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G. Colella
G. F. Rondinara
L. De Carlis
C. V. Sansalone
A. O. Slim
P. Aseni
O. Rossetti
A. De Gasperi
E. Minola
R. Bottelli
L. S. Belli
G. Ideo
D. Forti

Liver transplantation for hepatocellular carcinoma: prognostic factors associated long-term survival

G. Colella (✉) · G. F. Rondinara · L. De Carlis · C. V. Sansalone · A. O. Slim · P. Aseni · O. Rossetti · A. De Gasperi · E. Minola · R. Bottelli · L. S. Belli · G. Ideo · D. Forti
Department of Abdominal Organ Translation, Pizzamiglio II, Ospedale Niguarda, piazza Ospedale Maggiore, 3, I-20162 Milano, Italy

Abstract Between December 1985 and February 1995, 260 orthotopic liver transplantations (OLTX) were performed on 238 patients at Niguarda Hospital. Sixty-three patients had hepatocellular carcinoma (HCC); in 13 of the patients HCC was incidental. All patients had negative lymph nodes. According to the Child classification, 13 patients were Child A, 30 Child B, and 18 Child C. According to the TNM classification, 11 patients were stage I, 22 stage II, 15 stage III, and 15 stage IVa. Pre-OLTX chemoembolization was performed on 25 patients. The perioperative mortality rate was 27 % (17 patients). Overall survival and disease-free actuarial survival rates at 1, 3, and 5 years were 94 %, 76 %, 76 %, and 83 %, 75 %, 75 %, respectively. Survival curves were compared for 16 different variables. No difference was observed for all parameters analyzed except tumor site, TNM stage, pre-OLTX AFP levels and vascular infiltration. These results seem to demonstrate that the OLTX for unresectable HCC can be considered in specifically selected cases as the treatment of choice. An adequate tumor staging is also necessary for a better patient selection in order to increase survival.

Key words Hepatocellular carcinoma · Liver transplantation

Introduction

In recent years, hepatocellular carcinoma (HCC) has been diagnosed and treated with increasing frequency by means of several options including alcoholization, transarterial chemoembolization, resective surgery, and orthotopic liver transplantation (OLTX) [1, 2, 4, 5, 7, 8]. Up to now, if extrahepatic tumor spread is excluded, a complete surgical excision is generally considered the treatment of choice for potentially resectable HCC [1, 2].

OLTX was considered a controversial indication for primary liver neoplasms because of high recurrence rate [3, 4, 6] but up to now a consistent number of OLTX are still performed for malignancies, principally for HCC in cirrhosis. Recently, a critical review of previous experience demonstrates a significant relationship between tumor stage and patient survival after OLTX for HCC in cirrhosis [2, 5, 7]. Furthermore, hepatic resection appears to achieve poor long-term survival, while OLTX has recently shown improving trends in results.

We report here a retrospective analysis of 10 years' experience in OLTX for HCC in cirrhosis in order to define indications for OLTX.

Besides TNM tumor staging, several variables were investigated and related to post-OLTX tumor survival in order better to define the selection and management of patients undergoing OLTX for HCC.

Patients and methods

Patients

Between December 1985 and June 1995, 260 OLTX were performed on 238 patients at the Department of General Surgery and Abdominal Organ Transplantation, Niguarda Hospital, Milan, Italy. Of these, 63 patients (53 male, 10 female, mean age 52 years,

Table 1 Characteristics of the series of patients

Age	Median (range)	52 years (22–61 years)
Sex	Male/female	53/10
HbsAg	Positive	19 (30%)
HCVAb	Positive	28 (44%)
AFP	20–400 ng/ml	19 (31%)
	> 400 ng/ml	12 (19%)
Cirrhosis stage	Child A	13 (21%)
	Child B	30 (49%)
	Child C	18 (30%)
Cirrhosis etiology	Viral	35 (57%)
	Alcoholic	12 (20%)
	Mixed	7 (11.5%)
	Unknown	7 (11.5%)

Table 2 Pathological characteristics

Size (diameter)	Median (range)	3 cm (1–15 cm)
Number	Solitary	35 (56%)
	Multiple	28 (44%)
Localization	Monolobar	48 (76%)
	Bilobar	15 (24%)
Capsule	Present/not infiltrated	14 (27%)
(51 patients evaluable)	Absent/infiltrated	37 (73%)
Vascular invasion	Macroscopic	2 (4%)
(55 patients evaluable)	Microscopic	13 (24%)
TNM stage	I	11 (17%)
	II	22 (35%)
	III	15 (24%)
	IVa	15 (24%)

Table 3 Orthotopic liver transplantations (OLTX) for hepatocellular carcinoma (HCC) in cirrhosis: prognostic factors for survival

		3 years survival	5 years survival	3 years tumor-free	*P*
TNM stage	I	100%	100%	100%	0.01
	II	93%	93%	93%	
	III	50%	–	56%	
	IVa	52%	–	58%	
Location	Monolateral	96%	96%	92%	< 0.01
	Bilateral	47%	47%	52%	
Vascular invasion	Absent	96%	96%	96%	0.02
	Micro	33%	–	38%	
	Macro	0%	0%	0%	
AFP level (ng/ml)	< 20	100%	100%	100%	< 0.001
	20–400	75%	–	91%	
	> 400	17%	17%	18%	

range 22–61 years) had an HCC at the time of OLTX (Table 1). In 13 patients, HCC was an incidental finding; HCC was discovered in a cirrhotic liver after OLTX for end-stage liver disease. Only 2 patients out of the 63 were not cirrhotics. No patient had either extrahepatic tumor spread or lymph node tumor invasion at pathological examination at the time of OLTX.

According to the Child classification, 13 patients were Child A, 30 Child B, and 18 Child C. Pathological characteristics and tumor stage according to the TNM classification are reported in Table 2.

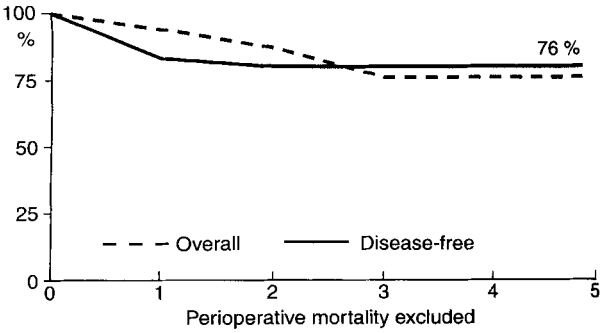

Fig. 1 Orthotopic liver transplantations for hepatocellular carcinoma in cirrhosis: actuarial survival

Pre-OLTX transarterial chemoembolization (TAE) was performed in 26 patients.

All patients underwent quadruple immunosuppression therapy in the early post-OLTX period and received cyclosporine (Cya) for chronic immunosuppression in the absence of clinical contraindication or severe rejection.

Statistical analysis

Perioperative mortality rate within 3 months was 27% (17 patients). Actuarial survival curves were calculated for the remaining 46 patients (median follow-up, 45 months) as cumulative survival rates by the Kaplan-Meier method and analyzed by the log-rank and Mantel-Haenszel tests.

Survival curves were compared for sex, age (< 50, > 50 years), tumor location (mono-, bilateral), diameter (< 3, > 3 cm), mono- or plurifocality, capsule status, pre-OLTX AFP level (< 20, 20–400, > 400 ng/ml), micro- or macro-vascular infiltration, incidental tumor, TNM stage, Child classification, pre-OLTX chemoembolization, additional immunosuppression for acute rejection, and etiology of cirrhosis.

Results

Overall survival and disease-free actuarial survival rates at 1, 3, and 5 years were 94%, 75%, 75%, and 83%, 76%, 76%, respectively (Fig. 1). Seven patients had tumor recurrence at 4, 5, 5, 7, 8, 9, and 15 months. Sites of recurrence (multiple in four cases) were liver (three patients), bone (three patients), lung (two patients), and brain (two patients); in three patients, recurrence was both hepatic and extrahepatic. All patients with tumor recurrence died within 34 months after OLTX, whereas all the patients alive are free of disease.

All the patient-related characteristics examined (age, sex, etiology of cirrhosis, Child stage) are not significantly related to tumor recurrence or patient survival.

Among the different tumor-related variables, tumor location (mono-, bilateral), TNM stage, pre-OLTX AFP levels, and vascular infiltration are significantly related to tumor recurrence and patient survival (Ta-

Table 4 OLTX for HCC in cirrhosis: prognostic factors for survival (*NS* not significant)

		3 years survival	5 years survival	3 years tumor-free	*P*
Capsule	Complete	100 %	100 %	100 %	NS
	Absent/ infiltrated	70 %	70 %	70 %	
Number of lesions	Single	90 %	90 %	87 %	NS
	Multiple	56 %	–	67 %	
Diagnosis	Incidental	100 %	100 %	100 %	NS
HCC	Pre-OLTX	67 %	67 %	73 %	
Diameter	< 3 cm	89 %	89 %	90 %	NS
	> 3 cm	60 %	60 %	66 %	

ble 3), while the number of lesions, capsule, diameter, and incidental HCC are not significantly related to tumor recurrence and patient survival (Table 4). All those patients (three) with a tumoral thrombus in a main portal vein branch suffered tumor recurrence within 1 year. Microvascular tumor invasion detected at pathological examination of whole liver specimens was associated with a 3-year disease-free survival rate of 38 %. On the contrary, 96 % of patients without micro- or macrovascular tumor invasion were disease-free after 3 years. Advanced HCC, considered as TNM stage T3–T4 or a bilateral tumor, had 3-year tumor-free survival rates of 56 % (T3), 58 % (T4), and 52 % (bilateral). In our series, no patients (32) with normal AFP levels suffered tumor recurrence after OLTX, while for six out of nine patients with AFP levels greater then 400 ng/ml recurrence was within 15 months, with a 3-year survival rate of 18 %. No patients with an incidental HCC or a completely encapsulated HCC suffered recurrence after OLTX. Patients with a solitary HCC or with HCC less than 3 cm diameter had 3-year tumor-free survival rates of 87 % and 90 % (73 % and 66 % for non-incidental and more than 3-cm diameter HCC). No differences in patient survival and tumor-free survival were evident for treatment-related variables; in particular, pre-OLTX chemoembolization and immunosuppression do not seem to affect recurrence rate.

Discussion

Indication to OLTX for HCC in cirrhosis is generally considered because of the low resection rate of HCC due to tumor location or liver impairment. OLTX undoubtedly has the capacity to cure both HCC and cirrhosis. Some HCC patterns are correlated with tumor recurrence and patients' survival [2, 5, 7]. Our results confirm this observation.

The TNM stage, the vascular invasion, the pre-OLTX AFP levels, and bilateral HCC are prognostic factors for survival after OLTX. Some of these parameters, such as AFP levels, are easy to verify before OLTX and can be utilized as selection criteria for candidates. Other parameters, such as TNM staging, can be used to complete the selection. Others, such as the extent of microvascular invasion, cannot be defined at the time of OLTX, and cannot be used as selection criteria for candidates, but have a prognostic value in the indication for adjuvant therapy.

These results seem to demonstrate that OLTX for unresectable HCC can be considered the treatment of choice for specifically selected patients. Because of the low recurrence rate after OLTX, this indication can be extended to young patients with potentially resectable HCC in cirrhosis. These patients are, in fact, considered suitable candidates for OLTX in some transplantation centers.

In conclusion, unresectable HCC in cirrhosis can be considered as the treatment of choice for selected patients; indication to OLTX for patients with a resectable HCC is still to be defined.

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