Liver Transplant for Hepatocellular Carcinoma: Experience in a Saudi Population

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Abstract

Objectives: **We present our experience with deceased-donor liver transplant and living-donor liver transplant for hepatocellular carcinoma. Between 2001 and 2007, we transplanted 133 organs (84 deceased-donor liver transplants, 49 living-donor liver transplants) in 126 patients (4 retransplants). Twenty-three patients had hepatocellular carcinoma (14 deceased-donor liver transplants and 9 living-donor liver transplants).**

***Materials and Methods*: The medical records of these patients were reviewed for recipient clinical, biochemical, and imaging characteristics. Slides of explants were assessed. Overall survival and tumor recurrence states were determined. All characteristics were tested for their prognostic significance.**

***Results*: The median age of the patients was 55 years and the median Mayo End-stage Liver Disease score was 16. The alpha-fetoprotein was ≥ 400 ng/mL in 4 patients. Histopathology revealed incidental cholangiocarcinoma in 2 patients and a hepatoblastoma in 1. The mean tumor size was 4 cm; the mean number of lesions was 2. Most tumors were graded as well or moderately differentiated; 4 were poorly differentiated. Gross macrovascular invasion was seen in 2 patients, while microvascular invasion was seen in 9. After a mean follow-up of 736 days, overall patient and graft survival rates were 80.9% and 76.2%; overall disease-free patient and graft survival rates were 76.2% and 71.4%. Two patients died of primary graft nonfunction within 1 week of the transplant. Three had tumor recurrence at 10, 13, and 18 months after transplant; 2 of these occurred in patients with cholangiocarcinoma. Two of these 3 died from an advanced tumor within few months. Significant risk factors for recurrence were gross major vessel invasion, microvascular invasion, tumor size, poor histologic differentiation, and absence of pretransplant tumor control therapy. The latter 2, in addition to Mayo End-stage Liver Disease score and preoperative alpha-fetoprotein, were independent predictors of mortality.**

Conclusions: **In our small experience, deceased-donor liver transplant and living-donor liver transplant for hepatocellular carcinoma showed good long-term outcomes. Liver transplant for hepatocellular carcinoma accompanying cholangiocarcinoma had a poor outcome with late tumor recurrence. Use of marginal donors in patients with hepatocellular carcinoma might compromise the outcome in these patients.**

Key words: *Vascular invasion, Tumor biology, Tumor recurrence, Overall survival, Pretransplant imaging*

Hepatocellular carcinoma is an aggressive cancer with an overall poor prognosis. Unfortunately, the incidence of hepatocellular carcinoma is rising world-wide. The prevalence of hepatitis C and hepatitis B infection explains up to half of this increased incidence (1). Because of the high prevalence of both hepatitis C and hepatitis B in Saudi Arabia, hepatocellular carcinoma is becoming a major health concern (2, 3)

Conventional treatments for hepatocellular carcinoma include surgical resection and nonsurgical treatments such as chemoembolization, ablation, and

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injection therapy. However, surgery is limiting because excision of the tumor is not always complete, and the patient's safety can be risked if functional reserve is compromised. And nonsurgical treatments, when applied to advanced hepatocellular carcinoma lesions, often result in incomplete tumor control and have high recurrence rates. On the other hand, liver transplant in well-selected patients offers the theoretical appeal of both complete removal of the tumor-bearing liver and restoration of normal liver function, although there is an additional risk of accelerated tumor recurrence from immunosuppression (5).

Until recently, deceased-donor liver transplant, rather than living-donor liver transplant was done for hepatocellular carcinoma; the role of living-donor liver transplant in the surgical treatment of these patients had not been firmly established. Moreover, the current selection criteria for liver transplant for patients with hepatocellular carcinoma were derived from the outcomes of deceased-donor liver transplants only. However, donor organ scarcity and long wait times became the main impetus for implementing living-donor liver transplant for hepatocellular carcinoma (6).

We present our experience with deceased-donor liver transplant and living-donor liver transplant for hepatocellular carcinoma, particularly in terms of tumor recurrence and long-term survival. Also in this study, to identify predictors of recurrence of hepatocellular carcinoma in our patients, we explore the pathologic features of the hepatic neoplasms identified in the explanted livers at our institution.

Materials and Methods

Patient population and clinical assessment

From April 2001 to April 2007, a total of 133 liver transplants (84 deceased-donor liver transplants and 49 living-donor liver transplants) were done in 129 patients (4 retransplants). Of these recipients, 23 patients (18%) with confirmed hepatocellular carcinoma on liver explant were identified. In 21 patients, the tumor was preoperatively diagnosed by computed tomography scanning or magnetic resonance imaging. It was confirmed by pretransplant biopsy in only 3 of these patients. In 2 patients, hepatocellular carcinoma was incidentally diagnosed on histologic examination of the explanted livers. Twenty-one patients met the Milan criteria; however, the criteria were exceeded in only 2 patients.

Clinical records were reviewed for the recipients' clinical, biochemical, and imaging characteristics including underlying cause of chronic liver disease, donor and liver transplant operation (deceased-donor liver transplant, living-donor liver transplant, and graft type), primary hepatocellular carcinoma lesion (timing of diagnosis, pretransplantation radiologic features: number, size of tumor, gross hepatic or portal vein invasion, bilaterality), pretransplant tumor control therapy, wait list time, Mayo End-Stage Liver Disease (MELD) score at transplant, pretransplant serum alpha-fetoprotein level, perioperative course, and type of initial immunosuppression.

Pathological assessment

The reports and slides of explants of all patients were retrieved from the pathology files. Each case was assessed for multiple standard pathological features that characterize tumor biology, including the following:

- Tumor number and tumor size as obtained from the gross pathology report. The tumor size was measured as the largest diameter of the major tumor in centimeters.
- Tumor edge: assessed for the presence or absence of a capsule.
- Degree of differentiation.
- Microsatellitosis: defined as microscopic multifocality, in which a satellite nodule was separated from the main tumor by a distance greater than the satellite diameter.
- Necrosis.
- Microvascular invasion: defined as invasion of either vascular (artery or vein) or lymphatic spaces within the parenchyma of the liver, as evidenced by identification of tumor cells within endothelial-lined spaces on standard slides stained with hematoxylin and eosin.
- Macrovascular invasion defined as gross vascular invasion into major portal vessels or hepatic veins on pathologic explant.

Postoperative follow-up

Patients were followed postoperatively with routine computerized tomography or magnetic resonance imaging and serum alpha-fetoprotein levels along with standard evaluation after liver transplant. Surveillance was done every 6 months for the first 2 years and annually thereafter. Tumor recurrence was determined on the basis of imaging and serum alpha-fetoprotein.

The timing, site, and criteria were noted. Other postoperative complications were also recorded. Patients were followed until death or study closure. Data were collected until June 1, 2007. Overall survival was defined as death as a result of any cause after liver transplant. Causes of death were noted, and recurrence-free survival, defined as death as a result of tumor recurrence, was reported.

Statistical analyses

Mean values with standard deviation and median values with ranges were used for numeric data. Statistically significant differences were assessed with the chi-square and *t* tests. The chi-square and *t* tests were used to compare pretransplant clinical features of deceased-donor liver transplant and living-donor liver transplant recipients as well as their outcomes. A Pearson correlation analysis was used to determine correlations between radiologic and pathologic findings. Demographic, tumor, and histopathologic characteristics were tested for their prognostic significance using univariate analyses. Multivariate analyses were done to determine features mostly associated with mortality. Recurrence-free survival and overall survival were evaluated by Kaplan-Meier analyses.

Results

Patient characteristics

Fifteen patients with hepatocellular carcinoma underwent a deceased-donor whole liver transplant and 8 underwent a living-donor liver transplant. The median age at the time of transplant was 55 years (range, 5-63 years), and the majority of patients were men (n=15; 65%). The patients had several underlying causes of cirrhosis, including hepatitis C in 14 patients, hepatitis B in 6 patients, unknown in 2, and congenital hepatic fibrosis in 1. Serum alpha-fetoprotein was significantly elevated (> 400 ng/mL) in only 4 patients. In these 4 patients, the level ranged from 622 to 13242 ng/mL.

Five patients (21%) underwent therapy before the transplant in the form of radiofrequency or percutaneous ethanol ablation or both, but the majority of patients received no treatment before liver transplant because of poor liver function or a prescheduled living-donor liver transplant operation (79%). Three patients underwent radiofrequency ablation, 1 patient underwent alcohol injection, and 1 patient underwent consecutive sessions of both modalities. Use of ablation did not result in any adverse outcomes in this series of patients who underwent eventual liver transplant.

The average waiting time for liver transplant was 11 months in the case of deceased-donor liver transplant. The median MELD score at transplant was 16 (range, 9-40). The median number of blood transfusions needed was 5 units (range, 0-19 units), and the median hospital stay was 16 days (range, 6-48 days).

The patient characteristics of the 15 deceased-donor liver transplant and 8 living-donor liver transplant recipients are compared in Table 1. These data revealed that there were no gross differences between the groups, but the MELD score was lower in patients in the living-donor liver transplant group.

Table 1. Demographic data, MELD score, and serologic profile of recipients

	Deceased-donor liver transplant	Living-donor liver transplant	*P* value
Age (y)			
Range	5 - 63	36 - 64	
Mean ± SD	48.78 ± 17.46	55.14 ± 8.05	.164
Sex			
Male	10	6	
Female	4	3	.2
MELD score at transplant			
Range	6 - 40	7 - 17	
Mean ± SD	16 ± 10	12 ± 3	.08

Abbreviations: MELD, Mayo End-Stage Liver Disease

Patient outcomes

Explant pathology

Histopathological examination of the explanted livers demonstrated cirrhosis in all and confirmed hepatocellular carcinoma that was preoperatively diagnosed in 20 patients, while in 2 patients, 3 tumors were identified incidentally. Two cases, preoperatively diagnosed as hepatocellular carcinoma, proved to be combined hepatocellular carcinoma and cholangiocarcinoma, associated with hepatitis–C-related cirrhosis in 1 and congenital hepatic fibrosis in the other (Figure 1). One patient (a 5-year-old child) had combined hepatocellular carcinoma and hepatoblastoma, both of which were identified incidentally (Figure 2). A case of grade-III hepatocellular carcinoma showed focal sarcomatoid changes (Figure 3).

The number of tumors ranged from 1 to 6. The tumors ranged in size from 1.3 to 6.5 cm. The size of the tumors before the transplant was correctly identified in 26% of patients (percentage agreement

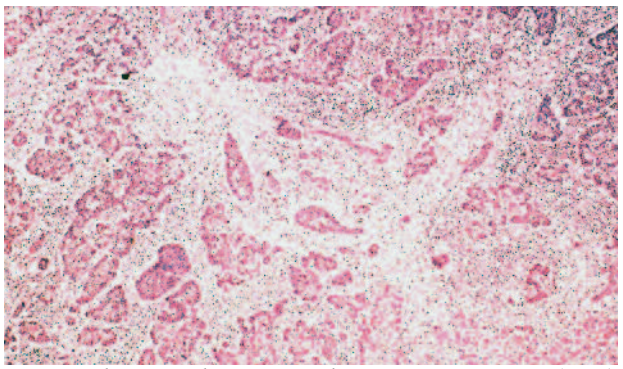

Figure 1. This patient has combined hepatocellular carcinoma (HCC) and cholangiocarcinoma. This photo depicts cholangiocarcinoma at low power.

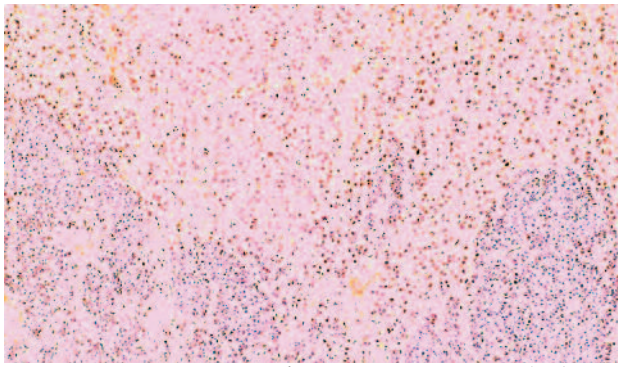

Figure 2. Case of combined hepatocellular carcinoma (top) and hepatoblastoma (bottom) in a 5-year old girl. (H & E × 200)

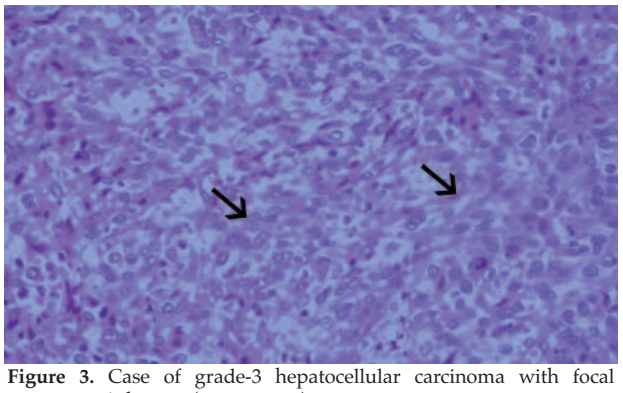

Figure 3. Case of grade-3 hepatocellular carcinoma with focal sarcomatoid changes (H & E × 400)

between radiologic and pathologic findings = 26%). The percentage of agreement for the number of tumors was 33.3%. Figures 4 and 5 demonstrate the correlation between the pathologic size and the number of tumors and those detected by pretransplant imaging (r=0.23, *P* = .27, and r=0.54, *P* = .01 respectively). Tumors were multifocal in 5 patients (21%). Most tumors were graded as well or moderately differentiated, only 3 tumors had areas of poor differentiation. Gross macrovascular invasion was seen in 2 of the explants on pathologic

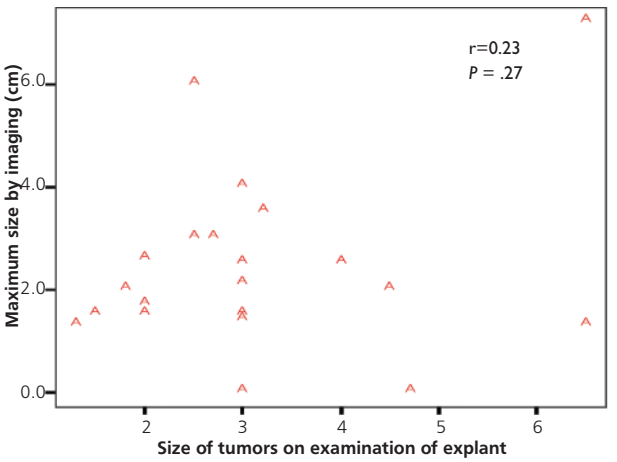

Figure 4. Correlation between the size of the tumors as detected by radiology and pathologic examination

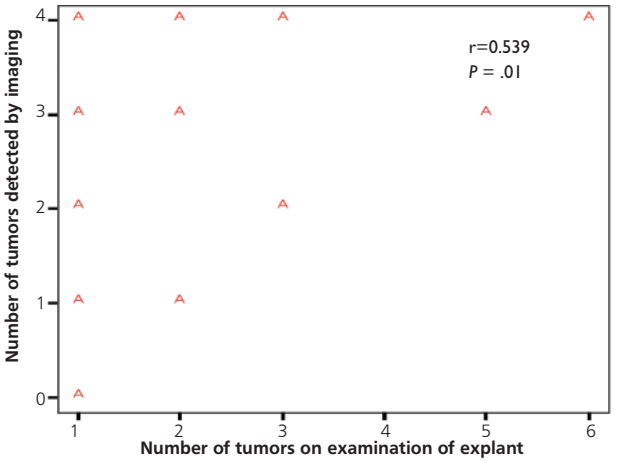

Figure 5. Correlation between the number of the tumors detected by radiology and pathology examination

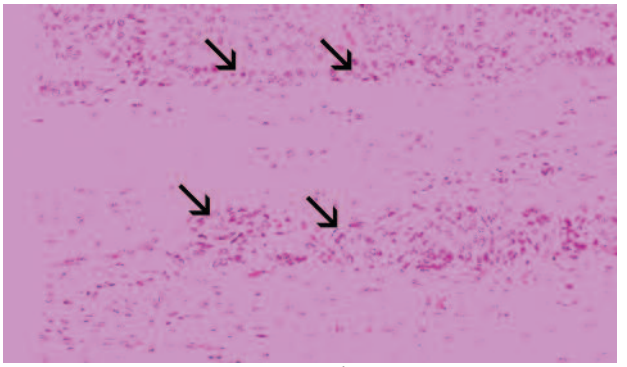

Figure 6. Hepatocellular carcinoma with vascular invasion

examination, whereas 12 explants demonstrated the presence of microvascular invasion (Figure 6). Both cases of combined hepatocellular and cholangiocarcinoma were multiple and showed microvascular invasion. No extrahepatic spread was seen in any of the explanted livers.

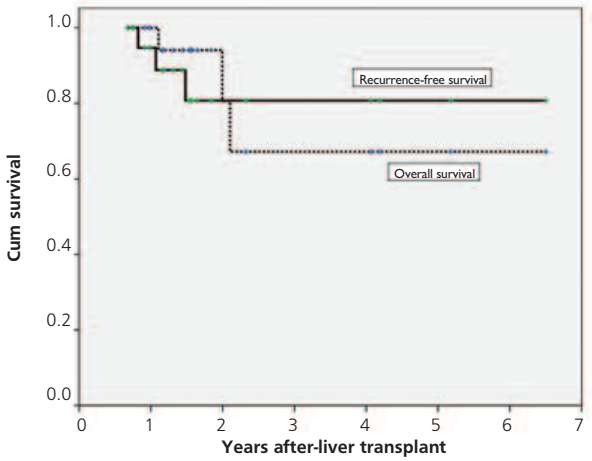

Figure 7a.

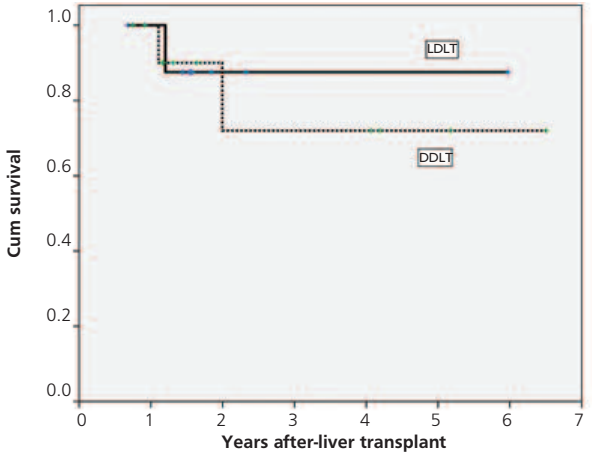

Figure 7b.

Abbreviations: DDLT, deceased-donor liver transplant; LDLT, living-donor liver transplant

Clinical course

After a follow-up ranging from 5 months to 6 years, 18 patients are currently alive and free of cancer (disease-free). The overall patient survival rates were 94%, 80.7%, and 67.2% at 1 year, 2 years, and 5 years. The overall recurrence-free patient survival rates were 88.8% at 1 year and 80.7% at 2 and 5 years (Figure 7a). One patient who underwent a living-donor liver transplant had a hepatic artery thrombosis and received a retransplant 14 days later using a deceased-donor organ. Two patients died within 1 week of the transplant of primary nonfunction of the graft. After excluding the 2 patients who died during the perioperative period after deceased-donor liver transplant, there was no significant difference in the cumulative survival rate of both groups. The deceased-donor liver transplant survival rate was 90% at 1 year and 72% at 5 years; the rate for living-donor liver transplant was 87.5% at 1 year and 5 years (Figure 7b).

Table 2. Outcome after deceased-donor liver transplant and living-donor liver transplant

	Deceased-donor liver transplant	Living-donor liver transplant	*P* value
Perioperative mortality/ morbidity	4	1	.32
Recurrence status	2	1	.52
Survival (mortality)	4	1	.01*

*P = significant.

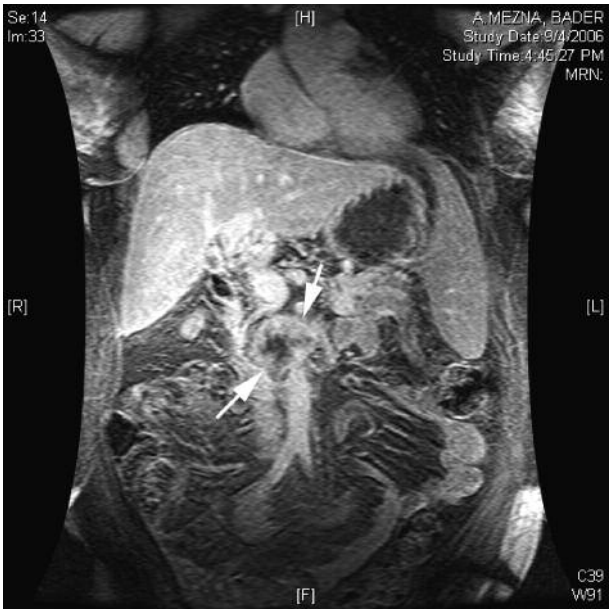

Figure 8 Recurrent Cholangiocarcinoma after deceased-donor liver transplant in the form of malignant para-aortic lymphadenopathy

The living-donor liver transplant group had more tumors and a higher rate of incidental tumors. The histopathological tumor size and grade were comparable (Table 2).

Tumor recurrence was diagnosed in 3 of the remaining 21 patients (recurrence was diagnosed at 10, 13, and 18 months after transplant); 1 of the 3 recurrences occurred in the patient with cholangiocarcinoma in the form of malignant para-aortic lymphadenopathy (Figure 8), the second in the form of lung metastases, and the third in the form of local liver metastases and para-aortic lymphadenopathy. The 3 with a recurrence died of an advanced tumor within a few months of the diagnosis of the recurrence. Other postoperative complications included acute cellular rejection in 2 patients, combined graft-versus-host disease and disseminated cytomegalovirus infection in 1 patient, and mild histologic recurrence of hepatitis C in 5 patients.

Predictors of tumor recurrence and patient survival: *Risk factor analysis for posttransplant hepatocellular carcinoma recurrence*

Univariate analyses were done on all the patients (both living-donor liver transplant and deceased-donor liver transplant) to determine the risk factors for tumor recurrence and mortality. The patterns of hepatocellular carcinoma recurrence in the deceased-donor liver transplant group seemed to be similar to those of the living-donor liver transplant group, and because of the small sample numbers, the groups were not separately evaluated. Significant risk factors were absence of pretransplant tumor control therapy, gross major vessel invasion, microvascular invasion, tumor size, and poor histologic differentiation. The 2 patients who exceeded the Milan criteria did not have a recurrence (Table 3).

Regarding patient survival, significant risk factors were MELD score, alpha-fetoprotein level, absence of pretransplant tumor control therapy, poor histologic differentiation, and gross major vessel invasion (Table 4). We also did multivariate analyses with the data of living-donor liver transplant and deceased-donor liver transplant all together (n=23), by which the absence of preoperative antitumor therapy, MELD score, poor histologic differentiation, and preoperative alpha-fetoprotein were proven to be independent predictors of mortality (Table 5).

Table 3. Univariate analysis of tumor recurrence factor

	Number	Recurrence rate (%)	Significance (*P* value)
Sex			.325
Male	14	7	
Female	9	22	
Virus			.098
Negative	3	33.3	
Hepatitis B	6	0.0	
Hepatitis C	14	14.3	
MELD score			.108
≤ 10	7	28.6	
> 10 to ≤ 20	14	7	
> 20 to ≤ 30	0	0	
> 30	2	0	
Preoperative alpha-fetoprotein			.215
< 20 ng/mL	10	10	
20 ng/mL to 200 ng/mL	6	16.6	
> 200 ng/mL to < 1000 ng/mL	2	0	
> 1000 ng/mL	3	33	
Pretransplant tumor control therapy			.042*
None	18	16.7	
Chemoembolization or RFA	5	0	
Tumor distribution (1)†			.41
Unilobar	17	11.7	
Bilobar	5	20.0	
Number of tumors			.11
1	15	13	
2	4	0	
3	2	50	
4	2	0	

Abbreviations: MELD, Mayo End-Stage Liver Disease; RFA, radiofrequency ablation.
†Number of missing data *significant *P* value.

Table 4. Univariate analysis of survival

	Number	Survival rate (%)	Significance
Sex			.21
Male	14	85.7	
Female	9	77.7	
Virus			.11
Negative	3	100	
Hepatitis B	6	86.0	
Hepatitis C	14	79.0	
MELD score			.05*
≤ 10	7	85.7	
> 10 to ≤ 20	14	85.7	
> 20 to ≤ 30	0	100	
> 30	2	50	
Preoperative alpha-fetoprotein			.042*
< 20 ng/mL	10	70	
20 ng/mL to 200 ng/mL	6	83	
> 200 ng/mL to < 1000 ng/mL	2	100	
> 1000 ng/mL	3	100	
Pretransplant tumor control therapy			.0001*
None	18	22.2	
Chemoembolization or RFA	5	100	
Tumor distribution (1)†			.061
Unilobar	17	76.5	
Bilobar	5	100	
Number of tumors			.103
1	15	80	
2	4	0	
3	2	50	
4 or more	2	0	
Tumor size (1)†			.013*
0 to ≤ 2 cm	6	66	
> 2 cm to ≤ 5 cm	14	60	
> 5 cm	2	100	
Microvascular invasion (2)†			.111
Yes	12	75	
No	9	91.6	
Gross vascular invasion (2)†			.41
Yes	2	50	
No	19	50	
Microsatellitosis (3)†			.16
Yes	3	100	
No	17	77.5	
Histologic differentiation (2)†			.025*
Well differentiated	8	87.5	
Moderately differentiated	10	90	
Poorly differentiated	3	66.7	
Tumor necrosis			.0028*
Present	3	66	
Absent	20	95	
Milan criteria			.11
Within	21	80.9	
Exceeded	2	100	

Abbreviations: RFA, radiofrequency ablation
†Number of missing data; *significant *P* value

Table 5. Multivariate analysis of the independent risk factors for survival in patients with hepatocellular carcinoma

Risk factor	Relative risk	95% confidence interval
MELD score	1.33	0.91 - 2.65
Preoperative alpha-fetoprotein	1.03	1.22 - 3.05
Histologic differentiation	1.28	0.52 - 4.11
No treatment before transplant	2.03	0.62 - 7.32

Abbreviations: MELD, Mayo End-Stage Liver Disease;

Discussion

Viral-related hepatocellular carcinoma is becoming a significant health problem in Saudi patients. In this study, about one-fifth of our transplant recipients had hepatocellular carcinoma, with more than 85% having underlying hepatitis B or hepatitis C infections.

Liver transplant can restore normal liver functioning with a high probability of prolonged survival; however, perioperative mortality and early recurrence of hepatocellular carcinoma do occur. The Milan criteria suggest that liver transplant may offer a chance of prolonged survival when the hepatocellular carcinoma lesion does not exceed their proposed eligibility criteria. According to these criteria, liver transplants for hepatocellular carcinoma are limited to patients with solitary tumors up to 5 cm in diameter, or those with no more than 3 nodules, each 3 cm or less in diameter. Patients with extrahepatic spread and/or macrovascular invasion are ineligible.

Mazzafero and coworkers stated that 5-year actuarial survival rates are approximately 75% in patients who meet the Milan criteria (7). The reports of Yao and colleagues and Teketoma stretched the Milan criteria equivalent results in terms of survival, stating that in well-selected patients, exceeding the Milan criteria in terms of tumor size did not necessarily reduce the survival rates after liver transplant (8, 9). Hwang and associates and Todo and associates (5, 10), in their report of the collective multicenter data from Korea and Japan, respectively, advocated living-donor liver transplant for hepatocellular carcinoma and proposed extensions of the Milan criteria with encouraging results. Todo and associates demonstrated that when the Milan criteria were applied, patient survival rates at 3 years were 78.7% in patients who met the criteria and 60.4% in those who did not (10). In the present study, the long-term 2-year and 5-year survival rates were 80.7% and 67.2%. Two patients fell outside the Milan criteria and are doing well at the time of this writing. MELD score in the current study, rather than Milan criteria, was the most important determining risk factor in the multivariate analysis of the factors for survival of the patients, followed by histologic differentiation. Hence, relying on this model in both deceased-donor liver transplant and living-donor liver transplant is helpful.

Our deceased-donor liver transplant program became hampered by a severe organ shortage. This had a negative impact on patients with cirrhosis with hepatocellular carcinoma, because during this time, patients either died or their tumors became so large that the tumor could not be resected. We therefore began doing living-related liver transplant as an alternative for these patients. Before, these patients were listed along with all the other non-HCC patients according to the priority of their liver disease: They received a transplant whenever a deceased-donor organ became available. Today, however, this has changed, and now, patients must get a graft from a living relative, or they will be given marginal deceased-donor livers. At our program, long-term survival rates from living-donor liver transplants and deceased-donor liver transplants do not differ significantly. The documented operative mortality rate in living-donor liver transplant is approximately 9% (11); in this series, none of the patients who had received a living-donor liver transplant died, and only 1 required a retransplant because of a hepatic artery thrombosis. The 2 patients who died immediately after surgery had received deceased-donor liver transplants; their deaths may be attributed to our trend to use marginal donors in patients with hepatocellular carcinoma.

In living-donor liver transplant, the safety of the living donor is of the utmost importance. Fortunately, there were no deaths of the living donors in our series to date, but we have never ignored the real incidence of serious donor complications, not to mention the real occurrence of living-donor death (11, 12, 13).

Tumor recurrence is the main concern during liver transplant for hepatocellular carcinoma. In the present series, the overall rate of recurrence for hepatocellular carcinoma after liver transplant was 13%. This is in accordance with most studies, which report recurrence rates ranging from 11% to 17% (8, 14). Regalia and associates reported that 70% of tumor recurrences occurred within the first 18 months after transplant (15). In the current series, tumor recurrence in 3 patients was diagnosed at 10, 13, and 18 months. It had been hypothesized that living-donor liver transplant may be associated with an adverse effect on the recurrence of hepatocellular carcinoma, because contrary to what happens when a deceased donor organ is used, regeneration of a partial liver graft in the early postoperative period is inevitable after transplant from a living donor and may be associated with acceleration of tumor cell growth (11).

This adverse effect was not seen in the current study. Only 1 of the patients who had received a living-donor liver transplant—a 5-year-old girl with

combined hepatocellular carcinoma and hepatoblastoma—had a recurrence after 18 months. Actually, after a living-donor liver graft has regenerated, there would be no difference in tumor biology between a deceased-donor liver transplant and a living-donor liver transplant. Therefore, the crude risk of hepatocellular carcinoma recurrence may be the same following either deceased-donor liver transplant or living-donor liver transplant, especially if the Milan criteria are applied in either scenario. In the current series, the 2 patients who exceeding the Milan criteria (1 deceased-donor liver transplant and 1 living-donor liver transplant) did not have a recurrence.

Currently, there are no widely accepted pretransplant criteria or explant pathology strategies to predict recurrence after liver transplant in patients with hepatocellular carcinoma. Among the preoperative variables is pretransplant alpha-fetoprotein, which is not included in the existing selection criteria for transplant for hepatocellular carcinoma.

Alpha-fetoprotein has been reported in some studies to be an important predictor of tumor recurrence, especially when above 1000 ng/mL, with this level independently predicting microvascular invasion in tumors larger than 5 cm on multivariate analysis (16). Yao and associates showed that an alpha-fetoprotein level greater than 1000 ng/mL, a total tumor diameter larger than 8 cm, and poorly differentiated histologic grade were significant predictors for reduced survival after liver transplant for hepatocellular carcinoma (17). Yang and associates devised new scoring criteria that included tumor size, tumor number (based on pretransplant imaging), and pretransplant alpha-fetoprotein level as prognostic factors; these scoring criteria correlated with risk of death and hepatocellular carcinoma recurrence (18). In our limited experience, only 5 of our patients had an alpha-fetoprotein level above 1000 ng/mL, and only 1 had a recurrence. Other patients with recurrence had alpha-fetoprotein levels lower than 200 ng/mL. Because of the limited number of persons in the study population, it was not possible to design a multivariate analysis to determine the risk factor of this variable in predicting recurrence.

In addition to the clinical findings, the decision of whether to proceed with transplant in patients with hepatocellular carcinoma with cirrhosis is also based on imaging findings. Pretransplant imaging is done to estimate the size and number of tumors and to detect those within Milan criteria, as well as major vascular invasion, nodal, or distant metastases. Assignment of liver allocation priority for hepatocellular carcinoma is predicated on accurate imaging staging. In our experience, there is a discrepancy between the pretransplant size and number of the tumors, and the pathologic size, especially if the interval of the pretransplant imaging was long. In this series, 33% of the patients had correct identification of the number of tumors present; only 26% had a tumor diameter that was correctly identified by pretransplant radiologic examinations. A similar finding was reported by Sotiropoulos and associates (19) who found a 14.3% agreement between the imaging and pathologic examination regarding size and a 33.3% agreement regarding the number, with a high incidence of false-negative and false-positive results. Libbrecht and associates reported that tumor stages are incorrectly diagnosed in 20% to 30% of patients even with current imaging techniques (20). The potential risk of underestimation of the tumors by imaging also was stated by Choi (21). In fact, to date, there is no general agreement on the most appropriate imaging technique to detect the tumor for correlation between pretransplant radiologic and pathologic size of the tumor. Hence, a critical appraisal of patient characteristics together with great caution when interpreting imaging studies is recommended to determine candidacy for transplant.

Use of interventional radiologic management for pretransplant tumor control, in the present series, seems helpful to diminish the risk of recurrence. All the patients who received radiofrequency ablation or alcohol injection did not have a tumor recurrence. Pretransplant treatment modalities appear to confer additional benefits to the recipients in reducing hepatocellular carcinoma recurrence; in addition, patients with a higher potential for recurrence would have been eliminated before living-donor liver transplant could be attempted (10). When Ravaioli and associates (22) evaluated 54 cases of hepatocellular carcinoma in liver explants, they found that while both satellitosis and partial necrosis correlated with hepatocellular carcinoma recurrence, only partial necrosis, which was related to preoperative transarterial chemoembolization, had independent prognostic value on multivariate analysis (18). In the present study, microsatellitosis was seen in only 2, and tumor necrosis in 1, of the 5 patients who underwent ethanol or radiofrequency ablation procedures; neither

was a statistically significant predictor of hepatocellular carcinoma recurrence.

A postoperative tool that enables prediction of tumor recurrence would be of benefit. Pathological scores have been devised but not universally used to predict recurrence. Because studies have shown that selected patients who do not meet the Milan criteria can still be cured with a transplant, the challenge now is to decide which histopathologic features, other than size and number, carry a sufficiently poor prognosis to deny transplant (10, 17, 22, 23). These features may better assess the biological behavior of hepatocellular carcinoma in these transplant recipients and add to the prognostic value. Iwatsuki and associates, proposed a prognostic scoring system derived from lobar distribution, largest tumor size, and vascular invasion. Tumor-free 5-year survival was 40% when the score was less than 15 (24). Pathologic risk factors for hepatocellular carcinoma recurrence in the present study were almost identical to those reported by others (10, 25, 26, 27, 29). Vascular invasion and poor histologic differentiation represented the most predictive risk factors for hepatocellular carcinoma recurrence in this series. In particular, macroscopic vascular invasion most definitely resulted in a disappointing outcome. This is in accordance with many series that document the poor outcome of macroscopic vascular invasion (10, 26, 27). Whether microvascular invasion is associated with the same adverse prognosis was unclear in some reports; however, others have stressed its prognostic value in determining the outcome (24, 25, 30). A significantly lower vascular invasion rate was observed in subjects with well-differentiated tumors (25%) when compared with subjects with moderately or poorly differentiated tumors (100%) (24, 27). In the current study, microvascular invasion was also a strong predictor of hepatocellular carcinoma recurrence and was observed in all the poorly differentiated tumors. In Hemming's report, the long-term recurrence rates were 65% and 4% in patients with and without vascular invasion, respectively (30). It is possible that the well-differentiated tumor with absent microvascular invasion might have contributed to the good outcome of our patient whose tumor size exceeded the Milan criteria. Teketoma reported that even when Milan criteria are exceeded, vascular invasion, grade of histologic differentiation of hepatocellular carcinoma, and high PIVKA-II over 300 mAU/mL were independent risk factors for hepatocellular carcinoma recurrence (9). Similarly, Haberal and associates (31), reported 26 patients with hepatocellular carcinoma, of which 13 exceeded Milan criteria but with no major vascular invasion. Those authors concluded that liver transplant provides long patient and disease-free survival, even in patients with hepatocellular carcinoma that exceeds the Milan criteria.

An incidental histopathological finding in 2 of our patients was combined hepatocellular and cholangiocarcinoma. Combined hepatocellular and cholangiocarcinoma of the liver is relatively infrequent, accounting for 1.0% to 6.5% of the primary hepatic cancers (32-37); its pathogenesis remains obscure (32). It is an aggressive tumor usually with poor outcomes (32-37). Yano and associates report that macrovascular invasion and a bilobar tumor might indicate a poor outcome, and that a tumor size of 6 cm is a marginally significant factor for survival (37). In the current series, 1 of the patients had 3 lesions with microvascular invasion and poor differentiation. She had a tumor recurrence and died 14 months after transplant. The other patient is still doing well after 5 months' follow-up. Sanada and associates defined diagnostic radiologic criteria of combined hepatocellular carcinoma and cholangiocarcinoma (especially type III) based on a dynamic computed tomography enhancement pattern (38). Lin and associates identified the imaging prognostic factors that can be relied on to estimate the outcomes of patients with combined hepatocellular and cholangiocarcinoma (39). Therefore, it should be worthwhile to bear the existence of this tumor in mind during pretransplant evaluation.

In summary, at our institution, hepatic neoplasms are seen in more than 18% of explanted livers. They are incidentally identified, frequently not associated with elevated serum levels of alpha-fetoprotein, and are associated with a relatively good prognosis. On the basis of our data, the risk factors of hepatocellular carcinoma recurrence were gross invasion of major hepatic vessels, microvascular invasion, and low-grade histologic differentiation. Current imaging requirements for radiologic staging before liver transplant remain inaccurate. Perhaps the combination of imaging techniques, rather than just 1, might optimize staging and avoid the small risk of underestimation of tumor size and number, together with the diagnosis of minimal vascular invasion and combined hepatocellular carcinoma and cholangiocarcinoma. Also, because some tumors can grow so rapidly, we also propose doing the imaging right

before the transplant—not a long time before the transplant— especially in patients with multicentric (> 3) hepatocellular carcinoma or large tumors (> 4 cm) to identify vascular invasion or rapid growth of the tumor before liver transplant. In selected patients, laparoscopy can be used as an additional investigation tool. Although microvascular invasion and histologic differentiation cannot be included in the routine pretransplant protocol for assessment of hepatocellular carcinoma, now that tumor biopsy is debatable, their identification in the explant is of extreme importance. Thorough examination of explanted livers is mandatory and patients identified as being at high risk for recurrent hepatocellular carcinoma after liver transplant may be candidates for adjuvant therapy or more intensive surveillance after liver transplant.

Although the follow-up was not long and the number of cases few in comparison to other studies, these preliminary results from our center show that liver transplant can achieve acceptable survival in Saudi patients with end-stage hepatitis C or hepatitis B cirrhosis and hepatocellular carcinoma. The outcomes and risk factors for hepatocellular carcinoma recurrence do not seem to be highly different between deceased-donor liver transplants and living-donor liver transplants. MELD score was the most important predictor of survival. Therefore, we believe that living-donor liver transplant is a good option for our patients, and they should not be denied a living-donor liver transplant based only on exceeding the Milan criteria. On the other hand, use of marginal donors in patients with hepatocellular carcinoma might compromise the outcomes for this patient population.

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