Transpl Int (1998) 11 [Suppl 1]: S193–S196

G. Colella
R. Bottelli
L. De Carlis
C. V. Sansalone
G. F. Rondinara
A. Alberti
L. S. Belli
F. Gelosa
G. M. Iamoni
A. Rampoldi
A. De Gasperi
A. Corti
E. Mazza
P. Aseni
A. Meroni
A. O. Slim
M. Finzi
F. Di Benedetto
F. Manochehri
M. L. Follini
G. Ideo
D. Forti

Hepatocellular carcinoma: comparison between liver transplantation, resective surgery, ethanol injection, and chemoembolization

G. Colella (✉) · L. De Carlis · C. V. Sansalone · G. F. Rondinara · P. Aseni · A. Meroni · A. O. Slim · M. Finzi · F. Di Benedetto · F. Manochehri · M. L. Follini · D. Forti
Department of Surgery and Abdominal Organ Transplantation, Niguarda Hospital, Pizzamiglio II, I-20162 Milan, Italy

R. Bottelli · A. Alberti · L. S. Belli · F. Gelosa · G. M. Iamoni · G. Ideo
Department of Medicine and Hepatology, Niguarda Hospital, I-20162 Milan, Italy

A. De Gasperi · A. Corti · E. Mazza
Department of Anesthesiology and Transplantation, Niguarda Hospital, I-20162 Milan, Italy

A. Rampoldi
Department of Radiology, Niguarda Hospital, I-20162 Milan, Italy

Abstract Between January 1989 and June 1997, 533 patients (423 male, 110 female, mean age 61 years, range 22–89 years) with hepatocellular carcinoma (HCC) were observed at our center. We report on 419 patients retrospectively compared for different treatments: liver transplantation (LT; 55 patients), resective surgery (RS; 41 patients), transarterial chemoembolization (TACE; 171 patients) and percutaneous ethanol injection (PEI; 152 patients). The 3- and 5-year actuarial survival rates were, respectively, 72% and 68% for LT, 64 and 44% for RS, 54 and 36% for PEI, and 32 and 22% for TACE. Survival curves were compared for sex, age, tumor characteristics, alphafetoprotein level, Child class, and etiology of cirrhosis. All patient-related characteristics examined (sex, age) are not significantly related to patient survival. Tumor-related variables and associated liver disease variables significantly conditioned survival in relation to different treatments. LT seems to be the treatment of choice for monofocal HCC less then 5 cm in diameter and in selected cases of plurifocal HCC.

Key words Hepatocellular carcinoma · Liver transplantation · Liver surgery · Transarterial chemoembolization · Percutaneous ethanol injection

Introduction

Hepatocellular carcinoma (HCC) has been diagnosed and treated with increasing frequency in recent years. If extrahepatic tumor spread is excluded, several treatment options are now available including liver transplantation (LT), resective surgery (RS), transarterial chemoembolization (TACE), and percutaneous ethanol injection (PEI). The choice of the treatment of HCC strictly depends to the associated liver disease, generally viral cirrhosis. The associated non-tumoral liver disease sometimes conditions prognosis more than the tumor itself. Transplantation is the only option that theoretically may cure both hepatic tumor and cirrhosis. Nevertheless the place of LT in the treatment of HCC is still debatable both because of reported controversial results

and donor shortage. In this study we retrospectively compare LT, hepatic resection, TACE, and PEI in the treatment of patients with HCC in order to determine the indications for each treatment.

Patients and methods

Between January 1989 and June 1997, 533 patients (423 male, 110 female, mean age 61 years, range 22–89 years) with HCC were observed at our center (median follow up 43 months). We report on 419 patients retrospectively compared for different treatments: LT (55 patients), RS (41 patients), TACE (171 patients), and PEI (152 patients). Incidental HCC at the time of LT and the fibrolamellar variant are excluded. No patient had extraepatic tumor spread at the time of treatment. Five patients out of 533 had no associated liver disease and 487 patients had cirrhosis. According to the Child-Pugh classification, 341 patients were Child A, 125 Child B and 20 Child C. The etiology of cirrhosis was viral (HBV, HDV, HCV) in 59.2% of patients, ethanolic in 16.8%, viral plus ethanolic in 23.5% and in 0.5% was associated with hemocromathosis. Actuarial survival curves were calculated 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, tumor characteristics, alphafetoprotein (AFP) level, Child class, and etiology of cirrhosis. All causes of death are considered.

Results

The 3- and 5-year actuarial survival rates were, respectively, 72 and 68% for LT, 64 and 44% for RS, 54 and 36% for PEI and 32 and 22% for TACE (Fig. 1). No patient out of 114 without specific treatment for HCC was surviving at 5 years. All patient-related characteristics examined (sex, age) are not significantly related to patient survival. Tumor-related variables and associated liver disease variables significantly conditioning survival are reported in Table 1. Patients with monofocal HCC less then 5 cm in diameter had 5-year survival rates of 83% (LT), 41% (RS), 37% (TACE), and 44% (PEI) ($P < 0.01$). Patients with monofocal HCC of 5–10 cm in diameter had 5-year survival rates of 53% after RS (10 patients). No patient survived 5 years after LT (2), PEI (2), and TACE (25) ($P < 0.01$). Patients with plurifocal HCC had 5-year survival rates of 58% (LT), 23% (TACE), and 23% (PEI); 2 patients unterwent RS and neither survived 5 years after surgery ($P = 0.01$). We consider in stage I all monofocal HCC less then 5 cm in diameter or plurifocal HCC (no more than three lesions

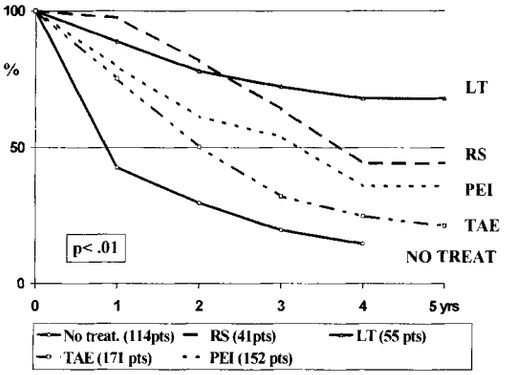

Fig. 1 Hepatocellular carcinoma: actuarial survival rates after liver transplantation (*LT*), resective surgery (*RS*), transarterial chemoembolization (*TACE*), and percutaneous ethanol injection (*PEI*). *pts* Patients

Table 1 Actuarial survival rates after liver transplantation (*LT*), resective surgery (*RS*), transarterial chemoembolization (TACE), and percutaneous ethanol injection (PEI) (*HCC* Hepatocellular carcinoma, *yrs* years)

	Prognostic factors	LT		RS		TACE		PEI		No treatment		*P* value
		3 yrs	5 yrs	3 yrs	5 yrs	3 yrs	5 yrs	3 yrs	5 yrs	3 yrs	5 yrs	
HCC	Single < 5 cm	83%	83%	55%	41%	37%	37%	68%	44%	29%	–	0.01
	Single > 5 cm	0%	0%	89%	53%	35%	0%	0%	0%	–	–	0.01
	Multiple	68%	58%	50%	–	31%	23%	34%	23%	12%	–	0.01
	Stage I[a]	84%	84%	58%	42%	36%	29%	68%	48%	28%	–	0.01
	Stage II[b]	46%	31%	70%	33%	31%	20%	32%	19%	15%	–	NS
Alphafeto-protein	0–20 ng/ml	85%	85%	82%	67%	32%	21%	63%	44%	28%	–	0.01
	21–400 ng/ml	77%	70%	56%	0%	34%	24%	51%	28%	13%	0%	0.01
	> 400 ng/ml	31%	–	0%	0%	28%	17%	32%	32%	16%	0%	NS
Cirrhosis	Viral	68%	61%	63%	28%	41%	25%	48%	27%	14%	–	0.01
	Alcoholic	63%	63%	50%	–	10%	5%	59%	47%	15%	0%	0.02
	Viral + alcoholic	90%	90%	57%	57%	31%	25%	68%	51%	30%	–	0.01
	Child A	85%	85%	64%	38%	37%	24%	58%	41%	24%	–	0.01
	Child B	78%	65%	–	–	19%	12%	30%	0%	12%	–	0.01
	Child C	60%	60%	–	–	–	–	–	–	9%	–	0.01

[a] Stage I: monofocal HCC less than 5 cm in diameter or plurifocal HCC (maximum of three lesions) < 3 cm
[b] Stage II: monofocal HCC > 5 cm or plurifocal HCC > 3 cm or more than three lesions

less then 3 cm) and in stage II all the other HCCs (single lesion more then 5 cm or plurifocal with more than three lesions or diameter more then 3 cm). Stage I summarizes specific inclusion criteria for LT at our center, whereas all patients with stage II HCC at preoperative staging are excluded from LT. The stage I 5-year survival rate is significantly better after LT (84%) than after all the other treatments (RS 42%, TACE 29%, PEI 48%; $P = 0.01$). No difference in survival is evident in stage II (LT 31%, RS 33%, TACE 20%, PEI 15%). Considering the AFP blood level under 20 ng/ml, the 5-year survival rate is significantly better ($P = 0.01$) after LT (85%) and RS (67%) than after TACE (21%) and PEI (44%). Survival is still better after LT for AFP levels up to 400 ng/ml ($P = 0.01$), but no difference in survival is evident for AFP levels greater than 400 ng/ml. Also considering the different etiology of associated cirrhosis (viral, alcoholic, or mixed), survival is significantly better ($P = 0.01$) after LT. Finally patients with a Child B and C cirrhosis had the best survival rate after LT, but also 5-year survival of patients in Child A class is significantly better ($P = 0.01$) after LT (85%) than after RS (38%), TACE (24%) or PEI (41%).

Discussion

The advent of modern imaging techniques and screening programs for patients at risk of HCC allows for an accurate pretreatment staging of HCC enabling better patient selection and choice of adequate treatment [1, 2]. Historically a complete surgical excision has generally been considered the treatment of choice if extrahepatic tumor spread was excluded and resection was feasible in terms of tumor location and hepatic functional reserve [3]. Actually several treatment options are available including LT, RS, TACE, and PEI. We chose the best treatment for the patient in consideration both of the HCC and the associated liver disease. We also had to consider the resources of the different centers and the limitations to transplantation, i.e., the high cost of this procedure and donor shortage. The role of liver transplantation in is still under discussion even if theoretically it seems the more appropriate treatment for diseases confined to the liver. Undoubtedly early results of LT for HCC were disappointing [4, 5], but actually good results are reported in early stages of HCC [3, 6–11]. It is difficult to imagine a randomized trial for comparing the different treatments for HCC even if a multicentre study may be advisable in order to better define the indications. In our retrospective study we try to have indications for treatment. Results seem to indicate that LT is the treatment of choice for monofocal HCC less than 5 cm in diameter with a 5-year survival rate of 83% ($P = 0.01$). In cases of plurifocal HCC, even if survival is better after LT we have to select patients in relation to the number of nodules. Presently we consider LT in cases of HCC with up to three nodules with a maximum diameter of 3 cm. The results using this limitation are good and 5-year survival rate after LT in these patients (stage I) is 84% ($P = 0.01$). On the contrary, results in patients with a stage II HCC is almost equivalent after every treatment. The pre-treatment dosage of AFP can easily be utilized for selection of patients [1, 2]. Treatments do not seem to influence survival significantly in the patients with an AFP blood level of more then 400 ng/ml. With a level less than 400 ng/ml, LT has the best survival rates. No limitation to LT seems to be proposed in consideration of the etiology of cirrhosis and Child-Pugh class in addition to the usual selection criteria. The other treatments considered (RS, TACE, and PEI) seem not to have a role in the cure of patients with Child B or C cirrhosis. Resection seems to be indicated in cases of a single lesion more than 5 cm in diameter because results are surprisingly good with a 5-year survival rate of 53% ($P = 0.01$) as confirmed by a previous report [3]. No difference seems to be evident in early survival of patients with small HCC treated with RS or PEI as reported by some authors [12, 13]. Long-term result reported are significantly better for RS than PEI [14].

In conclusion results seem to demonstrate that LT can be considered as the treatment of choice for monofocal HCC less than 5 cm in diameter and in selected cases of plurifocal HCC if the patient is eligible for LT using the general inclusion criteria.

References

1. The Liver Cancer Study Group of Japan (1994) Predictive factors for long term prognosis after partial hepatectomy for patients with hepatocellular carcinoma. Cancer 74: 2772–2780
2. Colella G, Rondinara GF, De Carlis L (1996) Liver transplantation for hepatocellular carcinoma: prognostic factors associated with long-term survival. Transpl Int 9(suppl 1):S109–S111
3. Bismuth H, Chiche L, Adam R, Castaing D, Diamond T, Dennison A (1993) Liver resection versus transplantation in the treatment of hepatocellular carcinoma in cirrhotic patients. Ann Surg 218: 145–151
4. Calne RY (1982) Liver transplantation for liver cancer. World J Surg 6: 76–80
5. Iwatsuki S, Gordon RD, Shaw BW, Starzl TE (1985) Role of liver transplantation in cancer therapy. Ann Surg 202: 401–407
6. Pichlmayr R, Weimann A, Ringer B (1994) Indication for liver transplantation in hepatobiliary malignancy. A consensus conference on indication of liver transplantation. Hepatology 20(suppl):33s–40s

7. Selby R, Kadry Z, Carr BI (1995) Liver transplantation for hepatocellular carcinoma World J Surg 19: 53–58
8. Colella G, De Carlis L, Rondinara GF (1997) Is Hepatocellular carcinoma in cirrhosis an actual indication for liver transplantation. Transplant Proc 29: 492–494
9. Gennari L, Mazzaferro V, Regalia E (1993) Reappraisal of the role of liver transplantation in the treatment of hepatocellular carcinoma and cirrhosis. J Surg Oncol 3(suppl):83–86
10. Iwatsuki S, Starzl TE, Shean DG, Yokoyama I, Demetris AJ, Todo S, Van Thiel DH, Carr B, Selby R, Madariaga J (1991) Hepatic resection versus transplantation for hepatocellular carcinoma. Ann Surg 214: 221–229
11. Schwartz ME, Sung M, Mor E (1995) A multidisciplinary approach to hepatocellular carcinoma in patients with cirrhosis. J Am Coll Surg 180: 596–603
12. Livraghi T, Bolondi L, Buscarini L (1995) No treatment, resection, and ethanol injection in hepatocellular carcinoma: a retrospective analysis and survival in 391 patients with cirrhosis. J Hepatol 22: 522–526
13. Castells A, Bruix J, Bru C (1993) Treatment of small hepatocellular carcinoma in cirrhotic patients: a cohort study comparing surgical resection and percutaneous ethanol injection. Hepatology 18: 1121–1125
14. Ryu M (1993) Reports on projects of the comprehensive ten-year strategy of cancer control supported by the Ministry of Health and Welfare of Japan. pp 176–181