Hepatocellular carcinoma : from ethanol injection to liver transplantation

H. Bismuth, P. Majno[1], R. Adam

Centre Hépatobiliaire, Hôpital Paul Brousse, Assistance Publique - Hôpitaux de Paris, Villejuif and Groupe de Recherche de Chirurgie Hépatique, Faculty of Medicine, Paris-Sud University, Paris, France.
(1) Current Address : Unité de Transplantation, Département de Chirurgie, Hôpitaux Universitaires, Genève, Suisse.

(Acta gastroenterol. belg., **1999**, 62, **330-341**).

Introduction

Hepatocellular carcinoma (HCC) is one of the commonest tumours world-wide, with an incidence of at least 250.000 cases each year (1). In the western world HCC develops in the presence of cirrhosis in 90% of the cases (2), and the number of new cases is growing steadily because of the epidemics of cirrhosis due to the hepatitis C virus, in which the ratio of malignant transformation is 2-8% per year (3). Once discovered at a late stage in the majority of cases, and beyond the possibility of curative treatment, an increasing number of HCC are now discovered at an early stage, because of increasing awareness and screening of asymptomatic patients with cirrhosis. Small tumours are accessible to a at least three potentially curative therapies : liver resection, liver transplantation and percutaneous ethanol injection. The choice between the three needs to take into account the biology of the disease, still imperfectly known, the constraints of the associated cirrhosis limiting the hepatic functional reserve, and other factors such as the shortage of donor organs for transplantation, local expertise and cost-containment issues. When the tumour is discovered beyond the possibilities of cure, palliative treatment by percutaneous ethanol injection, transarterial chemoembolisation or, in some cases, liver resection can be rewarded by long and worthwhile survival.

The present article will discuss the place of liver resection, liver transplantation, percutaneous ethanol injection, and transarterial chemoembolisation, on the basis of the experience in our centre and on the data published in the literature.

Liver resection

Generalities

Liver resection has until recently been the preferred treatment for tumours that could be totally excised. Thanks to the improvements in patient selection, surgical technique and postoperative care, the mortality from hepatocellular failure and the incidence of postoperative complications have been reduced in recent years. Systematic application of the principles of segmental liver resection (4) with the use of operative ultrasound has diminished per-operative bleeding to the point that the majority of patients do not need blood transfusions (5). The fall in operative mortality is also due to a more accurate prediction of the risk of hepatocellular failure, adapting the extent of the resection to the preoperative estimation of the hepatic functional reserve (6) (fig. 1), and to the awareness of the importance of preoperative patient conditions, such as adequate nutrition (7).

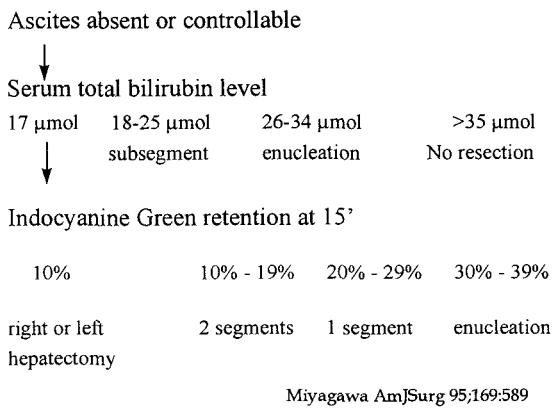

Fig. 1. — Algorithm to determine the maximum extent of liver resection for hepatocellular carcinoma associated with cirrhosis (modified from Miyagawa (7)).

Results on our centre and in the literature

In our centre 113 liver resections for HCC associated with cirrhosis were performed between January 1985 and June 1998. The characteristics and the results in 76 patients who underwent a curative resection between 1985 and 1995, for whom an adequate length of follow up is available are shown in tables I-II and fig. 2. The rates of patient survival (Kaplan-Meier) at 1,3 and 5 years were, respectively 82%, 53% and 40%. The Disease-free survival rates were 62%, 30% and 15%. Recurrence was documented and considered as the cause of death in 50 cases (66%), after a median delay

Address for correspondence : Professor Henri Bismuth, Centre Hépatobiliaire, Hôpital Paul Brousse, 94804 Villejuif, France.

Table I. — **Liver resection for hepatocellular carcinoma associated with cirrhosis at Paul Brousse Hospital 1985-1995 : Patients' characteristics (9 patients who underwent palliative resection or were treated with cryotherapy excluded)**

N° Patients	76
Age (mean ± SD)	59.8 (± 7.4)
Males/Females	70/6
Child A	60 (79%)
Child B	16 (21%)
Child C	—
Hepatitis B	16 (21%)
Hepatitis C	17 (22%)
Alcohol	27 (36%)
Other	16 (21%)
Size (mm) (mean ± SD)	49 ± 23
≤ 30mm (Number of Patients)	26 (34%)
31-50mm (Number of Patients)	26 (34%)
> 50mm (Number of Patients)	24 (32%)
Number of tumours (mean)	1.3
1 nodule	59 (78%)
2 nodules	12 (16%)
3 nodules	4 (5%)
4 nodules	2 (3%)
Vascular thrombus (tumoral)	5 (7%)
TACE	49 (64%)

TACE : trans arterial chemioembolisation.

Table II. — **Curative liver resection for hepatocellular carcinoma associated with cirrhosis at Paul Brousse Hospital 1985-1995 : results**

N° Patients	76
Type of resection	
≤ 1 segment	53 (70%)
2 segments	13 (17%)
≥ 3 segments	10 (8%)
Transfused units : median (interquartile range)	2 (0-4)
Mortality	4 (5%)
Complications	43 (53%)
Median FU (months)	28
Recurrence	50 (66%)
- liver	45 (90%)
- liver other than same or neighbouring segment	31 (68%)
- distant metastases (lungs)	2 (4%)
- unknown	3 (6%)
late mortality unrelated to HCC	8 (11%)

HCC : hepatocellular carcinoma

from the operation of 17 months (range 2 months to 7.5 years). Mortality unrelated to tumour recurrence was documented in 8 cases (11%). Four patients were alive without recurrence after 5 years from the operation. Recurrence was in the liver in the majority of cases (45/50 ; 90%), and in a segment distant from the site of the original resection in 31 of the 45 cases (68%) of liver recurrence.

The high incidence of recurrence in our centre is similar to the one of other series where disease-free survival is reported (5,8-21) (table III), and represents the main limit of liver resection for HCC. Several

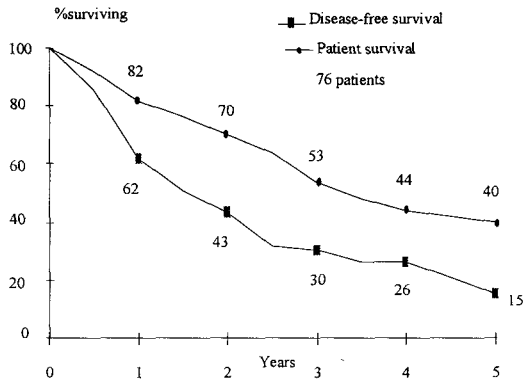

Fig. 2. — Actuarial patient survival and disease-free survival of 76 patients undergoing curative liver resection for hepatocellular carcinoma associated with cirrhosis at Paul Brousse Hospital 1985-1995.

strategies are investigated to decrease the incidence of recurrence after resection for HCC. A possible approach is to perform a larger liver resection to include a wider portal territory, based on the rationale that some of the recurrences originate from the original tumour through portal micro-metastases. Wider resections have been associated with increased disease-free survival in a preliminary retrospective study (22). It is difficult however to exclude a selection bias in favour of patients with better liver function, the only patients in whom larger resections are possible. Furthermore the advantage was shown for patients with tumours larger than 4 cm, in which the chances of portal dissemination are higher, and it is uncertain whether a similar advantage would be observed for smaller tumours.

More precise knowledge of the factors associated with recurrence is emerging and these factors can be used to guide treatment. An active hepatitis status with increased transaminase (14,17), high alpha-foetoprotein levels, and multicentricity are all associated with an increased recurrence rate and alternatives to resection should be preferred (23). High blood transfusion requirements during resection are also associated with an increased recurrence rate (5). The influence of size is more difficult to assess. Although large tumour size is associated with vascular invasion (24), patients with large tumours who qualify for resection do not, through a selection bias, have multicentric tumours nor distant metastases, and these patients may suffer from a more indolent form of the disease. Some strategies to decrease the incidence of de novo cancer occurrence are under study. The postoperative use of interferon is being investigated ; retinoids favouring cellular differentiation have been used with success (25) but their diffusion has been hampered by adverse reactions the most serious being hepatitis.

The second main limit of liver resection as curative treatment for HCC is that only a minority of patients with HCC associated with cirrhosis can withstand a hepatectomy. In published series, the proportion of

Table III. — **Liver resection for HCC. Results in the main single institution series**

Auteur	Period	Features	Patients	Follow-up (months)	Mortality %	Complications %	Recurrence %	% surviving (% disease-free) 1 year	3 years	5 years
Ringe 91 (8)	74-88	Liver disease 33% 14 fibrolamellar HCC	131	28.7	9-11	—		68 (48)	42 (34)	36 (30)
Belghiti 91 (9)	84-89	R0, cirrhosis, surviving > 6 months	47	—	—	—	—	(40*)	(57*)	(100*)
Bismuth 93 (10)	80-91	cirrhosis	60	—	10	40	—	80 (58)	52 (27)	—
Castells 93 (11)	87-91	cirrhosis, < 4cm	33	23	—	—	40	81 (58)	44 (25)	—
Nagasue 93 (12)	80-90	cirrhosis 75% hepatitis 21%	229	70	11†	20%	53	88 (22*)	53 (62*)	29(75*)
Yamamoto 94 (5)	84-89	cirrhosis R0, surviving > 1 month	178‡ 74§	19	—	—	74 50	(80) (65)	(50) (20)	(30) (15)
Lai 95 (13)	72-94¶	cirrhosis 73% > 5cm 78%	149|| 66**	—	21 6	73% 32%		60 (35) 68 (36)	33 (15) 44 (23)	24 (9) 35 (23)
Shirabe 95 (14)	85-94	cirrhosis, 1 nodule < 3 cm excluded : R2, mortality other than recurrence	20†† 37‡‡	—	—	—	63	(80) (91)	(6) (65)	(0) (42)
Takenaka 96 (15)		advanced 38%, cirrhosis 52%	280		2		71 (5 years)		50	
Balsells 96 (16)	87-93	cirrhosis	51	17	13	> 50%	53	(41*)	(80*)	—
Ko 96 (17)	83-94	R0, surviving > 12 months	13§§ 50¶¶ 47||||	—	—	—		(86) (28) (55)	(86) (23) (32)	
Nagashima 96 (18)		< 2 cm	50		12		70 (5 years)	90	75	53
Makuuchi 98 (19)	90-94 95-98	proportion cirrhosis ? R0	306	—	2 0	—	65	92 (62)	73 (32)	47 (13)
Maziotti 98 (20)	83-98	cirrhosis, R0	229	40	5 (0.8%)	42	42	85	62	41
Lise 98 (21)	75-95	cirrhosis 78%	100	21	11†	—	60	74 (47)	43 (15)	26(5)

Abbreviations : R0 = curative resection, R2 =Macroscopically non-curative resection
* Intrahepatic recurrence
† Hospital mortality
‡ Not transfused
§ Transfused
¶ 343hepatectomies out of 1975 patients referred (operability 17,4%)
|| Patients operated before 87
** Patients operated after 92
†† Transaminase < 100 on follow-up
‡‡ Transaminase > 100 on follow-up
§§ Persistent hepatitis
¶¶ Active hepatitis
|||| Cirrhosis

patients referred to the patients resected is seldom reported, and in each centre it is affected by a referral bias. In Paul Brousse the proportion of patients resected is 9.6% of al patients with HCC referred (113 / 1176 from 1985 to 1998), the proportion is 3.3% in Pisa (C. Bartolozzi, personal communication 1997) and 343/1975 (17.4%) in Hong Kong (13). This proportion may change in the future as screening of patients with cirrhosis is likely to discover tumours at an earlier stage in their evolution and in the evolution of the cirrhosis, both factors that should increase the resectability. Whether this will result in a true survival advantage rather than in a cohort effect will need to be demonstrated. Strategies to increase resectability, such as preoperative portal vein embolisation to obtain the hypertrophy of the non-tumoral liver (initially described as a counter measure to the spread of tumour thrombi in the portal venous system (26), or preoperative transarterial chemoembolisation to decrease the size of the tumour can be used with success in some patients (27).

Liver transplantation

Generalities

Liver transplantation is in theory a more satisfying therapy than liver resection for HCC limited to the liver because it removes the tumour as well as the underlying cirrhosis, treating the risk of hepatic recurrence, and the mortality of complications of hepatocellular failure and portal hypertension. The place of liver transplantation in the treatment of HCC, however, has been questioned because of the poor results of the early experience, and because of the need to reserve the limited supply of donor organs for patients with benign disease. Several factors have probably contributed to the poor reputation of liver transplantation for HCC. In the early years of liver transplantation the operative mortality was high, ranging between 24 % and 70% (8,28-31), with an obvious negative influence on survival. Furthermore transplantation was performed for tumours that were unresectable because they were multiple, or because of their large size, factors that are correlated with the incidence of distant spread. Cases with lymph node invasion, and therefore extremely prone to recurrence, were included in some series (8). It is therefore not surprising that a period of disillusion followed an initial wave of enthusiasm, with liver transplantation for malignancy in Europe falling from 29% of all indications in the period 1983-1987 to 15% in the period 1988-1992 (32). In some large centres, however, attention was attracted on the good prognosis of patients transplanted with small tumours

discovered on the hepatectomy specimen (33). It was the analysis of the results from patients with small HCC who could not undergo liver resection because of poor liver function, in a series excluding from transplantation patients with extrahepatic disease, that first drew attention to the fact that patients with small HCC, traditionally considered the best candidates for liver resection, had a significantly better disease-free survival with liver transplantation (10).

The experience in our centre

The characteristics of 125 patients with HCC transplanted between January 1985 and December 1995 are represented in table IV. The indications for liver transplantation were either the known presence of the tumour (92 cases, 74%), or the severity of the underlying cirrhosis, the tumour being an incidental finding during the pre-transplant assessment (13 cases, 10%) or on the hepatectomy specimen after transplantation (20 cases, 16%). There were two different periods in the selection of the patients during the course of the study : in the six year period between 1985 and 1991, 60 patients with known tumours were transplanted, mostly because the tumour was not resectable, because of poor hepatic function, multicentricity or excessive size, the only contraindication being the presence of extrahepatic metastases. Analysis of the results obtained during this first period (10) directed the selection of the 45 patients with known tumours transplanted during the period 1992-1995, favouring patients with smaller and fewer tumours and the absence of vascular involvement. The patient characteristics in these two periods are represented in table V. With regard to the choice between liver resection or transplantation, in the first period liver resection was still considered the as the first option for patients with good liver function and liver transplantation reserved for tumours that were either multiple or unresectable because of poor liver function. In the second period liver transplantation was considered in preference, and liver resection was generally restricted to the treatment of patients with excellent hepatic function and easily accessible solitary lesions, or with contraindications to liver transplantation.

Table IV. — **Patient and tumour characteristics of the tumour in the 125 patients transplanted for hepatocellular carcinoma at Paul Brousse Hospital 1985-1995**

Males	107	(86%)
Females	18	(14%)
Mean age (range)	52.6 (16-66)	
Hepatitis B	27	(22%)
Hepatitis C	56	(45%)
Hepatitis B+C	12	(10%)
Alcohol	14	(11%)
PBC	4	(3%)
Other	12	(10%)
Child A	39	(31%)
Child B	49	(39%)
Child C	37	(30%)
Number of nodules		
1	52	(42%)
2-3	41	(33%)
> 3	32	(25%)
Maximum size		
≤ 30	78	(62%)
30-50	29	(22%)
> 50	19	(15%)
Portal vein thrombus (tumoral)		
Trunk	2	(2%)
Main portal branch	6	(5%)
Sectorial / segmental branch	10	(8%)
Alfa-foetoprotein		
normal	54	(55%)
increased	44	(45%)
TACE	65	(52%)
Blood transfusion		
0	3	(2%)
1-5	34	(27%)
5-10	35	(28%)
> 10	53	(42%)
Postoperative chemotherapy	51	(41%)

TACE : trans-arterial chemioembolisation.
PBC : primary biliary cirrhosis.

Table V. — **Comparison of the two periods of the Paul Brousse experience of liver transplantation for hepatocellular carcinoma. Figures include only patients with known tumours (N = 105)**

Patients' characteristics	1985-91 N = 60	1992-95 n = 45	p
• Number of tumours			
≤ 3 nodules	37 (62%)	39 (87%)	
> 3 nodules	23 (38%)	6 (13%)	0.01
• Size			
≤ 30 mm	31 (52%)	29 (64%)	
> 30 mm	29 (48%)	16 (36%)	NS
• Number and Size	22 (37%)	28 (28%)	
≤ 30 mm, ≤ 3 nodules			
> 30 mm, > 3 nodules	14 (23%)	5 (11%)	0.02
• Recurrence	21 (33%)	5 (11%)	0.008
• Survival at 5 years			
Overall	53%	76%	0.01
Disease-free	43%	74%	0.004

Preoperative assessment and technique

The preoperative assessment aimed at excluding tumour dissemination (bone radionuclide scan and abdominal and chest CT scan) and vascular involvement. Tumoral thrombosis in the portal trunk discovered peroperatively was considered as a contraindication during the second part of the study (92-95). No biopsy of the tumour was done in our unit for fear of needle tract seeding. In patient with preserved hepatic function (Child A), and in the absence of other contraindications such as hepatofugal portal flow or peripheral vascular disease, trans-arterial chemoembolisation with lipiodol and cisplatin was performed (65 patients, 52%), this with the double aim of diagnosing nodules that may have escaped detection on ultrasound and computerised tomography, and of achieving preoperative control of the disease (27). The laparotomy at

the time of transplantation was used as the final confirmation that liver transplantation was not contraindicated, while a second recipient was kept on stand-by. In total, 9 patients (8.5% of the total number of patients for whom the indication to liver transplantation had been retained) were not transplanted for contraindications emerged during the laparotomy (Peritoneal nodules in 3 cases, and lymph node invasion, neoplastic thrombosis in the portal vein and abdominal wall invasion in 2 cases each). The cell-saver was not used until after the hepatectomy to decrease the risk of disseminating tumour cells which may be shed during manipulation of the liver, and extracorporeal bypass was used only after clamping of the portal vein in order to avoid dislodging intrahepatic tumoural cells during aspiration of the portal trunk. Chemotherapy with doxorubicin and 5-fluoro-uracil was given in the presence of adverse histologic features (microvascular invasion, satellite nodules, absent or invaded tumour capsule).

Results

Of the 125 patients transplanted, after a mean follow up of 45 months (2 -134 months) for the whole series, 53 have died (42%) and 72 are alive (58%) of whom 71 without recurrence, with a mean follow up in survivors of 76 months (12-152 months). The actuarial survival for the whole group of transplanted patients was 80% at 1 year, 65% at 3 years and 58% à 5 years (fig. 3) with a disease-free survival respectively of 74%, 62% et 57%. Survival was similar for incidental and histologic forms of tumours (69% 5 year survival) and this was greater than in cases where the tumour represented the indication for transplantation (55% survival at 5 years).

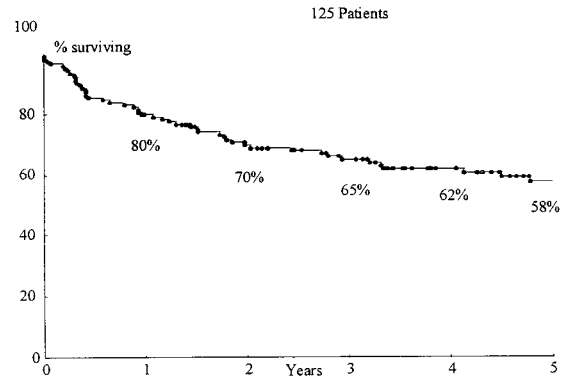

Fig. 3. — Actuarial survival of 125 patients transplanted with hepatocellular carcinoma and cirrhosis at Paul Brousse Hospital in the period between 1985-1995.

Recurrence was observed in 26 patients (21%) at a mean of 18 months after transplantation. (range 2 months -7 years and 10 months). The majority of recurrences were observed during the first year (13/26 - 50%) or the second year (8/26 - 31%). Only a few cases were observed after this time (5/26 - 19%). The initial sites of recurrence were, in decreasing order of frequency : the lungs (8 cases - 31%), the liver (6 cases - 23%), the bone (5 cases - 19%), the lymph nodes (4 cases - 15%) and the adrenals (3 cases - 12%). Recurrence was observed more frequently in cases where the tumour was the main indication for transplantation (25/92 -27%). There was only one recurrence among the patients in whom the tumour was discovered incidentally on pathological examination of the explanted liver (1/20, 5%, $p = 0.001$) and no recurrence in the 13 cases in whom the tumour was discovered during the pre-transplant evaluation. Three factors were found to have a significant influence on the incidence of recurrence after transplantation : the size of the tumour, the number of nodules and the presence of tumoural portal vein thrombosis (table VI).

Table VI. — **Risk of recurrence after transplantation as related to the features of the tumoral disease**

	Recurrence N° of recurrences / cases observed (%)	p
Size		
< 30 mm	10/78 (13%)	
31-50 mm	8/28 (29%)	0.009
> 50 mm	8/19 (42%)	
Number of nodules		
1	4/52 (8%)	
2-3	9/41 (22%)	0.001
>3	13/32 (41%)	
Size and Number		
≤ 30 and ≤ 3	5/66 (8%)	
> 30 and ≤ 3	8/27 (30%)	0.001
≤ 30 and > 3	5/12 (42%)	
> 30 and > 3	8/20 (40%)	
Portal Thrombosis* (tumoral)		
Absent	10/107 (9%)	0.001
Sectorial-Segmental	5/10 (50%)	
Trunk-Main Branch	7/8 (87%)	

* Patients with known tumours.

The size of the tumour: Patients whose tumours were smaller than 30 mm had a significantly better survival than patients with tumours between 30 and 50 mm or larger than 50 mm (5 year survival : 71% vs 43% and 37%, respectively - $p < 0.01$ - fig. 4).

The number of nodules : Patients with single tumours had a better survival than patients with 2 or 3 nodules, and than patients with more than 3 nodules (5 year survival : 68%, 58% and 42%, respectively - p : NS). The difference was statistically significant when patients with 1 to 3 nodules were compared with patients with more than 3 nodules (fig. 5).

Combination of size and number : Patients small tumours (< 30 mm) and no more than 3 nodules had a markedly better survival than patients with larger (30 mm) and multinodular tumours (> 3 nodules) : 5 year survival : 72% versus 33% - $p < 0{,}001$). For

patients with disease in the intermediate categories (with tumours larger than 30 mm but with no more than 3 nodules, or with more than 3 nodules not larger than 30 mm) survival was in between the two figures (fig. 6).

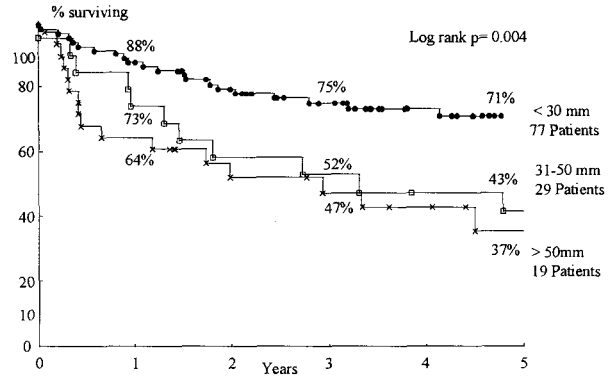

Fig. 4. — Actuarial survival after liver transplantation with hepatocellular carcinoma according to the maximum size of the tumour.

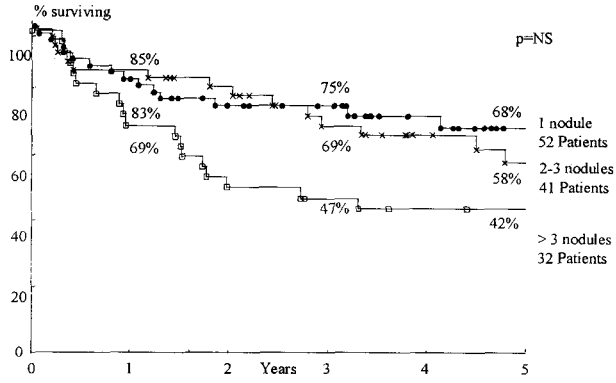

Fig. 5. — Actuarial survival after liver transplantation with hepatocellular carcinoma according to the number of tumours.

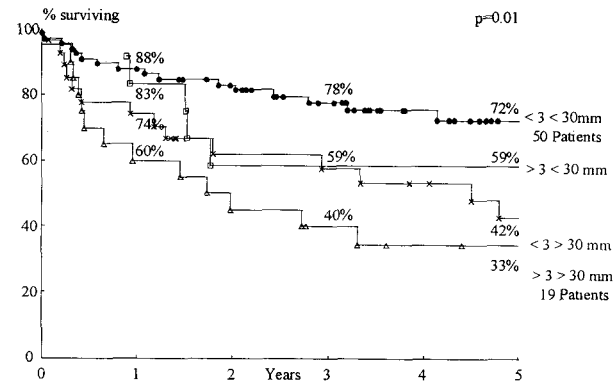

Fig. 6. — Actuarial survival after liver transplantation with hepatocellular carcinoma according to the maximum size and number of the tumours.

Portal thrombosis: The survival was significantly worse when the tumour was associated with portal vein thrombosis, confirmed on histology, whether distal (segmental or sectorial branch - 5 year survival : 28%) or proximal (portal trunk or main branch - 5 year survival : 0%), as compared to patients without portal vein involvement (5 year survival : 68% - p = 0.002) (fig. 7).

The importance of the size of the tumours, of the number of nodules and of the vascular involvement in the incidence of recurrence of HCC after liver transplantation is shown in the evolution of the results in our centre. In patients transplanted between 1992 and 1995, who were selected taking into account the negative prognostic value of a tumoural size exceeding 30mm, of more than 3 tumour nodules and of portal vein thrombosis (and in whom where these features were significantly less represented) the incidence of recurrence fell from 33% to 11% and the disease-free survival at 5 years increased from 43% to 74%, an outcome comparable to the outcome of liver transplantation for non-malignant disease (fig. 8). These good

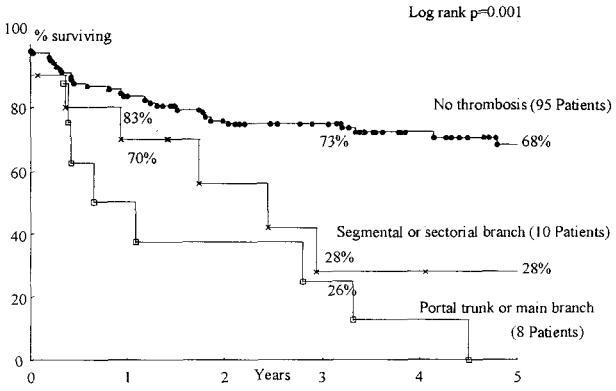

Fig. 7. — Actuarial survival after liver transplantation with hepatocellular carcinoma in patients with known tumours : patients without thrombosis of the portal vein as opposed to the presence of a tumoural thrombus in a distal portal branch (segmental or sectorial) or in the proximal portal vein (main branch or portal trunk).

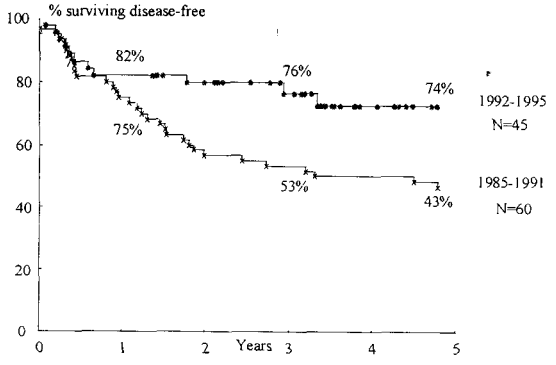

Fig. 8. — Actuarial survival after liver transplantation for hepatocellular carcinoma before and after 1992, when a policy of favouring liver transplantation in patients with up to three tumour nodules, up to 30mm in size and no tumour involvement of the portal vein was implemented.

Table VII. — **Liver Transplantation for Hepatocellular carcinoma. Results of the main unicentric series**

Author	Year	Patients	Operative mortality (%)	Recurrence (% of survivors)	Survival 1 year	Survival 3 years (%)	Survival 5 years (%)
Iwatsuki (28)	85	37*	24†	43	68	25	—
O'Grady (29)	88	19	31‡	69	43	32	32
Ringe (30)	89	29	34†	32	35	20	20
Ismail (31)	90	10	70†	66	10	0	0
Ringe (8)	91	79	30†	—	38	15	15
Iwatsuki (33)	91	71	15‡	—	70	52	49
Haug (35)	92	16	17‡	23	63	32	—
Mc Peake (36)	93	40	29‡	48	—	—	—
Bismuth (10)	93	60§	5‖	35	75	49	—
Chung (37)	94	29*	31‡	0	61	46	—
Romani (38)	94	27¶	11**	8	82	71	—
Schwartz (39)	95	57	19‡	7	75	60	—
Selby (40)	95	105*	—	43	66	39	36
Tan (41)	95	15	13‖	15	80	63	—
Olthoff (42)	95	25*	0	16	75	46	—
Mazzaferro (34)	96	48	6	8		83†† (4years)	
Figueras (43)	97	38¶	—	8	82	75	63
Colella (44)	98	55				72	68
Bechstein (45)	98	52¶			88††	—	60††
Otto (46)	98	50*‡‡	8	36	—	53††	
Present series		125	3‖	22	82	68	59
		45§§	3‖	11	82††	76††	74††

* includes patients with and without cirrhosis
† mortality at 30 days
‡ mortality at 90 days
§ Tumours discovered after hepatectomy excluded
‖ mortality at 60 days
¶ includes only patients with tumours < 50 mm in size
** hospital mortality
†† Disease-free
‡‡ 36% of patients with tumours > 5 cm
§§ Patients transplanted '92-'95

results have been confirmed by other teams applying the same or a similar restrictive policy to the selection of patients with HCC for liver transplantation, such as the group from the National Cancer Institute in Milan, (< 3 nodules less than 3 cm or a single nodule < 5 cm) (34) and are summarised in table VII (35-46).

Other factors important for the prevention of recurrence after transplantation for HCC are currently been evaluated, especially in cases without the favourable prognostic tumour characteristics mentioned above, unfortunately still the majority of patients at presentation. While the viral status of the host does not appear correlated to the incidence of recurrence or survival, some biological features of the tumour may be more relevant. The presence of negative oestrogen receptors in the tumour was associated with a more favourable outcome (47). In a study from our unit, patients with tumours larger than 30 mm that decreased in size after trans-arterial lipiodol chemoembolisation had a 5 year disease-free survival after transplantation of 74%, equal to patients transplanted with smaller tumours (27), and these criteria may be used for widening the indication to liver transplantation in patients previously considered as poor candidates. Postoperative chemotherapy is under evaluation in some centres, including our unit (48,49).

Resection vs transplantation

When patient survival at 3 and 5 years is considered, there is no significant difference between resection and transplantation (log rank p = 0.10) (fig. 9), when the disease-free survival is considered, however, the results of liver transplantation are significantly better (Log rank p = 0.0001) (fig. 10). The difference is particularly striking when only patients with small tumours (< 30 mm) and preserved liver function (Child A) are considered (fig. 11). The superiority of liver transplantation in the treatment of small HCC has tended to confine liver resection in our unit 1): to the treatment of patients with contraindications to transplantation, generally in terms of age, associated extrahepatic diseases or psycho-social factors, and 2): to the treatment of the patients with easily accessible solitary tumours and

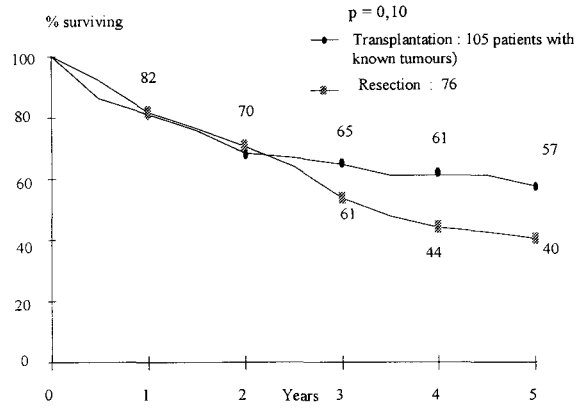

Fig. 9. — Actuarial survival of patients undergoing a potentially curative liver resection or liver transplantation for hepatocellular carcinoma during the study period. Only patients with known tumours are included.

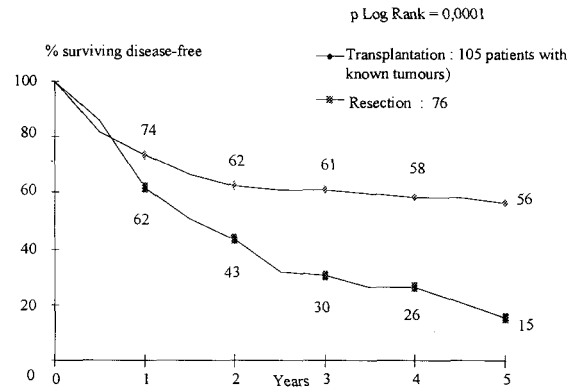

Fig. 10. — Actuarial disease-free survival of patients undergoing a potentially curative liver resection or liver transplantation for hepatocellular carcinoma during the study period. Only patients with known tumours are included.

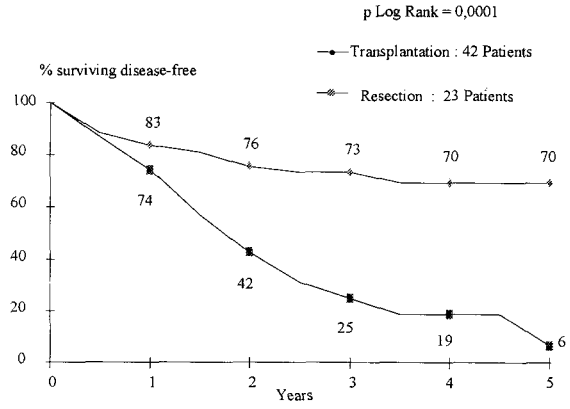

Fig. 11. — Actuarial disease-free survival of patients undergoing a potentially curative liver resection or liver transplantation for hepatocellular carcinoma during the study period. Only patients with known tumours ≤ 30 mm in size are included.

very good hepatic function when a long delay before transplantation is anticipated. This represents a reversal of the previous attitude that for early HCC resection should be performed, and liver transplantation reserved for unresectable tumours. In fact resection and transplantation are indicated for similar stages of the tumoral disease (where radical treatment is still possible) and the choice between them depends on 1) whether the patient belongs to a population in whom liver transplantation may or may not be possible 2) on the availability of suitable grafts within a reasonable delay (38).

Other centres comparing resection and transplantation for HCC with cirrhosis have reached similar conclusions (44,46,51,52). Although all suffer from the methodological bias of a non-randomised allocation of patients in the different treatment groups, the difference in disease-free survival concerning early HCC is so striking that it makes a protocol of randomisation limited to comparing resection and transplantation ethically questionable.

Percutaneous ethanol injection

Generalities

Injection of ethanol in living tissues produces an immediate coagulation necrosis by dehydrating the cytoplasm and induces lesions in the endothelial cells leading to microvascular thrombosis. Hepatocellular carcinoma lends itself well to percutaneous ethanol injection (PEI) as the tumour is soft, favouring the retention and spread of alcohol, and the surrounding tissue hard, countering its diffusion ; this treatment is much less effective in tumours with opposite features such as colorectal liver metastases (53).

The procedure was first described in Chiba in 1983 (54), but it is only after publications in the international literature by an Italian (55) and a Japanese team (56) that it started to gain a wider diffusion.

The equipment consists of a sterile needle with a hatched tip so that it can be visualised more easily on ultrasound, and 99% ethanol with local anaesthetic. The procedure is planned preoperatively with the help of a spiral contrast CT with an arterial acquisition phase at 30 seconds and venous acquisition phase at 120 seconds, and of a Doppler ultrasound clarify the anatomy of the nodule. The only contraindications are represented by a platelet count $< 40\,000$ or prothrombin time $< 40\%$. Ascites is not a contraindication but is better treated beforehand. The procedure is performed under light sedation and analgesia in the outpatient operating theatre. A technique with two operators, one manipulating the ultrasound probe and the other performing the puncture and the injection, is preferred in our centre. The volume of the alcohol injected is $V = 4/3\ \pi\ (d/2+0.5)^3$, where 0.5 represents the safety margin (57). The injection is repeated, usually the following days, for a number of times twice the diameter of the lesion. The efficacy of the injection is monitored initially by Doppler ultrasound that has to show the complete extinction of the vascular signal, and by a spiral contrast CT when the operator is confident that no more tumoral tissue is present. The tumour is replaced by a hypodense lesion and any residual areas taking up contrast medium must be retreated. Contrast-enhanced magnetic resonance imaging can be useful, especially if the patient has undergone transarterial lipiodol chemoembolisation. More sophisticated techniques may be used in special circumstances. When the tumour is poorly visualised on ultrasound but enhances on CT, the operator can take advantage of CO2 micro-bubbles as an ultrasound contrast agent that increase the echogenicity of the nodule. Nodules that are particularly vascular, sometimes accompanied by an arterio-portal fistula, can be treated by an injection directly into the feeding artery, identified with the power-Doppler technology. This is especially useful to prevent bleeding and rupture of peripheral HCC nodules not covered by liver parenchyma, where intra-lesional alcohol injection may be hazardous because of the risk of extravasation.

Results

Several series have reported the long term results of percutaneous alcohol injection of HCC nodules in cirrhotic patients and are summarised in table VIII (57-61). The most important report a survival ranging from 55 to 80% at three years and between 0 and 63% at five years, according to the size and number of the nodules and the severity of the underlying cirrhosis.

Although no randomised study is available comparing percutaneous ethanol injection to liver resection, the results of two retrospective studies conclude to a similar effectiveness of the two treatments, with lower mortality, lower costs and a lower complication rate for ethanol injection, counterbalanced by a higher incidence of recurrence for tumours larger than 4 cm (59,62). The incidence of local recurrence (at the periphery of the treated nodule, as opposed to distant intrahepatic recurrence) was 3-7% in specialised units and 17% in a multicentric series (table VIII). These results have been possible thanks to the improvement of imaging techniques, and to the attitude of verifying systematically and re-treating lesions treated incompletely. In view of the very low local recurrence rate, the place of PEI in the treatment of HCC patients is evolving. In addition to being the treatment of choice for patients with poor liver function that can not tolerate resection, and for recurrence after resection, PEI can probably be used instead of resection for treating tumours smaller than 3 cm with a locally curative intent. Whether PEI can be used safely for the treatment of HCC nodules before liver transplantation is still unknown : in spite of the low incidence of needle-tract dissemination in published series (approximately 1%, possibly due to the biopsy rather than the injection procedure itself), it is conceivable that the true incidence of needle tract dissemination is masked, in patients who are not transplanted, by the mortality associated with intrahepatic recurrence and the progression of the cirrhosis. For this reason techniques of coaxial PEI are being used in pre-transplant recipients in some units.

Transarterial chemoembolisation

The treatment of hepatocellular carcinomas by transarterial chemoembolisation is based on the principle that tumours depend solely on the arterial supply, in contrast to normal liver that is also supplied by the portal flow. The procedure is carried out by injecting an emulsion of iodised poppy-seed oil (lipiodol) and of a chemotherapeutic agent (cisplatin or adriamycin), followed by embolisation with absorbable gelatine particles, either of the hepatic artery proper or, more selectively, of the vessels supplying the tumour. Lipiodol leaks through the larger fenestrations of the tumoral blood vessels and persists in the tumour because of the absence of Kupffer cells and of an effective lymphatic drainage, and is easily detectable by computed tomography carried out 3-5 weeks after the procedure. Small tumours, which may have escaped detection, can then be identified, allowing a more accurate staging of the disease. Chemoembolisation, especially when performed non-selectively into the hepatic artery, damages to some extent the non-tumoral liver and it is hazardous in patients with diminished hepatocellular function (Child B or C), and in patients with absent or hepatofugal portal blood flow.

Table VIII. — **Results of percutaneous ethanol injection for the treatment of hepatocellular carcinoma : main series**

Author	Year	Study	Patients	Child	Size (cm)	Number	Survival 3 years	Survival 5 years	Comments
Ebara (57)	92	unicentric	60	A	< 3	s/m	72	51	local
			33	B			72	48	recurrence
			19	C			25	0	4%
Shiina (58)	93	unicentric	98	ABC	< 6.5	s/m	62	52	local recurrence 7%
Castells (59)	93	PEIT	30	ABC	< 4	1	55 (20*)	34	75%
		vs							vs
		resection	33	AB	< 4	1	44 (25*)	44 (4 years)	60% (3 years)
Livraghi (60)	95	multicentric	746	ABC	< 5	1	79	47	local
			293	A		> 1	68	36	recurrence
			121	A	> 5	1	53	30	17%
			28	A	< 5	1	63	29	
			149	B	< 5	1	12	0	
			20	C					
Lencioni (61)	97	prospective	184	ABC	23.9 (mean)		67	41	15/50/80†
		(mean fu 24	94	ABC	²3	1	78	54	28‡
		months,	50	ABC	> 3	1	61	32	16‡
		range 2-94	40	ABC	²3	²2	51	21	0‡
		months)	70	A	²3	1	90	63	42‡

s : single, m : multiple
* disease-free survival
† Recurrence rate ; local recurrence : 6 cases (3%), new nodules 93 cases (51%)
‡ survival rate at 7 years.

Table IX. — **Results of the main series of transarterial lipiodol embolisation for the treatment of hepatocellular carcinoma**

Author Year	Study features	Patients	Child A/B/C	Number / Size (cm)	Survival % 1 year	Survival % 2 years	Complications/ mortality (%)	Comments
Lin '88	Multiple TAE	21	Hepatic de-	unspecified	42	25	cholecystitis 2pts	RR 66%
(63)	1 TAE + Chemo	21	compen-		21	21	gastric ulcer 1 pt	48%
	Chemo alone	21	sation or PT		13	12	pain - fever 33pts	10%
	PR		excluded					
Vernook '90	TACE (doxo)	51	median % liver			severe 6 pts	RR 50%	
(64)	R	Acites 10%	replaced			death 2 pts		
		PT excluded	50% (15%-95%)					
Vetter '90	TACE (doxo)	30	15/12/3 ; PT 5*	8-11 (median)	59	30	- / 3	PT (autopsy) 1
(65)	No treatment	30	12/12/6	8-11 (median)	0	0		PT (autopsy) 15
	R							
Bismuth '92	TACE (doxo)	140 (60%)	Child A	Okuda I / II / III	71	49	3 / 3*	RR 29%
(66)	R	78 (33%)	Child B	150 / 121 / 20 :	53	29	8 / 8*	
		16 (7%)	Child C		18	9	37 / 23*	
Stuart'93	TACE (doxo)	52	(6.5x5.1)	60	48	> 50 / 17	RR 43%	
(67)	R	Ascites 14, PT 11						
Mondazzi '94	TACE (doxo)	84	57% / 43%	s < 5 : 29%, m>5 : 43%	62	31	—	
(68)	R							
Chang '94	TACE (cis)		13/9/0	s 9 ; m 9 ; d 4 /-	53	26	10 / 0	RR 68%
(69)	TAE	22	17/7/0	s 11 ; m 11 ; d 2	72	40	5 / 0	RR 67%
	PR	24						
Ryder '96	TACE (doxo)	67		≥4 : 18/4-8 : 33 / > 8 :11	40	10	22 / 9	RR 56% (< 4cm)
(70)	R		(4)/10/37/16					
Trinchet '97	TACE (cis)	50	Child A	s ≥5 : 40% m 38%	62	38	20 / 2	RR 53% (PT 7%)
(71)	conservative	46	Child A	s ≥5 : 16% m 57%	43	26	—	RR 3% (PT 26%)
	PR							
Bruix '98	TAE	40	5.8 ± 0.7	Okuda I/II : 27/13	68	49	PES 83 / 0	RR 57%
(72)	No treatment	40	6.0 ± 1.1	Okuda I/II : 27/13	70	50		RR 77%
	PR							

TAE : transarterial embolisation. TACE : transarterial chemoembolisation ; PR prospective randomised study ; R : retrospective study ; Doxo : Doxorubicin ; Cis : Cisplatin ; RR : response rate ; PT : portal thrombosis ; s : single ; m : multiple ; d : diffuse ; PES : post-embolization syndrome (fever, abdominal pain, nausea).

* Mortality at 60 days.

TACE was first introduced as a palliative treatment for patients with inoperable disease, with good results reported in many retrospective series and a less clear benefit in more recent prospective studies, summarised in table IX. In the most authoritative prospective randomised trial (71) the survival advantage did not reach the expected target, despite an undoubted anti-tumoral efficacy, possibly because in the study protocol the treatment was standardised rather than adapted to the hepatocellular reserve and the tumoral disease in each case. With careful respect of the contraindications and the choice between selective and more general chemoembolisation, the risk of mortality and of serious complications can be reduced to acceptable levels. TACE has been used preoperatively in patients undergoing resection or transplantation to increase the detection of additional tumour nodules, to increase resectability and to control the disease during the waiting time (27). Concerns were raised on the possible increased incidence of extrahepatic metastases (73) and of hepatic or peri-hepatic recurrence (74). In fact the studies reporting these complications were done in patients with advanced disease that would not be considered for curative resection or transplantation, and a significant increase in distant metastases has not been confirmed in more recent reports (27,34). The anti-tumoral effect of TACE was studied in the authors' unit on 54 patients undergoing liver transplantation and on 49 patients undergoing liver resection. Although no clear survival benefit was evident in patients having undergone TACE as opposed to patients without TACE, response to TACE under the form of down-staging and/or total necrosis of the tumour, observed in 69% of patients undergoing resection and in 56% of patients undergoing transplantation, was associated with an increased disease-free survival. In particular in patients transplanted with tumours larger than 3 cm that responded to chemoembolisation, the disease-free survival was as good as in patients with smaller tumours (27). Other investigators found a similar rate of response to TACE (75,76).

Pending further and more conclusive prospective studies, it seems reasonable to use TACE for the palliation of patients with unresectable tumours and preserved hepatic function, and for more accurate staging and control of the tumoral disease before resection (or alcohol injection) and before liver transplantation.

Some studies have reported the results of the association of percutaneous ethanol injection with transarterial lipiodol chemoembolisation for palliative treatment of large HCC. The rationale of the association is that transarterial embolisation disrupts the fibrous septa in the tumour with a consequent increase in the diffusion and effectiveness of ethanol. The advantage of such approach compared to transarterial chemoem-

bolisation alone has been confirmed in two prospective randomised studies reporting an increase in 3 year survival from 43% to 72% in total of 53 patients (77) and from 20% to 50% in 100 patients (78).

Conclusions

HCC is severe complication of liver cirrhosis, and for the majority of patients the chances of cure are limited. The recent experience in liver transplantation for HCC in the authors' unit and in other centres allows to define a subgroup of patients, with small tumours (up to 30 mm, or 50 mm if solitary), no more than 3 nodules and the absence of portal vein thrombosis in whom liver transplantation offers a disease-free survival that is better than after liver resection, and is similar to the survival of liver transplantation for benign liver disease. The main directions in which further progress is needed are 1) to detect patients at low risk of recurrence despite apparently advanced disease, currently excluded from liver transplantation, and 2) to increase the number of available grafts, by encouraging organ donation and by expanding new techniques such as the split or "domino" liver transplantation, living donor liver transplantation or by exploring strategies such as reserving liver transplantation for recurrence after local treatment of the tumours by resection or percutaneous tumour ablation.

Patients with contraindications to transplantation, patients in whom a long waiting time before transplantation is anticipated, and patients in countries with limited access to transplantation can be treated with a palliative intent by liver resection and, probably equally effectively for small HCC, by percutaneous ethanol injection according to the liver function and to the local expertise. Other forms of treatment, such as radio-frequency thermal ablation or cryo-therapy offer advantages similar to PEI without the need of multiple sessions, and are currently being evaluated. Further progress will probably come from a wider use of screening to detect a larger proportion of treatable lesions, from strategies to prevent carcinogenesis in the cirrhotic liver, and possibly from innovative treatments such as gene therapy.

References

1. BOSCH X., MUNOZ N. Hepatocellular carcinoma in the world : epidemiologic questions. *In* : TABOR E., DI BISCEGLIE A.M., PURCELL R.H. (eds). Etiology, pathology and treatment of hepatocellular carcinoma in North America. Woodlands, TX : Portfolio Publ Co 1991 : 35-54.
2. OKUDA K. Hepatocellular carcinoma. Recent progress. *Hepatology*, 1992, **15** : 948-955.
3. GANNE-CARIÉ N., CHASTANG C., CHAPEL F. *et al.* Predictive score for the development of hepatocellular carcinoma and additional value of liver large cell dysplasia in western patients with cirrhosis. *Hepatology*, 1996, **23** : 1112-1118.
4. BISMUTH H. Surgical anatomy and anatomical surgery of the liver. *World J. Surg.*, 1982, **6** : 3-9.
5. YAMAMOTO J., KOSUGE T., TAKAYAMA T. *et al.* Perioperative blood transfusion promotes recurrence in hepatocellular carcinoma after hepatectomy. *Surgery*, 1994, **115** : 303-309.
6. MIYAGAWA S. MAKUUCHI M., KAWASAKI S., KAKAZU T. Criteria for safe hepatic resection. *Am. J. Surg.*, 1995, **169** : 589-94.
7. FAN S.T., LO C.M., LAI E.C., WONG J. Perioperative nutritional support in patients undergoing hepatectomy for hepatocellular carcinoma. *N. Engl. J. Med.*, 1994, **331** : 1547-52.
8. RINGE B., PICHLMAYER R., WTTEKIND C. *et al.* Surgical treatment of hepatocellular carcinoma : Experience with liver resection and transplantation. *World J. Surg.*, 1991, **15** : 270-285.
9. BELGHITI J., PANIS Y., FARGES O. *et al.* Intrahepatic recurrence after resection for hepatocellular carcinoma complicating cirrhosis. *Ann. Surg.*, 1991, **214** : 114-117.
10. BISMUTH H., CHICHE L., ADAM R. *et al.* Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. *Ann. Surg.*, 1993, **218** : 145-151.
11. CASTELLS A., BRUIX J., BRU C. Treatment of small hepatocellular carcinoma in cirrhotic patients : a cohort study comparing surgical resection and percutaneous ethanol injection. *Hepatology*, 1993, **18** : 1121-1126.
12. NAGASUE N., UCHIDA M., MAKINO Y. *et al.* Incidence of factors associated with intrahepatic recurrence following resection of hepatocellular carcinoma. *Gastroenterology*, 1993, **105** : 488-494.
13. LAI E.C.S., FAN S.T., LO C.M., CHU K.M., LIU C.L., WONG J. Hepatic resection for hepatocellular carcinoma. An Audit of 343 patients. *Ann. Surg.*, 1995, **221** : 291-298.
14. SHIRABE K., TAKENAKA K., TAKETOMI A. *et al.* Postoperative hepatitis status as a significant risk factor for recurrence in cirrhostic patients with small hepatocellular carcinoma. *Cancer*, 1996, **77** : 1050-1055.
15. TAKENAKA K., KAWAHARA N., YAMAMOTO K. *et al.* Results of 280 liver resection for hepatocellular carcinoma. *Arch. Surg.*, 1996, **131** : 71-76.
16. BALSELLS J., CHARCO R., LAZARO J. *et al.* Resection of hepatocellular carcinoma in patients with cirrhosis. *Br. J. Surg.*, 1996, **83** : 758-61.
17. KO S., NAKAJIMA Y., KANEHIRO H. *et al.* Significant influence of accompanying chronic hepatitis status on recurrence of hepatocellular carcinoma after hepatectomy. *Ann. Surg.*, 1996, **224** : 591-595.
18. NAGASHIMA I., HAMADA C., NARUSE K. *et al.* Surgical resection for small hepatocellular carcinoma. *Surgery*, 1996, **119** : 40-45.
19. MAKUUCHI M., TAKAYAMA T., KUBOTA K. *et al.* Hepatic resection for hepatocellular carcinoma. — Japanese experience. *Hepato-gastroenterology*, 1998, 1267-1274.
20. MAZIOTTIA, GRAZI G.L., CAVALLARI A. Surgical treatment of hepatocellular carcinoma on cirrhosis : a western experience. *Hepato-gastroenterology*, 1998, 1281-1287.
21. LISE M., BACCHETTI S., DA PIAN PNITTI D., PILAT P.L., PIGATO P. Prognostic factors affecting long term outcome after liver resection for hepatocellular carcinoma. *Cancer*, 1998, **82** : 1028-1036.
22. BELGHITI J., FARGES O. *et al.* Resection hépatique large et récidive de carcinome hépatocellulaire. Abstract presented at the 5th meeting of the ACHBT, Paris June 1998.
23. Liver Cancer Study Group of Japan. Predictive factors for long term prognosis after partial hepatectomy for patients with hepatocellular carcinoma in Japan. *Cancer*, 1994, **74** : 2272-2280.
24. YUKI H., HIROHASHI S., SAKAMOTO M. *et al.* Growth and spread of hepatocellular carcinoma. A review of 240 consecutive autopsy cases. *Cancer*, 1990, **66** : 2174-2179.
25. MUTO Y., MORIWAKI H., NINOMIYA M. *et al.* Prevention of second primary tumors by an acyclic retinoid, Polyprenoic acid, in patients with hepatocellular carcinoma. *N. Engl. J. Med.*, 1996, **334** : 1561-1567.
26. KINOSHITA KINOSHITA H., SAKAI K., HIROHASHI K. *et al.* Preoperative portal vein embolization for hepatocellular carcinoma *World J. Surg.*, 1986, **10** : 803-808.
27. MAJNO P., ADAM R., BISMUTH H. *et al.* Influence of pre operative transarterial lipiodol chemoembolisation on resection and transplantation for hepatocellular carcinoma in patients with cirrhosis. *Ann. Surg.*, 1997, **226** : 688-703.
28. IWATSUKI S., GORDON R.D., SHAW B.W., STARZL T.E. Role of liver transplantation in cancer therapy. *Ann. Surg.*, 1985, **202** : 401-407.
29. O'GRADY, J.G., POLSEN R.J., ROLLES K. *et al.* Liver transplantation for malignant disease : Results in 93 consecutive patients. *Ann. Surg.*, 1988, **207** : 373-379.
30. RINGE B., WITTEKIND C., BECHSTEIN H. *et al.* The role of liver transplantation in hepatobiliary malignancy : A retrospective analysis of 95 patients with particular regard to tumor stage and recurrence. *Ann. Surg.*, 1989, **209** : 88-98.
31. ISMAIL T., ANGRISANI L., GUNSON B.K. *et al.* Primary hepatic

malignancy : The role of liver transplantation. *Br. J. Surg.*, 1990, **77** : 983-987.
32. PICHLMAYR R., WEIMANN A., RINGE B. Indications for liver transplantation for hepatobiliary malignancy. *Hepatology*, 1994, **20** : 33s-40s.
33. IWATZUKI S., STARZL T.E., SHEAHAN D.G. *et al.* Hepatic resection versus transplantation for hepatocellular carcinoma. *Ann. Surg.*, 1991, **214** : 221-229.
34. MAZZAFERRO V., REGALIA E., DOCI R. *et al.* Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N. Engl. J. Med.*, 1996, **334** : 693-9.
35. HAUG C.E., JENKINS R.L., ROHRER R.J. *et al.* Liver transplantation for primary hepatic cancer. *Transplantation*, 1992, **53** : 376-382.
36. MCPEAKE J.R., O'GRADY J.G., ZAMAN S. *et al.* Liver transplantation for primary hepatocellular carcinoma : Tumor size and number determine outcome. *J. Hepatol.*, 1993, **18** : 226-234.
37. CHUNG S.W., TOTH J.L., REZIEG M. *et al.* Liver transplantation for hepatocellular carcinoma. *Am. J. Surg.*, 1994, **167** : 317-321.
38. ROMANI F., BELLI L.S., RONDINARA G.F. *et al.* The role of transplantation in small hepatocellular carcinoma complicating cirrhosis of the liver. *J. Am. Coll. Surg.*, 1994, **178** : 379- 84.
39. SCHWARTZ M.E., SUNG M., MOR E. *et al.* A multidisciplinary approach to hepatocellular carcinoma in patients with cirrhosis. *J. Am. Coll. Surg.*, 1995, **180** : 596-603.
40. SELBY R., KADRY Z., CARR B. *et al.* Liver transplantation for hepatocellular carcinoma. *World J. Surg.*, 1995, **19** : 53-58.
41. TAN K.C., RYDER S.D., RIZZI P.M. *et al.* Experience of orthotopic liver transplantation and hepatic resection for hepatocellular carcinoma of less than 8 cm in patients with cirrhosis. *Br. J. Surg.*, 1995, **82** : 253-256.
42. OLTHOFF K.M., ROSOVE M.H., SHACKLETON C.R. *et al.* Adjuvant chemotherapy improves survival after liver transplantation. *Ann. Surg.*, 1995, **221** : 734-743.
43. FIGUERAS J., JAURRIETA E., VALLS C. *et al.* Survival after liver transplantation in cirrhotic patients with and without hepatocellular carcinoma : a comparative study. *Hepatology*, 1997, **25** : 1485-1489.
44. COLELLA G., BOTTELLI R., DE CARLIS *et al.* Hepatocellular carcinoma. : comparison between liver transplantation, resective surgery, ethanol injection and chemoembolisation. *Transplant. Int.*, 1998, **11** : s193-196.
45. BECHSTEIN W.O., GUCKELBERGER O., KLING N. *et al.* Recurrence-free survival after liver transplantation for small hepatocellular carcinoma. *Transplant. Int.*, 1998, **11** : s189-192.
46. OTTO G., HEUSCHEN U., HOFMAN W., KRUMM G., HINZ U., HERFARTH C. Survival and recurrence after liver transplantation versus liver resection for hepatocellular carcinoma. *Ann. Surg.*, 1998, **227** : 424-432.
47. JONAS S., BECHSTEIN W.O., HEINZE T. *et al.* Female sex hormone receptor status in advanced hepatocellular carcinoma and outcome after surgical resection. *Surgery*, 1997, **121** : 456-461.
48. STONE N.J., KLINTMALM G.B.G., POLTER D. *et al.* Neoadjuvant chemotherapy and liver transplantation for hepatocellular carcinoma : a pilot study in 20 patients. *Gastroenterology*, 1993, **104** : 196-202.
49. CHERQUI D., PIEDBOIS P., VAVASSEUR D. *et al.* Liver transplantation with combined adjuvant treatment in hepatocellular carcinoma. *HPB Surgery*, 1993, **6** : 121.
50. SARASIN F.P., MENTHA G., GIOSTRA E., HADENGUE A. Partial hepatectomy or orthotopic liver transplantation for the treatment of resectable hepatocellular carcinoma ? A cost-effectiveness perspective. *Hepatology*, 1998, **28** : 436-42.
51. BRONOWICKI J.P., BOUDJEMA K., CHONE L. *et al.* Comparison of resection, liver transplantation and oily chemoembolisation in the treatment of hepatocellular carcinoma. *J. Hepatol.*, 1996, **24** : 293-300.
52. MICHEL J., SUC B., MONTPEYROUX F. *et al.* Liver resection or transplantation for hepatocellular carcinoma? Retrospective analysis of 215 patients with cirrhosis. *J. Hepatol.*, 1997, **26** : 1274-80.
53. AMIN Z., BROWN S.G., LEES W.R. Local treatment of colorectal metastases : a comparison of interstitial laser photocoagulation (ILP) and percutaneous ethanol injection (PAI). *Clin. Radiol.*, 1993, **48** : 166-171.
54. SUJURA N., TAKARA K., OHTO M., OKUDA K., HIROOKA N. Treatment of small hepatocellular carcinoma by percutanous injection of ethanol into tumor with real time ultrasound monitoring (in Japanese). *Acta Hepatol. Jpn.*, 1983, **24** : 920.
55. LIVRAGHI T., TESTI D., MONTO M., SALMI A., VETTORI C. US guided percutaneous alcool injection of small hepatic and abdominal tumors. *Radiology*, 1986, **161** : 309-312.
56. SHIINA S., YASUDA H., MUTO H., TAGAWA K., UNUMA T., IBUKURO K., INOUE Y, TAKANASHI R. Percutaneous ethanol injection in the treatment of liver neoplasms. *AJR*, 1987, **149** : 949-952.
57. EBARA M., KITA K., YOSHIKAWA M., SUGIURA N., OHTO M. Percutaneous ethanol injection in patients with small hepatocellular carcinoma. *In* : TOBE T., KAMEDA H., OKUDAIARA M., OHTO M., ENDO Y., MITO M. (eds). Primary liver cancer in Japan. Springer. Berlin Heidelberg, New York, 1992, 291-300.
58. SHIINA S., TAGAWA K., NIWA Y. *et al.* Percutaneous ethanol injection therapy for chepatocellular carcinoma : results in 146 patients. *AJR*, 1993, **160** : 1023-1028.
59. CASTELLS A., BRUIX J., BRUIX C. *et al.* Treatment of small hepatocellular carcinoma in in cirrhotic patients : a cohort study comparing surgical resection and percutaneous ethanol injection. *Hepatology*, 1993, **18** : 1121-1126.
60. LIVRAGHI T., GIORGIO A., MARIN G. *et al.* Hepatocellular carcinoma and cirrhosis is 746 patients : long term results of percutaneous ethanol injection. *Radiology*, 1995, **197** : 101-108.
61. LENCIONI R., PINTO F., ARMILLOTTA N. *et al.* Long term results of percutaneous ethanol injection therapy for hepatocellular carcinoma in cirrhosis : a European experience. *Eur. Radiol.*, 1997, **7** : 514-519.
62. KOTOH K., SAKAI H., SAKAMOTO S. The effect of percutaneous ethanol injection therapy on small solitary hepatocellular carcinoma is comparable to that of hepatectomy. *Am. J. Gastroenterol.*, 1994, **89** : 194-198.
63. LIN D.Y., LIAW Y.F., LEE T.Y., LAI C.M. Hepatic arterial embolization in patients with unresectable hepatocellular carcinoma — a randomized controlled trial. *Gastroenterology*, 1988, **94** : 453-456.
64. VERNOOK A.P., STAGG R.J., LEWIS B.J. *et al.* Chemoembolisation for hepatocellular carcinoma. *J. Clin. Oncol.*, 1990, **6** : 1108-1114.
65. VETTER D., WENGER J.J., BERGIER J.M., DOFFOEL M., BOCKEL R. Transcatheter oily chemoembolisation in the management of advanced hepatocellular carcinoma in cirrhosis : Results of a western comparative study in 60 patients. *Hepatology*, 1991, **13** : 427-433.
66. BISMUTH H., MORINO M., SHERLOCK D. *et al.* Primary treatment of hepatocellular carcinoma by arterial chemoembolisation. *Am. J. Surg.*, 1992, **163** : 387-94.
67. STUART K., STOKES K., JENKINS R., TREY C., CLOUSE M. Treatment of hepatocellular carcinoma using doxorubicin/ethiodized oil/gelatin powder chemoembolisation. *Cancer*, 1993, **72** : 3202-3209.
68. MONDAZZI L., BOTTELLI R., BRAMBILLA G., RAMPOLDI A., REZAKOVIC I., ZAVAGLIA C., ALBERTI A., IDÉO G. Transarterial oily chemoembolisation for the treatment of hepatocellular carcinoma : A multivariate analysis of prognostic factors. *Hepatology*, 1994, **19** : 1115-1123.
69. CHANG J.M., TZENG W.S., PAN H.B., YANG C.F., LAI K.H. Transcatheter arterial embolization with or without cisplatin treatment of hepatocellular carcinoma. *Cancer*, 1994, **74** : 2449-2453.
70. Groupe d'etude et de traitement du carcinome hepatocellulaire : a comparison of lipiodol chemoembolisation and conservative treatment for unresectable hepatocellular carcinoma. *N. Engl. J. Med.*, 1995, **332** : 1256-1261.
71. RYDER S.D., RIZZI P.M., METIVIER E., KARANI J., WILLIAMS R. Chemoembolisation with lipiodol and doxorubicin : applicability in British patients with hepatocellular carcinoma. *Gut*, 1996, **38** : 125-128.
72. BRUIX J., LLOVET J.M., CASTELLS A. *et al.* Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma : results of a randomized controlled trial in a single institution. *Hepatology*, 1998, **27** : 1578-1583.
73. WU C.C., HO Y.Z., LIN HO W., WU T.C., LIU T.J., P'ENG F.K. Preoperative transcatheter arterial chemoembolisation for resectable large hepatocellular carcinoma : a reappraisal : *Br. J. Surg.*, 1995, **82** : 122-126.
74. ADACHI E., MATSUMATA T., NISHIZAKI T. *et al.* Effects of preoperative transcatheter chemoembolization for hepatocellular carcinoma. *Cancer*, 1993, **72** : 3593-3598.
75. SPREAFICO C., MARCHIANO A., REGALIA E. *et al.* Chemoembolisation of hepatocellular carcinoma in patients who undergo liver transplantation. *Radiology*, 1994, **192** : 687-690.
76. HARADA T., MATSUO K., INOUE T., TAMESUE S., INOUE T., NAKAMURA H. Is preoperative arterial chemoembolisation safe and effective for hepatocellular carcinoma ? *Ann. Surg.*, 1996, **224** : 4-9.
77. BARTOLOZZI C., LENCIONI R., CARAMELLA D. *et al.* Treatment of large HCC : transcatheter arterial chemoembolisation combined with percutaneous ethanol injection versus repeated transcatheter arterial chemoembolisation. *Radiology*, 1995, **197** : 812-818.
78. YAMAMOTO K., MASUZAWA M., KATO M. *et al.* Evaluation of combined therapy with chemoembolisation and ethanol injection for advanced hepatocellular carcinoma. *Sem. Oncol.*, 1997, **24** (s6) : 50-55.