Indications and Role of Liver Transplantation for Malignant Tumors

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Key Words. Hepatic malignancies · Liver transplantation

ABSTRACT

Purpose. The indication for liver transplantation in malignant liver tumors has been controversial due to disappointing results and shortage of donor organs. The authors evaluated the experience and results of a single center in order to define present indications and selection criteria in hepatobiliary malignancy.

Patients and Methods. Retrospective analysis of 212 patients who underwent liver transplantation for malignant tumors between 1972 and 1995: Primary hepatobiliary tumors: hepatocellular carcinoma, \( n = 124 \) (with underlying cirrhosis, \( n = 86 \); fibrolamellar subtype, \( n = 8 \)); intrahepatic bile duct (cholangiocellular) carcinoma, \( n = 24 \); proximal bile duct carcinoma, \( n = 29 \); other uncommon entities (\( n = 15 \)); secondary liver tumors: neuroendocrine, \( n = 11 \), and nonendocrine, \( n = 9 \).

Results. Survival rates in primary liver cancer were correlated to International Union Against Cancer (UICC) tumor stage. For hepatocellular and proximal bile duct carcinoma significantly better outcome was found in UICC-tumor stage I and II versus III and IV. No long-term survival was found after transplantation for intrahepatic bile duct carcinoma, hemangiosarcoma and nonendocrine liver metastases. Comparison of transplant and resected patients with hepatocellular carcinoma stage I and II with underlying cirrhosis showed better survival after transplantation: 1-, 3-, 5-year survival rate of 83.3% versus 76.9%, 75.8% versus 44.0%, 60.6% versus 44.0%, and median survival 96.5 versus 23.2 months. Although this difference was not significant, no patient died from tumor recurrence in the transplant group versus three in the resection group.

Discussion and Conclusions. Patients with malignant tumors can be selected for transplantation with predictable likelihood for long-term survival. According to the present data, liver transplantation can be considered in unresectable UICC-stage II hepatocellular and proximal bile duct carcinoma, the uncommon entities fibrolamellar carcinoma, epithelioid hemangioendothelioma and hepatoblastoma as well as liver metastases from neuroendocrine tumors. UICC-stage III and IV hepatocellular carcinoma as well as intrahepatic bile duct carcinoma, hemangiosarcoma and metastases from nonendocrine tumors should be excluded from transplantation alone. For hepatocellular carcinoma, multimodality treatment protocols have had a proven impact on the prevention of early recurrence and prolongation of survival. There is evidence that liver transplantation in still resectable hepatocellular carcinoma with underlying cirrhosis might be more appropriate in order to cure the cancer-bearing disease. The Oncologist 1997;2:164-170

INTRODUCTION

Improvements in surgical technique, anesthesiology, and critical care medicine have extended surgical feasibility and have made liver transplantation a standard procedure. Worldwide, the enthusiasm to treat or even cure patients with unresectable malignant tumors of the liver by total hepatectomy and liver transplantation has waned due to disappointing long-term results, shortage of organ donors with regard to growing numbers of transplant candidates with benign diseases, and limited economic resources. General agreement exists that resection whenever feasible remains the surgical treatment of choice in hepatobiliary malignancy [1-7]. Liver transplantation may be considered an option only for selected patients [8-16]. In order to cure the cancer-bearing disease itself, an ongoing discussion centers on whether transplantation might be even more appropriate in small, still resectable, hepatocellular carcinoma with underlying cirrhosis [17-22]. This article presents a single-center experience and reviews the recent literature in order to define the role and present indications for liver transplantation in malignant tumors.
Table 1. Liver transplantation for hepatobiliary malignancy, Medizinische Hochschule Hannover 1972-1995

<table>
<thead>
<tr>
<th>Indications for Hepatic Transplantation Malignant Diseases</th>
<th>Children</th>
<th>Adults</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma + cirrhosis</td>
<td>86</td>
<td></td>
<td>161</td>
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<tr>
<td>Hepatocellular carcinoma</td>
<td>1</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Fibrolamellar carcinoma</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Intrahepatic bile duct carcinoma</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelioid hemangioendothelioma</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mixed hepato-cholangiocellular carcinoma</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemangiosarcoma</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystadenocarcinoma</td>
<td>1</td>
<td></td>
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<tr>
<td>Biliary:</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal bile duct carcinoma</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gall bladder carcinoma</td>
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</tr>
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<td>Neuroendocrine</td>
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</tr>
<tr>
<td>Colorectal carcinoma</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic carcinoma</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total:</td>
<td>6</td>
<td>206</td>
<td>212</td>
</tr>
</tbody>
</table>

Patients and Methods

At our institution, 1,090 liver transplantations were performed between 1972 and 1995. During this period, 212 patients underwent liver transplant for hepatobiliary malignancies (Table 1). Of the 212 patients, 124 (58.4%) were transplanted for hepatocellular carcinoma (eight of the fibrolamellar subtype), 24 (11.3%) for intrahepatic “cholangiocellular” carcinoma (four of the mixed type), and 29 (13.7%) for extrahepatic proximal bile duct carcinoma. Thirty patients with hepatocellular carcinoma underwent liver transplant for anatomical unresectability in noncirrhotic liver, eight of them with tumor recurrence after previous resection. Eighty-six patients had transplantation for either anatomical or functional restrictions due to underlying cirrhosis. An “incidental” hepatocellular carcinoma was found during histological examination of the heptectomy specimen in nine patients transplanted for liver cirrhosis. Incidental bile duct carcinoma occurred in seven patients who underwent transplantation for sclerosing cholangitis. Other indications of primary and secondary hepatic malignancy were epithelioid hemangioendothelioma (n = 6), hepatoblastoma (n = 4), hemangiosarcoma (n = 2), gallbladder cancer (n = 2), cystadenocarcinoma of the liver (n = 1), and various secondary tumors (n = 20). The secondary tumors were neuroendocrine (n = 11): carcinoids (n = 6), gastrinoma (n = 2), growth factor releasing hormone tumor (GFRoma) (n = 1), no endocrine activity (n = 2); colorectal carcinoma (n = 4), melanoma (n = 2), choriocarcinoma (n = 2), and pancreatic carcinoma metastases (n = 1).

Tumors of the hepatocellular, intrahepatic and extrahepatic bile duct carcinoma type were staged according to rules of the International Union against Cancer (UICC) [23].

No tumor could be found in the heptectomy specimen at the time of transplantation in five patients with hepatocellular carcinoma, four of whom were postchemoembolization. One patient had undergone a prior extended left heptectomy. Because of an R1 resection, the decision for transplantation was made and performed two months later. Eighteen patients with tumor stage IVB were classified according to autopsy findings while the presence of extrahepatic tumor was unknown at the time of transplantation.

Liver transplantation was performed according to standard technique as previously described [24]. No patient with the possibility of hepatic resection underwent liver transplantation. Extrahepatic tumor was investigated by preoperative diagnostic imaging and intraoperative exploration. Patients with extrahepatic tumor, especially lymph node metastases, were usually excluded from transplantation. Systemic lymphadenectomy in the hilar region and along the common hepatic artery has become a standard procedure during the past years. Nineteen patients underwent pretransplant chemoembolization with iodized oil (lipiodol) and varying chemotherapeutic agents. A standardized pretransplant chemoembolization protocol including iodized oil, gelfoam, and cisplatin was introduced in 1995.

Survival after liver transplantation versus resection was compared in early hepatocellular carcinoma in stage I or II with underlying cirrhosis. Eighteen of 86 transplant patients and 14 of 46 resected patients with cirrhosis could be taken into account.

Statistical analysis of patient survival (including operative mortality) was performed according to the Kaplan-Meier method calculated from the time of surgery until August 31, 1996, using SAS and SPSS software (SAS-Institute Inc.; Carey, North Carolina, and SPSS Inc.; Chicago, Illinois). At that time, with no patient lost for follow-up, 54 (25.5%) patients were alive. For comparison of survival rates, the Log-Rank and Chi Square tests (Yates correction) were used with p values below 0.05 considered to be significant.

Results

Primary Liver Tumors

Overall survival rates are listed in Table 2 and depicted in Figure 1. For patients with hepatocellular carcinoma without underlying cirrhosis, 1-, 3-, 5-, and 10-year survivals were 53.3%, 29.6%, 25.9%, and 18.5%, respectively.
Without significant difference for those with hepatocellular carcinoma and liver cirrhosis, survivals of 52.0%, 31.2%, 24.6%, and 16.6% were found. No difference was noted for 30-day mortality (13.3% versus 17.4%) and median survival (13.2 months versus 12.9). Survival was strictly correlated with UICC tumor stage and showed significantly better outcome in early stage I and II (Fig. 2). So far, 20 patients survived for more than five years (16.1%). It has to be noted that 10 of them had a stage IV tumor. The longest survivor, transplanted for hepatocellular carcinoma without underlying cirrhosis in 1975, had a centrally located stage II tumor. The best outcome, with 1-, 3-, 5-, and 10-year survivals of 62.5%, 50.0%, 37.5%, and 25.0%, as well as a median survival time of 35.1 months, respectively. None of these patients were lost due to postoperative complications.

For intrahepatic bile duct carcinoma, 1-, 3-, and 5-year survivals were 19.4%, and 4.9% with no survivor beyond five years. Median survival time was 5.5 months only. The longest survivor at this writing, who has gone almost four years without evidence of recurrence, was transplanted after attempted ex situ resection for a stage II tumor involving segments I and IV. Suspected tumor infiltration of the hilar vessels and the caval vein during the backtable resection led to the decision for liver transplantation. Vascular tumor involvement could not be verified during histopathologic examination of the hepatectomy specimen. In patients transplanted for proximal bile duct carcinoma (n = 28), 1-, 3-, 5-, and 10-year survival rates were 63.6%, 23.0%, 18.4%, and 12.3%, respectively, with a median survival of 16.9 months. Prognosis was also correlated with tumor stage (Fig. 3). From four long-term survivors for more than five years, three are still alive for 9, 10, and 11 years, respectively, without evidence of tumor recurrence.

For patients with the uncommon entities epithelioid hemangioendothelioma, hepatoblastoma, hemangiosarcoma, and cystadenocarcinoma (n = 13), 1-, 3-, 5-, and 10-year survival rates were 61.5%, 53.9%, 53.9%, and 53.9%, respectively. In six patients with epithelioid hemangioendothelioma (three of them alive), the longest survival at present is 11 years. Just one of the two nonsurvivors died from tumor recurrence 15 months after transplantation. In four patients with hepatoblastoma, two of them died 1.6 and 9.7 months after liver transplantation from sepsis and tumor metastasis. Table 2 shows survival rates for various tumor entities.

**Table 2.** Overall survival rates after liver transplantation for hepatocellular carcinoma (HCC) without (-) and with (+) underlying cirrhosis, fibrolamellar carcinoma (FLC), intrahepatic cholangiocellular carcinoma (CCC) and proximal extrahepatic bile duct carcinoma (BDC)

<table>
<thead>
<tr>
<th>Tumor Entity</th>
<th>30 day (%)</th>
<th>1 yr (%)</th>
<th>3 yr (%)</th>
<th>5 yr (%)</th>
<th>Median (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC – (n = 30)</td>
<td>13.3</td>
<td>53.3</td>
<td>29.6</td>
<td>25.9</td>
<td>13.2</td>
</tr>
<tr>
<td>HCC + (n = 86)</td>
<td>17.4</td>
<td>52.0</td>
<td>31.2</td>
<td>24.6</td>
<td>12.9</td>
</tr>
<tr>
<td>FLC (n = 8)</td>
<td>0</td>
<td>62.5</td>
<td>50.0</td>
<td>37.5</td>
<td>35.1</td>
</tr>
<tr>
<td>CCC (n = 24)</td>
<td>20.8</td>
<td>19.4</td>
<td>4.9</td>
<td>0</td>
<td>5.5</td>
</tr>
<tr>
<td>BDC (n = 28)</td>
<td>10.7</td>
<td>63.6</td>
<td>23.0</td>
<td>18.4</td>
<td>16.9</td>
</tr>
</tbody>
</table>

Figure 1. Liver transplantation for primary liver malignancy (Medizinische Hochschule Hannover 1972-1995): FLC = fibrolamellar carcinoma; HCC = hepatocellular carcinoma without (-) and with (+) underlying cirrhosis; CCC = cholangiocellular carcinoma; BDC = proximal extrahepatic bile duct carcinoma; others: epithelioid hemangioendothelioma, hepatoblastoma, hemangiosarcoma, cystadenocarcinoma.

Figure 2. Actuarial survival after liver transplantation for hepatocellular carcinoma with underlying cirrhosis (n = 86) according to UICC - tumor stage.
recurrence, respectively. The two patients alive have survived for seven and 15 years without recurrence. One of the two patients with hemangiosarcoma died from perioperative complications, the other from tumor recurrence after five months. One patient with cystadenocarcinoma has been alive for 5.5 years. The patients with gallbladder carcinoma died after 12 and 13 days from perioperative bleeding complications.

Seventeen patients with hepatocellular carcinoma and underlying cirrhosis underwent pretransplant chemoembolization. Besides necrosis, no vital tumor could be found in four of them during histopathologic examination of the hepatectomy specimen. So far, maximum survival is 42 months. Nine patients are still alive.

Comparison of transplant and resected patients with hepatocellular carcinoma stage I and II in underlying cirrhosis showed better survival after transplantation: 1-, 3-, and 5-year survival rates of 83.3% versus 76.9%, 75.8% versus 44.0%, 60.6% versus 44.0%, and median survival 96.5 versus 23.2 months. However, this difference was not significant. Thirty-day mortality was 11.1% versus 7.7%, which was also not significant. There were four survivors beyond five years in the transplant (none of them beyond eight years) and two in the resection group. No transplant patient died from tumor recurrence, while this occurred in three patients of the resection group. These differences were also not significant.

Secondary Liver Tumors

Transplantation for liver metastases shows a highly significant difference between neuroendocrine tumors and other entities such as colorectal carcinoma, melanoma, choriocarcinoma, and pancreatic carcinoma: five-year survival of 81.8% versus no survivor beyond three years. Eight of the 11 transplant patients with neuroendocrine tumors are alive, three of them without evidence for tumor recurrence. So far, the longest survival is 10 years. In colorectal carcinoma, one of the four patients died from tumor recurrence 11 months after transplantation. Two patients died from perioperative complications, in one case from graft failure due to acute rejection on postoperative day 8. The fourth patient died from tumor recurrence after 33 months. In melanoma, one of the two patients died from tumor recurrence 4.5 months after transplantation, the other patient on postoperative day 9 from septic multiorgan failure. The two patients with choriocarcinoma died from tumor recurrence after five weeks and from perioperative complications leading to multiorgan failure after one month. The patient with liver metastases from pancreatic carcinoma died from sepsis after three weeks.

DISCUSSION

Overall Results

The presently available results show overall five-year survival for hepatocellular carcinoma following liver transplantation in the range of 25%-36% [10, 25], varying between more than 60% in stage II and 10%-20% in stage IV. For other tumor entities such as fibrolamellar carcinoma and liver metastases from neuroendocrine tumors, a higher five-year survival up to even 80% may be obtained. Therefore, patients with malignant tumors can be selected for transplantation according to a predictable likelihood for long-term survival. On the other hand, it is a particular dilemma to exclude patients with advanced tumors from transplantation even though at least some prolongation of lifetime may be obtained and even long-term survival has been observed, as demonstrated for hepatocellular carcinoma in our series. Split-liver transplantation may be a reasonable possibility for transplanting patients with malignant disease without neglecting those with benign disorders [26, 27]. Our present data are in agreement with a former cumulative unselected survey from the Cincinnati Transplant Tumor registry by Penn [28] and other authors [29]. “Favorable” indications for transplantation are UICC-stage II hepatocellular and proximal bile duct carcinoma as well as the uncommon entities fibrolamellar carcinoma, epithelioid hemangiendothelioma, hepatoblastoma, and liver metastases from neuroendocrine tumors. Patients with advanced tumors and extrahepatic spread should not be considered candidates for liver transplantation. Meticulous tumor staging is required according to the UICC rules. UICC-stage III and IV hepatocellular carcinoma, as well as intrahepatic bile duct carcinoma, hemangiosarcoma, and metastases from nonendocrine tumors should be excluded from liver transplantation alone. In these conventionally unresectable tumors, extended resections by use of ex situ (“bench procedure”), in situ, and ante situm techniques should be performed whenever feasible [30].
Selection Criteria According to Tumor Stage

UICC classification of hepatocellular carcinoma based on imaging includes a considerable risk to under-stage the tumor preoperatively [21]. While iodized oil computerized tomography may differentiate T4 tumors from stages T1-T3 with good sensitivity of 88% and predictive value of 100% [31], for small hepatocellular carcinoma nodules a lesion-by-lesion analysis showed sensitivity of just 53% [32]. Assessment of vascular invasion and regional lymph nodes may be very difficult. However, for decision-making about the appropriate treatment, differentiation of T2 and T3 and stage II and III, respectively, is required. A recent autopsy study by Ko et al. [33] in 20 cases of unresected hepatocellular carcinoma revealed extrahepatic tumor spread in multiple nodular, massive, and diffuse tumors. Only patients with a single nodular type no larger than 3 cm had no extrahepatic metastasis. Diagnostic imaging has to identify these patients with better accuracy. Ojogho et al. [13] showed a higher recurrence rate of hepatocellular carcinoma after liver transplantation in cases of nonincidental versus incidental tumors. Solitary tumors with an average size of 10.1 cm recurred significantly more frequently at extrahepatic sites than did multiple tumors with a maximum size of 6 cm. This paradoxical finding was explained by either problems of preoperative imaging or tumor progression while awaiting transplantation.

Iwatsuki et al. [17] demonstrated significantly better survival rates after transplantation in cirrhotic patients in each tumor stage—in stage II, 75% five-year survival versus no four-year survivor after resection. For cirrhotic patients with small uninodular or binodular hepatocellular carcinoma smaller than 3 cm, Bismuth et al. [8] found survival rates of 83% after transplantation versus 18% after resection. Recently, Mazzaferro et al. [19] showed an actuarial survival rate of 75% and a recurrence-free survival of 83% for unresectable small hepatocellular carcinoma after transplantation. Bronowicki et al. [34] retrospectively compared resection, liver transplantation, and chemoembolization, and did not find a difference in the five-year probability of survival close to 45%. Our retrospective comparison between transplantation and resection in patients with hepatocellular carcinoma in stages I and II with underlying cirrhosis revealed five-year survival rates of 60.6% versus 44.0%. It has to be emphasized that so far none of these transplant patients died from tumor recurrence, while this did occur in 3 of 14 patients who underwent resection. Although not significant, this observation provides further arguments for early transplantation in order to cure the cancer-bearing disease itself. Molecularbiologic studies about the issue of local recurrence or de novo carcinogenesis in the cirrhotic liver are pending. However, Ko et al. [35] recently demonstrated that patients with chronic aggressive hepatitis and liver cirrhosis have lower recurrence-free survival rates after curative resection for hepatocellular carcinoma. This also might be an indicator for multicentric carcinogenesis. In agreement with other authors [20], it may be justified to consider patients with liver cirrhosis candidates for liver transplantation in cases of significant elevation of alpha-fetoprotein level or nodules suspicious for hepatocellular carcinoma, most likely even if resectability can be assumed.

Extension of Surgical Radicality by Multivisceral Procedures

In order to treat advanced tumors with extrahepatic involvement and to increase surgical radicality, Starzl et al. [36] inaugurated upper abdominal exenteration and “cluster” transplantation of liver-pancreas-duodenum en bloc or liver transplantation alone (“modified cluster”). According to a five-year experience in different types of primary and secondary hepatobiliary malignancy, Alessiani et al. [37] observed long-term survival in 3 of 12 patients with metastases of extrahepatic bile duct cancer confined to the liver and concluded that besides patients with fibrolamellar carcinoma and liver metastases from endocrine tumors, those might benefit most from this radical procedure. As for liver transplantation alone, prognostic factors were absence of lymph node involvement and vascular invasion as well as metastases confined to the liver [37]. These results and the observation of intrahepatic tumor recurrence after transplantation bring up the question of whether more advanced tumors, even without detectable extrahepatic metastases, have to be considered a systemic disease and whether they can be cured by extensive surgery at all. Besides enhanced surgical radicality, another rationale for multivisceral procedures is the avoidance of tumor cell spread by the no-touch technique [38]. For unresectable proximal bile duct carcinoma, Neuhaus and Blumhardt [39] and Cherqui et al. [40] combined liver transplantation and pancreatoduodenectomy. Although technical feasibility of these procedures has been proven, the real benefit requires further evaluation with regard to long-term survival versus increased postoperative morbidity.

Multimodality Treatment

Improvement of the unsatisfying results of surgery alone requires multimodality treatment approaches. The rationale should be reduction of local tumor mass before transplantation, lowering the risk for intraoperative dissemination and control of potentially extrahepatic systemic spread with free tumor cells and micrometastases. Several multimodality protocols have currently been investigated for hepatocellular carcinoma [41]. Despite one report from France that lipiodol chemoembolization treatment as opposed to no treatment does not improve survival [42], pretransplant
chemoembolization is part of most multimodality treatment protocols, as it is in our institution [8, 12, 43-46]. Cherqui et al. [43] combined chemoembolization with one fraction radiotherapy (5 Gy) and postoperative administration of mitoxantrone. Stone et al. [47] started very early with neoadjuvant doxorubicin chemotherapy which was continued intra- and postoperatively. Carr et al. [48] performed intrahepatic arterial chemotherapy with doxorubicin, and cisplatin with subcutaneously administered interferon alpha. Olihoff et al. [49] suggested adjuvant chemotherapy with intravenously administered fluorouracil, doxorubicin and cisplatin for six months after transplantation. For children, pretransplant chemotherapy has been presented by Otte et al. [14] and Broughan et al. [50].

Many practical problems and additional costs arise from the incalculable waiting time for a donor organ which must not disadvantage patients with benign end-stage liver disease. With regard to treatment intervals and bone marrow depression, it is not usually possible from an oncological point of view to have a graft available at the most appropriate time. Postoperative morbidity by toxicity of the pretransplant oncological treatment, as well as tumor progression, have to be avoided. Another issue is the necessity for updating diagnostic imaging in certain intervals to reevaluate tumor stage. When a donor organ is available, another backup candidate with benign disease has to be prepared simultaneously in order to save the organ and to avoid long ischemia in the event that extrahepatic tumor spread is found during surgery.

Despite promising results and calculable toxicity, the most appropriate treatment protocol has not yet been defined. It remains open whether pre-, intra-, or posttransplant treatment or a combination of all will really improve survival rates. Most likely, it will be reasonable to treat even early-stage hepatocellular carcinoma to prevent tumor progression during the waiting period. There is agreement that randomized studies will be required, but data have not yet been published. Further multimodality treatment protocols, especially for intrahepatic cholangiocarcinoma, have to be developed. The impact of immunosuppression [51] and perhaps the significance of “chimerism” by surviving donor lymphocytes [37] on tumor recurrence also have to be more elucidated in the future.

In conclusion, the issue of liver transplantation in malignant disease will be strictly limited by donor organ resources. In order to transplant patients with good chances for long-term survival, there has been a shift in indications to early tumor stage or more favorable tumor biology. For more advanced tumors with potentially extrahepatic spread, selection criteria will have to be reevaluated according to interdisciplinary efforts and scientific progress in the fields of diagnostic imaging, multimodality treatment, and immunology.

REFERENCES