

## Transplantation for Liver Tumors

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The use of transplantation to treat malignancies is quite unique to the liver. Indeed, transplantation of other solid organs such as lungs or kidneys has not been clinically evaluated as a form of treatment for tumors originating from these organs. The liver is a frequent site of primary and secondary malignancies with a dismal prognosis.

During the 1980s, it appeared that liver transplantation might be the only curative treatment for patients with untreatable primary liver tumors. Among liver tumors, large, unresectable hepatocellular carcinoma (HCC) represented the most frequent indication for transplantation. Unfortunately, most series from this period showed overall 3-year survival rates of 30% or less (1,2). The most frequent cause of death was tumor recurrence, which was dramatically accelerated by postoperative immunosuppression. These poor results illustrated the inaccuracy of preoperative staging and the difficulties in detecting established micrometastases as the source of early recurrence.

Because of these poor results, in the 1990s, the proportion (but not the total number) of patients transplanted for malignancies had fallen dramatically throughout the world. Indeed, it became evident that the risks and constraints of transplantation were not justified if only a few additional months of survival could be expected. In addition, the limitations in graft availability and healthcare resources implied that liver transplantation should be restricted to the subset of patients expected to have the best prognosis. During this period, transplantation was almost abandoned for tumors other than HCC. In patients with HCC, selection criteria were established to identify those candidates with the lowest risks of recurrence (i.e., those with small tumors). In patients fulfilling these selection criteria, the results of transplantation proved to be nearly as good as those obtained in patients without malignancies.

The good results reported in the 1990s have made an increasing number of surgeons and physicians more confident with transplantation as a treatment for liver tumors.

We are now facing a trend of many centers re-expanding indications for transplantation to less-select patients who otherwise still have a poor prognosis. In particular, the advent of living donor transplantation, a technique by which patients can be transplanted without affecting the pool of cadaveric donors, prompted some centers to recommend an extended use of transplantation in cases of malignancy, even in those patients with a high risk of recurrence.

The aims of this chapter are to review the practice and results of liver transplantation for liver tumors, to analyze therapeutic interventions that may help improve these results, and to consider future directions in the era of living donor transplantation.

### LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA

HCC usually occurs in patients who have underlying cirrhosis or extensive fibrosis of any origin (1). As a result, cirrhosis can be considered in itself an oncogenic condition. HCC is present in 5 to 15% of patients at the time liver disease is recognized (2) and its annual incidence in those who did not have liver disease at presentation is about 1 to 5% (3,4). In Western countries, chronic hepatitis C has been an increasingly prevalent source of cirrhosis and HCC (5).

When symptomatic, HCC is generally too large for a curative treatment to be performed. Due to the widely applied systematic screening by ultrasonography, an increasing proportion of HCC tumors are recognized at an early stage and, in such cases, treatments have the potential to be curative. Small tumors may be treated either by surgical resection (Chapter 12) or by percutaneous destruction (ethanol injection or radiofrequency ablation) (Chapters 15 and 16). However, the efficacy of these treatments is limited by the

TABLE 17-1

Results of Liver Transplantation for Hepatocellular Carcinoma in Patients with Cirrhosis Reported in the 1990s

Author	Year	Patients	Tumor > 5 cm (%)	1-Year Survival (%)	3-Year Survival (%)	5-Year Survival (%)
Haug, et al. (13)	1992	24	—	71	42	—
Bismuth, et al. (11)	1993	60	25	75	49	—
Chung, et al. (14)	1994	29	38	61	46	—
Romani, et al. (15)	1994	27	0	82	71	—
Selby, et al. (16)	1995	105	—	66	39	36
Tan, et al. (17)	1995	15	—	80	63	—
Mazzaferro, et al. (12)	1996	48	0	90	75	—
Ojogho, et al. (18)	1996	26	—	73	65	—
Bronowicki, et al. (19)	1996	17	25	70	65	50
Figueras, et al. (20)	1997	38	11	82	79	75
Belghiti, et al. (21)	2000	73	0	79	61	—
Hemming, et al. (22)	2001	112	—	78	63	57

fact that HCC is likely to recur within the remaining cirrhotic liver (6). In addition, complications of cirrhosis such as end stage liver insufficiency, bacterial infections, and refractory ascites may themselves lead to a fatal outcome. As a consequence, liver transplantation represents an attractive alternative allowing both resection of the tumor and correction of the underlying liver disease.

Although transplantation represents an attractive option, the results of early series in the 1980s, including a majority of patients with large HCC, were disappointing. Three-year survival rates as low as 30% were reported and recurrence was the most common cause of death (7–10). It rapidly became evident that even in the absence of detectable extrahepatic metastases, recurrence was a major concern, and the large size of the tumor before transplantation was a risk factor.

In the early 1990s, several series of patients transplanted for HCC showed that results comparable to those patients without HCC could be obtained, provided the initial tumor was small (11,12). These excellent results have been confirmed by a number of more recent studies in the field (Table 17-1) (11–22). Therefore, even in the current context of organ shortage, there is no obvious justification for restricting the access to liver transplantation for patients with small HCC, even those who otherwise could be candidates for resection (Figure 17-1). The main issue is to determine the optimal candidates for whom the expected results of transplantation are close to the results in patients without malignancy.

### Selection Criteria for Transplantation According to Tumor Status

Selection criteria are aimed at identifying optimal candidates for transplantation. For HCC, the prognosis is strongly related to the risk of recurrence. Obviously, there is no consensus con-

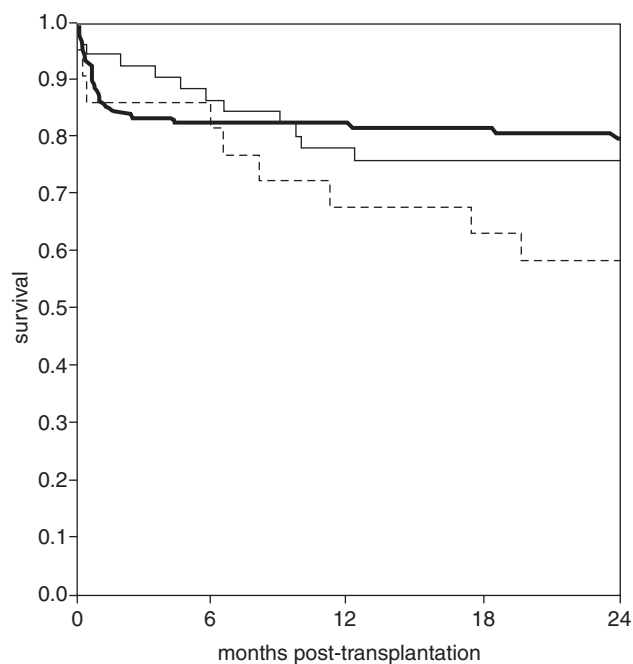


FIGURE 17-1

Results of liver transplantation at our institution in patients with cirrhosis and no malignancy (bold line), in patients with cirrhosis and HCC before 1997 (dashed line), and in patients with cirrhosis and HCC from 1997 to 2000 (solid line). The mortality of patients transplanted for HCC before 1997 was significantly higher than that of patients transplanted without malignancy, due to post-transplantation recurrence. The use of strength selection criteria after 1997 (one nodule less than 5 cm, and two or three nodules less than 3 cm) made it possible to obtain results comparable to those of patients transplanted for cirrhosis without malignancy.

cerning the risk of recurrence that would justify the use of a graft that, otherwise, could have been allocated to a patient without malignancy. However, a 10 to 20% 5-year rate of recurrence is currently considered to be acceptable because it allows global results close to those of transplantation in patients without HCC, and markedly superior to those of surgical resection.

The four main factors affecting recurrence after transplantation for HCC are (a) macroscopic vascular invasion, (b) the size of the nodules, (c) the total number of nodules (in the case of multifocal tumor), and (d) the differentiation of the tumor.

HCC has a great potential for vascular invasion, especially within portal vein branches (see Chapter 1). It has been clearly demonstrated that macroscopic vascular invasion predicts early post-transplantation recurrence in almost all cases (7,23). Indeed, even if there is no obvious extrahepatic involvement, vascular invasion implies that there are circulating tumoral cells with a potential for recolonization of the graft (24). As a consequence, evidence of vascular invasion is considered to be a definite contraindication for transplantation, whatever the size and number of nodules.

Until now, it has not been demonstrated that a clear-cut tumor size threshold differentiates patients at high versus low risk of recurrence. However the results of previous studies showed that single nodules less than 5 cm in diameter carried a low (below 20%) 5-year rate of recurrence (11,16). These studies also suggested that recurrence rates rapidly increase with tumors over 5 cm in diameter. As a result, for single nodules, a 5 cm limit is currently considered acceptable for selecting candidates for transplantation.

Apart from the size of the tumor, the number of nodules also represents a significant prognostic factor. Patients with multiple nodules are at higher risk of recurrence than those with a single nodule (11,16). However, multifocal tumors should not be considered as a contraindication for transplantation in all cases. Indeed, patients with two or three nodules, each less than 3 cm in diameter, carry a risk of recurrence comparable to that of patients with a single nodule less than 5 cm in diameter (12). Again, it seems that above this empirical limit of three nodules, each less than 3 cm in diameter, the risk of recurrence increases rapidly. It is important to note that very small nodules are frequently unrecognized with current imaging techniques. Therefore, patients with more than three detectable nodules are in fact likely to be found with many more nodules after pathological examination of the resected liver. This could explain at least in part the high rate of recurrence in these patients, even when the size of each nodule is small.

It has been shown that differentiation of HCC itself has an independent influence on recurrence (22,23). Patients with poorly differentiated tumors were found to have a post-transplantation recurrence rate about twice as high as patients with well-differentiated tumors (23). On the basis of these findings, it has been suggested that systematic percutaneous biopsy and histopathologic grading before transplantation might improve selection criteria (22). However, at least two reasons make the use of percutaneous biopsy controversial. First, the proportion

of patients with poorly differentiated tumors is low (less than 20%) (23). Second, there is concern about the risks of needle tract seeding after biopsy. Practically, it is estimated that this risk is less than 2% (25), and in our experience, none of the patients who were found to have parietal seeding at the time of transplant surgery had recurrence after transplantation, provided local excision was performed (25). At present, there is not sufficient evidence that pretransplantation determination of tumor differentiation has a practical impact to justify the use of systematic percutaneous biopsy.

The selection of candidates for transplantation is based on the use of preoperative imaging techniques including Doppler ultrasonography (Doppler-US), computed tomography (CT scan), and magnetic resonance imaging (MRI) (see chapter 4). In most centers, CT scan represents the reference technique. In particular, with the advent of helical CT scan, it is currently possible to detect hypervascular nodules less than 0.5 cm in diameter. MRI tends to be more accurate than the other imaging techniques in differentiating HCC from nonmalignant nodules (6); however, it is less sensitive than helical CT scan for detecting small nodules. It has been argued that hepatic angiography with intra-arterial injection of lipiodol followed by a CT scan 3 to 4 weeks later could be more sensitive than conventional CT scan (26). However, small lipiodol fixations are difficult to interpret and, in some instances, may lead to a significant proportion of false positives. Despite technical improvements, current imaging techniques are limited by their inability to detect very small nodules and to differentiate them from nonmalignant nodules, as well their inability to detect macroscopic vascular invasion within distal portal vein branches. On average, preoperative staging underestimates the extent of HCC as compared with the findings of pathological examination of the resected liver (27). In addition, malignant nodules less than 2 cm in diameter can be indistinguishable from benign regenerative nodules, which may occasionally lead to unnecessary liver transplantation. In such instances, percutaneous biopsy and tissue analysis, when feasible, should always be performed before deciding on transplantation (25).

Even if widely accepted, the current criteria based on tumor size, number of nodules, and detectable (proximal) vascular invasion are obviously not perfect. In particular, some patients (10 to 20% on average) with small HCC corresponding to the above-mentioned criteria still have early post-transplantation recurrence. Conversely, early series showed that some patients with large tumors may have prolonged survival without recurrence. Therefore, the presence of vascular invasion is probably the key predictive factor for recurrence (22). Vascular invasion, involving either proximal or distal portal branches, is correlated to the size and number of nodules (16). However, the size and number of nodules as a set of criteria do not allow identification of patients with large and/or multifocal HCCs but without vascular invasion, who could be at low risk for recurrence. Nor does this set of criteria allow identification of patients with small HCCs but with vascular invasion, who are likely to have early recurrence. This concept is supported by the

**TABLE 17-2**  
Results of Liver Resection for Hepatocellular Carcinoma Less Than 5 cm in Diameter in Patients with Cirrhosis

Author	Year	Patients	1-Year Survival (%)	3-Year Survival (%)	5-Year Survival (%)
Franco, et al. (29)	1990	43	66	42	—
Ringe, et al. (9)	1991	18	—	—	42
Bismuth, et al. (11)	1993	46	—	39	—
Kawasaki, et al. (30)	1995	93	73	54	40
Nakajima, et al. (31)	1996	50	90	75	53
Lee, et al. (32)	1996	48	—	68	50
Belghiti, et al. (21)	1998	122	82	55	33

strong correlation found between recurrence and vascular invasion, including invasion of distal portal vein branches, on the resected liver (12). Nonetheless, the practical limitation of this concept is that current imaging techniques are not sensitive enough to detect distal vascular invasion, a criteria that can be obtained only by examination of the resected liver, after transplantation. Efforts should be made in the future to improve the ability of imaging techniques to detect distal vascular invasion.

Because a high (> 300 ng/mL) alpha-fetoprotein (AFP) level is often associated with macroscopic vascular invasion, this criterion also could be considered when selecting candidates for transplantation (20).

### Selection Criteria for Transplantation According to Liver Status

**HCC in patients with cirrhosis.** As indicated already, most patients with HCC have underlying cirrhosis. Cirrhosis can be either compensated (Child's grade A) or decompensated (Child's grade B or C); the latter grades mean that complications such as severe liver insufficiency, ascites, or jaundice are present.

Patients with decompensated cirrhosis who have small HCCs are unsuitable for surgical resection (see Chapter 12). Resection, even if limited, would be associated with major postoperative complications and high mortality rates (6). As a result, liver transplantation, which allows both removal of the tumor and reversal of the complications of cirrhosis, is the best therapeutic option, provided there are no additional risk factors such as advanced age or concomitant extrahepatic disease.

Patients with compensated cirrhosis who have small HCCs can be either resected or transplanted. Despite the current context of organ shortage and resource limitations, growing evidence suggests that transplantation should be preferred over resection. Indeed, surgical resection has major limitations, the most important of which is a 5-year recurrence rate as high as 80% (28). In addition, because the patients are left with a cirrhotic liver, complications other than tumor recurrence may occur some months or years after resection (6). These limitations are illustrated by several series of cirrhotic patients who underwent resection for tumors less than 5 cm

in diameter (Table 17-2) (9,11,21,29-32). Based on these results, it can be expected that only 30 to 50% of patients will be alive 5 years after resection, and that less than 20% will be recurrence free (21). At the present, there is no clear evidence that the cause of the underlying liver disease has a significant impact on recurrence. Patients with extensive fibrosis but without cirrhosis should be considered for transplantation in the same way as those with compensated cirrhosis.

Even if there is now general agreement that the results of transplantation are superior to those of resection, it has been emphasized recently that due to organ shortage and prolonged waiting times, this difference tends to narrow when the results are interpreted on an intention-to-treat basis (33). Even though mean waiting times vary greatly from country to country—the duration could be 5-fold longer in one country versus another—patients listed for transplantation are likely to stay on the waiting list for several months. During this period the tumor is likely to progress, increasing the risk of recurrence after transplantation and, most importantly, causing drop-outs. Intention-to-treat analyses suggest that if drop-outs and deaths on the waiting list are taken into account, the global results of resection are in fact superior to those of transplantation (33). However, it remains clear that survival in those patients who have been transplanted is significantly better than in those who had surgical resection. As a consequence, efforts should be made to provide access to transplantation to these patients with small HCCs and to use more aggressive treatments to prevent tumor progression for those on the waiting list. Alternatives to “conventional” cadaveric transplantation such as split liver and living-related liver transplantation may help provide access to an increasing number of patients.

**HCC in patients without underlying chronic liver disease.** In most cases, for patients without cirrhosis, HCC does not seem to be related to any identifiable cause of chronic liver disease, although it sometimes has been reported in association with chronic hepatitis B virus infection and nonalcoholic fatty liver disease (34). Occasionally, these tumors have specific characteristics including eosinophilic hepatocytes separated into bands of fibrous lamellar septa, which define the rare fibrolamellar variant (35; also see Chapter 1). Patients who do not have chronic liver disease are not sub-

**TABLE 17-3**  
Results of Transplantation and Resection for Fibrolamellar Hepatocellular Carcinomas

Study	Transplantation		Resection	
	Patients	5-Year Survival (%)	Patients	5-Year Survival (%)
O'Grady et al., 1988 (38)	7		50	—
Penn I., 1991 (7)	33	55	—	—
Ringe et al., 1992 (39)	6	40	14	40
Pinna et al., 1997 (40)	13	36	28	75
El Gazzaz et al., 2000 (37)	9	76*	11	100*

\* 3-year survival (%)

jected to systematic screening. Therefore, liver tumors are usually recognized at an advanced stage, when they become symptomatic. Fortunately, because of the absence of underlying liver lesions and the potential for regeneration, tumors larger than 10 cm can be resected in most cases using extended hepatectomy.

Survival after resection is much better in patients without underlying chronic liver disease than in those with cirrhosis and tumors of comparable size. Obviously, the advantage in terms of survival is mostly due to the absence of postoperative complications of cirrhosis; however, this advantage is also related to a lower rate of recurrence (36). Five-year survival rates as high as 50% have been reported in both fibrolamellar and nonfibrolamellar HCC (36,37; also see Chapter 12).

Because HCCs within noncirrhotic liver parenchyma seem to be relatively slow growing, transplantation may be considered as an alternative when resection is impossible (which is uncommon). In three series, the results of resection and transplantation in patients with fibrolamellar HCC were compared (Table 17-3) (7,9,37-40). Because long-term results of these two therapeutic options are comparable, these series suggest that resection, when possible, should be preferred to transplantation. In our experience, HCC in patients with normal or near-normal liver parenchyma can be resected in more than 90% of cases. A second resection is routinely considered in cases of intrahepatic recurrence. It is important to note that although recurrence of HCC is generally limited to the liver, recurrence of the fibrolamellar variant frequently involves extrahepatic sites, in particular lymph nodes (39). As a result, liver transplantation for unresectable fibrolamellar HCC remains questionable.

## Incidental HCC

Although current imaging techniques offer the possibility of detecting tumors less than 1 cm in diameter, very small nodules may be undetected until transplantation. These tumors discovered in the explanted liver are termed *incidental HCCs* and are found in about 10 to 20% of cirrhotic recipients (41-43). The size of these tumors is usually less than 1 cm, but may occasionally be as large as 3 cm (41). Large incidental HCCs (> 1 cm) reflect an inadequate screening during waiting time.

Importantly, incidental HCCs do not seem to affect survival as compared to cirrhotic patients transplanted without HCC (7,11); in other words, the risk of recurrence seems to be nearly nil. Because incidental HCCs are on average smaller than detected HCCs, it can be expected that due to improvements in imaging techniques, a more accurate detection of very small nodules could help transplant patients at an earlier stage and reduce the risk of recurrence (44).

## Strategies to Decrease the Risk of Recurrence

Although liver transplantation is potentially curative in patients with small HCCs, recurrence is still a major concern. During recent years, there has been much interest in innovative strategies that could help decrease the risk of recurrence after transplantation. These strategies are based on: (a) the detection of circulating and/or malignant hepatocytes before transplantation, (b) adjuvant local therapies before transplantation, and (c) adjuvant post-transplantation interventions.

**Pretransplantation detection of circulating and/or malignant hepatocytes.** Recurrence of hepatocellular carcinoma after total hepatectomy and liver transplantation in patients without evidence of extrahepatic involvement probably originates from circulating micrometastases. This concept is supported by the major influence of macroscopic vascular invasion on recurrence (20). Polymerase chain reaction techniques allow detection of small amounts of circulating albumin-mRNA, a quite specific marker of hepatocytes (see Chapter 3). It has been postulated that this very sensitive technique might be able to identify patients with circulating micrometastases who are thus presumably at higher risk for recurrence (24). Although this concept is very attractive, early results have been disappointing. Indeed, circulating albumin-mRNA is frequently found in cirrhotic patients without HCC (albumin-mRNA is not specific to tumoral cells) (45). Furthermore, in patients with HCC, the presence of circulating albumin-mRNA is poorly predictive of recurrence (45). It has been shown recently that preoperative and postoperative detection of AFP-mRNA in the serum, a putative marker of circulating malignant hepatocytes, is a reliable tool for predicting recurrence after surgical resection of HCC (46). The risk of recur-

rence was more than twice as high in patients with postoperative positive AFP-mRNA as in those with postoperative negative AFP-mRNA (46). As compared with albumin-mRNA, AFP-mRNA seems more specific and attractive. However, whether pretransplantation AFP-mRNA in the serum helps identify patients at high risk of recurrence has yet to be clearly demonstrated.

**Pretransplantation neoadjuvant therapies.** Because of organ shortage, waiting time for transplantation may be as high as 6 months to 1 year, a period during which tumors are likely to progress. Because it seems evident that tumor progression increases the risk of post-transplantation recurrence, neoadjuvant therapies such as arterial chemoembolization (see Chapter 8), percutaneous ethanol injection (see Chapter 16), and radiofrequency ablation (see Chapter 15) are widely used before transplantation (11,12,47,48). It is expected that these adjuvant therapies slow tumor progression and lower the risk of recurrence. Even if there is a risk of needle tract seeding, this risk is low (less than 5% for ethanol injection) and, again, there is no clear evidence that parietal seeding precludes the results of transplantation (25).

Unfortunately, percutaneous ethanol injection and radiofrequency ablation are not applicable to patients who have severe coagulation disorders and/or persistent ascites. In these patients, intra-arterial chemoembolization can represent an alternative, provided there is no major liver insufficiency. (In patients with liver insufficiency, intra-arterial chemoembolization may further deteriorate liver function and be a source of serious complications.) Patients with a tumor larger than 3 cm have shown a survival advantage after response to intra-arterial chemoembolization (49). However, it must be kept in mind that intra-arterial chemoembolization, in particular when repeated, frequently induces local arteritis. Hepatic artery lesions can compromise the possibility of living donor transplantation as well as split liver transplantation, techniques for which the integrity of the hepatic artery branches is crucial.

Finally, in patients with compensated cirrhosis and for whom waiting time is anticipated to be long, a strategy of elective surgical resection followed by listing for transplantation can be used. This policy is justified by (a) the low mortality and morbidity of elective hepatectomy in the absence of extrahepatic risk factors, (b) the possibility of assessing precisely important parameters such as tumor differentiation and vascular invasion by gross examination of the resected liver, and (c) the possible superiority of surgical resection over percutaneous ethanol injection and radiofrequency ablation. However, this latter item might be tempered by recent reports suggesting that the results of surgery and percutaneous ethanol injection are comparable in patients with tumors less than 3 cm in diameter (50). In patients with tumors located in the superior part of the right lobe, surgical resection prior to transplantation can be performed using a thoracic approach. In our experience, this technique helps limit the consequences of

pretransplantation surgery in terms of technical difficulties and perioperative bleeding (51).

There is no universal agreement on the optimal hierarchy of the different pretransplantation interventions. A practical approach suggests that in patients for whom prolonged waiting time (more than 6 months) is anticipated and who have minimal operative risk, pretransplantation resection should be considered as a priority over other treatments. If the patient is not suitable for resection or if waiting time is likely to be short, intra-arterial chemoembolization or percutaneous treatment such as radiofrequency or ethanol injection should be considered. Unfortunately, some patients, especially those with end stage liver insufficiency, are not suitable for any pretransplantation treatments.

**Post-transplantation adjuvant interventions.** Although systemic chemotherapy has been ineffective in the treatment of hepatocellular carcinoma, early results with post-transplantation chemotherapy have been encouraging (47,52,53; also see Chapter 12). Uncontrolled series have suggested that adjuvant chemotherapy using doxorubicin or a combination of doxorubicin, fluorouracil, and cisplatin within the first 6 months post-transplantation may improve survival by reducing the rate of recurrence in patients transplanted for advanced HCC (50,52). These early results offering an interesting perspective need to be confirmed by larger studies. In patients with pretransplantation chronic hepatitis C, post-transplantation recurrence of hepatitis C virus infection is quite universal. Antiviral therapy by interferon reduces the risk of HCC in patients with chronic hepatitis C. More recently, it has also been shown that postresection interferon therapy reduces the risk of recurrence in patients with chronic hepatitis C (54). Because the efficacy of antiviral therapies is markedly reduced by concomitant immunosuppression, these interesting results should not be extrapolated to liver transplant recipients without further investigations. As this is becoming one of the most significant issues in transplantation, an entire chapter (Chapter 31) has been dedicated to this topic.

## Liver Transplantation for HCC in the Setting of Living Donor Liver Transplantation

Adult-to-adult living-donor liver transplantation is now an accepted alternative to cadaveric transplantation. Improvements in recent years have made the results of this technique comparable to those of cadaveric transplantation (55,56). The advent of adult-to-adult living-donor liver transplantation has two major implications in the field of HCC.

First, the availability of a living donor makes it possible to schedule the procedure rapidly and to eliminate the problem of tumor progression during waiting time. It also makes pretransplantation interventions obsolete. Because tumor progression is the main limiting factor of transplantation for HCC, living-donor transplantation is especially appropriate. This advantage of living-donor transplantation may be

especially relevant in countries where the priorities for the allocation of liver grafts depend on the severity of liver insufficiency (which results in prolonged waiting times for patients with compensated cirrhosis and small HCC). Moreover, it can be anticipated that the early postoperative risk of transplanting patients with small-for-size grafts (a frequent situation in living donor transplantation) is smaller in those with compensated cirrhosis and small HCC than in those with decompensated cirrhosis. Overall, small HCC with compensated cirrhosis seems to be one of the most attractive indications for living-donor transplantation.

Second, it has been argued that if a potential donor and a recipient have received appropriate information, it is their own decision as to whether to proceed with transplantation for recipients who are beyond the usual criteria and for whom transplantation would otherwise be contraindicated. On the one hand, one should consider that selection criteria were established in the context of organ shortage, and that transplanting patients with large and/or multifocal HCCs with a living donor is acceptable because it does not preclude the allocation of a cadaveric donor to a patient with a better prognosis. On the other hand, whether the donor is living or cadaveric, the results of liver transplantation for large HCC are dismal. In addition, the distance between low- and high-risk patients proved to be narrow, with recurrence rates increasing sharply above the current selection criteria. Therefore, it seems difficult to place a healthy donor at risk for transplanting a patient with a major risk of recurrence within a few months, even if the procedure is felt as a “last chance” option for the family. In our opinion, there is no clear justification for extending the indications for transplantation using living donors (55).

### Summary: Current Indications and Perspectives

In summary, most centers agree that a cut-off level of one nodule less than 5 cm, or two or three nodules each less than 3 cm in the absence of detectable vascular invasion, is reliable for selecting candidates for transplantation. These criteria were shown to be associated with 5-year survival rates as high as 70% (12,20). With decompensated cirrhosis, transplantation is the only curative option; for compensated cirrhosis, surgical resection is an alternative. Due to organ shortage, not all groups accept resectable HCCs as an indication for transplantation. In this situation, some authors suggest resection first and, in case of recurrence, “salvage” transplantation, a strategy that could be graft-saving as compared with “primary” transplantation (57). However, it seems difficult to exclude patients with resectable HCC from primary transplantation, because the results of transplantation are superior to those of resection and are comparable to those of transplantation for cirrhosis without malignancy. Therefore, we favor transplantation in patients with small HCCs who otherwise could undergo resection. Living-donor transplantation, by lowering the waiting time, offers the major advantage of reducing the risks of tumor progression and drop-outs before the procedure.

The good results of transplantation for HCC prompted several groups to propose two different extensions of criteria for transplantation. The first alternative is represented by downstaging. According to this concept, some patients with large HCCs (and who are beyond the usual criteria) who have a good response to any of the adjuvant interventions listed earlier might then become suitable candidates for transplantation. As an example, a patient with five malignant nodules, three in the right lobe and two in the left lobe, each less than 3 cm (a situation that is beyond the current selection criteria) could be considered for transplantation after left lobectomy (the patient would be left with three nodules, each less than 3 cm). Even though early results of downstaging have been encouraging, whether the risk of recurrence is related to the initial tumor status or to tumor status after downstaging needs to be clarified. Whatever the net change in tumor status, downstaging usually takes several months, which gives the opportunity to differentiate those patients with a rapid tumor progression (who should not be suitable for transplantation) from those with stable or slow growing tumors (who are likely to be good candidates for transplantation).

Another perspective is to extend the criteria for transplantation to larger tumors, whatever the results of pretransplantation interventions. A recent study suggested that tumor size limits could be expanded to a single nodule less than 6.5 cm (rather than 5 cm), or two or three nodules with the largest lesion below 4.5 cm and a total tumor diameter below 8 cm (rather than two or three nodules each less than 3 cm) without affecting survival (58). These results are interesting; however, it is important to note that in this study, the staging of the tumor was based on the examination of the explanted liver, which represents a significant bias because imaging techniques tend to underestimate the extension of HCCs. In addition, even if the survival of patients who met the proposed “modified criteria” was satisfactory, the expansion was modest. Overall, there is no clear demonstration that tumor size limits can be significantly expanded without affecting survival, unless downstaging has been achieved (59).

## LIVER TRANSPLANTATION FOR OTHER MALIGNANT TUMORS

### Cholangiocarcinoma

In contrast to HCC, cholangiocarcinoma usually develops in patients who do not have underlying cirrhosis. The tumor can be located either next to extrahepatic (proximal cholangiocarcinoma) or intrahepatic (distal cholangiocarcinoma) bile ducts. In a significant proportion of cases, tumors originating from the common bile duct at its upper part extend up to right and left bile ducts.

Because of the absence of underlying cirrhosis, most patients with intrahepatic cholangiocarcinoma, even those

with large tumors, can undergo surgical resection. However, in some instances, the tumor may be unresectable because of a concomitant extension to right and left bile ducts or because of a severe underlying liver disease (primary sclerosing cholangitis in most cases).

Provided the tumor does not involve the lower part of the common bile duct (under the level of the cystic duct) and there is no evidence of extrahepatic invasion, it may appear logical to perform liver transplantation in patients with unresectable cholangiocarcinoma. Unfortunately, the results of liver transplantation in such patients were poor, with 5-year survival rates not exceeding 20% and a high rate of early post-transplantation recurrence (60). Currently, most centers agree that patients with unresectable cholangiocarcinoma should not be transplanted.

Even if the majority of patients with intrahepatic cholangiocarcinoma can undergo surgical resection with a low early post-operative risk, the results of resection are dismal. Five-year survival rates range between 20 and 40% (60,61), and the principal cause of death is represented by tumor recurrence. Because of these dismal results, liver transplantation has been proposed as an alternative to resection. Unfortunately, the results of liver transplantation in patients with otherwise resectable cholangiocarcinoma proved to be comparable to those of resection (60,61). Again, the main limitation of liver transplantation was tumor recurrence, which is not surprising because early extrahepatic extension involving lymph nodes and microscopic perineural invasion were the main causes of recurrence after resection. Overall, the benefits of liver transplantation over resection, if any, do not seem to be sufficient to justify the use of a graft in a context of organ shortage.

Recently, encouraging results have been reported in highly selected patients receiving multimodal therapy including irradiation followed by exploratory laparotomy (in order to detect extrahepatic involvement), systemic chemotherapy, and then liver transplantation (62). In these series, less than 10% of the patients had tumor recurrence after transplantation, which renewed interest in liver transplantation for cholangiocarcinoma. However, it must be noted that the results were based on small series comprising selected patients with small tumors. Because most patients with intrahepatic tumors remain asymptomatic until advanced stages, and as a result have large tumors at the time of diagnosis, it is unlikely that liver transplantation could be widely applicable to cholangiocarcinoma, even if an aggressive therapeutic regimen is applied after the procedure.

## Angiosarcoma

Angiosarcomas account for only 0.5 to 2% of primary liver malignancies (see Chapter 29). An association with previous exposure to Thorotrast (thorium dioxide, a contrast material used during the first half of this century), arsenicals, and vinyl chloride has been clearly identified. Angiosarcomas are rapidly growing tumors with ill-defined limits that make surgical resection rarely possible. A multicenter series of 14 patients

transplanted worldwide has been reported (1). Median 2-year survival rate was 15%, and none of the patients survived for more than 2.5 years. As a result, angiosarcomas represent a contraindication for transplantation.

## Epithelioid Hemangioendothelioma of the Liver

Epithelioid hemangioendotheliomas are rare tumors of vascular origin whose natural history is quite variable from patient to patient (see chapter 29). Most patients have large multifocal tumors at the time of diagnosis. About 20% die within 2 years after the diagnosis, whereas about 20% survive more than 5 years after the diagnosis (63). Generally, the progression of the tumor is slow and patients surviving for more than 10 years without any specific treatments have been reported (63). Systemic chemotherapy as well as radiotherapy have no significant influence on the progression of the tumor. Because most patients have large tumors involving both lobes, resection is possible only in a minority. In addition, 40 to 50% of the patients have metastases at the time of diagnosis, involving lungs, bones, spleen, and peritoneum. Preoperative identification of peritoneal invasion is especially difficult.

On the grounds that the progression of the tumor is slow and surgical resection is rarely possible, transplantation has been proposed. Only small series of patients have been reported. However, these series suggest that transplantation is associated with 2- and 5-year survival rates of about 80 and 40%, respectively, death being largely attributable to tumor recurrence (1,63,64). Given the large size of the tumor, these results can be considered encouraging. However, it must be kept in mind that in some instances, long-term survival can be achieved without radical treatment, which makes the net benefit provided by transplantation difficult to determine. In addition, in our experience as well as in others', the majority of the patients who were considered for transplantation were found to have extrahepatic extension after detailed evaluation. Although prolonged survival has been reported occasionally after transplantation in patients with extrahepatic involvement (64), whether focal lung metastases or limited peritoneal invasion represent definitive contraindications is still debated. Overall, liver transplantation is possibly a useful option in some patients with epithelioid hemangioendotheliomas; however, the heterogeneous indications and results make it difficult to establish guidelines for evaluation of such patients.

## Liver Metastases of Neuroendocrine Tumors

Neuroendocrine tumors include several subtypes of malignancies, all characterized by their relatively slow progression (see Chapter 28). They usually originate from the pancreas or small intestine and may give rise to liver metastases. Apart from their slow progression, liver metastases of neuroendocrine tumors have two principal characteristics. First, the large size and multiplicity of metastatic nodules fre-

**TABLE 17-4**  
Patient Survival after Transplantation for Metastatic Neuroendocrine Tumors

Study	Number of Patients	Extrahepatic Resection	1-yr Survival (%)	3-yr Survival (%)	5-yr Survival (%)
Alessiani et al., 1995(65)	14	14/14	64	64	64
Routley et al., 1995(66)	11	—	82	57	28
Curtiss et al., 1995(67)	3	2/3	100	—	—
Anthuber et al., 1996(68)	4	2/4	25	0	0
Le Treut et al., 1997(69)	31	14/31	58	47	36
Lang et al., 1997(70)	12	3/12	82	82	82

quently contrast with the small size of the primary tumor. Because of this, it is sometimes difficult to localize precisely the primary tumor within the pancreas or small intestine with imaging techniques, making exploratory laparotomy mandatory. Second, metastases, even if large and multiple, tend to remain limited to the liver for prolonged periods.

Therapeutic options for liver metastases of neuroendocrine tumors include surgical resection of the primary tumor (which may by itself slow the progression of metastases), systemic and/or intra-arterial chemotherapy, and surgical resection of metastases. However, resection is almost universally followed by recurrence within the remaining liver parenchyma, and multiple metastases involving right and left lobes may be unresectable.

Liver transplantation is still considered a potential alternative in patients in the following situations: (a) pancreatic or gastrointestinal tumors with concomitant unresectable liver metastases, (b) unresectable liver metastases occurring after surgical resection of the primary tumor, (c) unresectable liver metastases occurring in the remaining liver after concomitant resection of the primary tumor and hepatectomy, and, occasionally, (d) unresectable liver tumors without evidence of primary tumor. In all these circumstances, transplantation is unlikely to be curative. However, even with the possibility of recurrence, the slow progression of the tumor allows transplantation to provide enough of a survival advantage to justify the use of a graft and the inconvenience of long-term immunosuppression. The results of liver transplantation for neuroendocrine tumors reported by several groups are shown in Table 17-4 (65-70).

In clinical practice, liver transplantation for neuroendocrine tumors has two principal limitations. First, apart from the tumor itself, patients with neuroendocrine malignancies are frequently at high risk for transplantation complications because of their past history of abdominal surgery (which is a source of technical difficulties and increases the risk of major operative bleeding) as well as past systemic chemotherapy (which is a potential source of renal and cardiac injury). In addition, it must be noted that those patients who had previous intra-arterial chemotherapy are likely to have significant hepatic artery lesions at the time of transplantation, which is also a source of technical difficulties in split-liver transplanta-

tion or living-donor liver transplantation. However, some patients have a long-term, recurrence-free survival. Because recurrence seems quite universal after resection of large hepatic metastases, a possible perspective could be to decide on transplantation at an earlier stage and to avoid, as much as possible, surgical procedures that are likely to have a deleterious impact on transplantation.

Given that transplantation is unlikely to be curative, pre- and post-transplantation chemotherapy must be considered, especially in patients who demonstrate pretransplantation response to chemotherapy.

Overall, indications and timing for transplantation in patients with liver metastases of neuroendocrine tumors need to be clarified.

## Non-neuroendocrine Liver Metastases

Some patients with unresectable isolated liver metastases several years after primary resection were transplanted in the 1980s (see Chapter 29). The results were disappointing because of recurrence of both initial and secondary tumors, with a 2-year survival rate of less than 15% (1,2). Accordingly, patients with non-neuroendocrine tumors should no longer be considered as candidates for transplantation.

## CONCLUSIONS

Because of the scarcity of organs, liver transplantation should not be proposed to patients with poor prognoses such as those with non-neuroendocrine metastases and cholangiocarcinomas (unless in highly selected cases). Among liver malignancies, HCCs represent the most frequent indication for transplantation. HCCs are also the tumors for which the benefits of transplantation is most clear, as compared with other therapies (including resection). However, this advantage exists only for small tumors. Therefore, efforts should be made to detect HCCs at an early stage. Efforts also should be made to better define the optimal candidates, to give access to transplantation to optimal candidates by the use of alternative techniques such as living donor transplantation, and to develop efficient

pre- or post-transplantation therapies to reduce the risk of recurrence, which remains a major concern.

## SELECTED READINGS

Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL Conference. *J Hepatol* 2001;35:421–430. This excellent overview of the management of patients with HCC includes results of various treatment.

Hemming AW, Cattral MS, Reed AI, et al. Liver transplantation for hepatocellular carcinoma. *Ann Surg* 2001; 223:652–659. This is a study of 112 transplanted patients with HCC confirming the excellent prognosis (77% 5-year survival rate) of well-selected cases without vascular invasion. The analysis and the discussion of tumor characteristic in the outcome of liver transplantation is excellent.

Llovet JM, Fuster J, Bruix J. Intention to treat analysis of surgical treatment of early hepatocellular carcinoma: resection versus transplantation. *Hepatology* 1999;30: 1434–1440. This study showed that a long duration on the waiting list can have a major impact on the survival of patients transplanted for HCC. According to this very important study, either adjuvant therapy such as arterial chemoembolization and percutaneous treatment or the use of living donor should be considered.

De Vreede I, Steers JL, Burch PA, et al. Prolonged disease-free survival after liver transplantation plus adjuvant chemoradiation for cholangiocarcinoma. *Liver Transpl* 2000; 6:309–316. An improvement of disease-free survival after liver transplantation for cholangiocarcinoma was observed in a group of patients treated by preoperative irradiation and chemotherapy. This highly selected group was assessed by pre-OLT exploratory laparotomy.

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