excision of recurrent tumor with or without chemotherapy may have prolonged survival, but, if so, only minimally. Cytoreductive chemotherapy was clearly ineffective. Adjuvant chemotherapy from the outset did not improve survival. However, the impression that it may have been harmful (see Tables 4 and 5) reflected in part the selection for chemotherapy of patients with advanced tumor stage. Of the 16 patients who received adjuvant chemotherapy, 6 had stage IVA and 10 had stage IVB tumor. Eleven patients had positive lymph nodes, and 15 patients had vascular invasion by the tumor.

Because of the limited number of cases at stages II and III, a conventional analysis of stratification-specific prognostic factors could not be performed. However, the good results obtained with hepatic resection or transplantation for FL-HCC that was staged at IVA or IVB in >90% of cases can be construed as evidence of the indolent growth, favorable natural behavior, and suitability for aggressive treatment of these tumors.

In conclusion, the therapeutic approach that we recommend for FL-HCC is wide hepatic resection including the adjacent structures if they are invaded by the tumor. PHx is the treatment of choice if at least one liver segment can be saved. If the presence of underlying liver disease or the location of the tumor preclude PHx, THx with OLT should be considered. Adjuvant chemotherapy so far has not shown any benefit in patient survival and tumor-free interval. An aggressive surgical approach of tumor recurrences after primary treatment can extend the patient survival.

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