Recurrence of Hepatocellular Carcinoma Following Liver Transplantation

A Review of Preoperative and Postoperative Prognostic Indicators

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Objective: To review the preoperative and postoperative variables that predict hepatocellular carcinoma (HCC) recurrence following orthotopic liver transplantation (OLT).

Data Sources: A collective review of the literature was conducted by searching the MEDLINE database using several key words: hepatocellular carcinoma, recurrence, liver transplantation, and salvage transplantation.

Study Selection: Reviews and original articles containing basic scientific observations and long-term clinical outcomes were included.

Data Extraction: Critical observations from peer-reviewed sources were incorporated in this review.

Data Synthesis: Overall, 11 studies were reviewed to determine the incidence of HCC recurrence following OLT and to identify prognostic variables of recurrence. Four studies were evaluated to determine the efficacy of salvage transplantation following liver resection.

Conclusions: Liver transplantation is a viable treatment option for select patients with HCC and end-stage liver disease. However, in approximately 20% of patients, recurrent HCC is the rate-limiting factor for long-term survival. Despite identification of clinical parameters that may stratify patients at high risk and exhaustive preoperative staging, cancer recurrence is likely the result of microscopic extrahepatic disease. With a desperate donor organ shortage, locoregional ablation techniques and resection are being employed in patients on the waiting list to serve as a bridge to OLT. Furthermore, some have advocated aggressive surgical resection of isolated metastasis in both the liver and extrahepatic viscera. Whether these creative strategies confer a survival advantage is unknown; it will require long-term follow-up to determine their efficacy.

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Orthotopic liver transplantation (OLT) is the preferred treatment for select patients with hepatocellular carcinoma (HCC) and end-stage liver disease. With the universal application of the Model for End-stage Liver Disease (MELD) system for organ allocation in the United States, patients with HCC have been given increased priority on the waiting list for cadaveric organs. As a result, the number of patients who undergo transplantation for HCC is rising. Liver transplantation offers a reasonable long-term survival benefit for patients with small tumors and no evidence of extrahepatic disease. However, a debate still exists over which patients should be considered for transplantation. While several groups have reported a 70% 5-year survival rate following OLT, it is generally accepted that patients should not be considered for transplantation unless a minimum survival rate of 50% at 5 years is anticipated.

Chronic inflammation in the cirrhotic liver promotes a dysplastic field. While transplantation offers the theoretic advantage of complete tumor excision with removal of the diseased liver, recurrence of HCC following OLT is the rate-limiting factor for long-term survival. Unfortunately, HCC recurrence is reportedly as high as 40% after transplantation. Mechanisms of cancer recurrence include the presence of microscopic extrahepatic foci at the time of transplantation. Thus, HCC may resurface in the form of metastatic foci in distant organs, such as the lungs, brain, bone, and in the transplanted allograft.

See Invited Critique at end of article
INCIDENCE OF TUMOR RECURRENCE

Several clinical variables have been identified that independently influence tumor recurrence and patient survival. Early observations by Iwatsuki and colleagues identified lymph node metastasis and vascular invasion of the tumor as significant negative predictors. Subsequent experience has confirmed that both microvascular and macrovascular invasion portend a worse outcome and correlate with an increased incidence of post-OLT tumor recurrence. Additionally, tumor size larger than 5 cm, tumor grade, bilobar disease, and total number of lesions may influence patient survival. Elevated serum α-fetoprotein levels have also been implicated.

Several studies have chronicled the actual incidence of recurrent HCC after transplantation (Table 1). Roayaie and colleagues observed an 18% incidence of tumor recurrence in more than 300 patients who had transplantations for HCC. Five-year survival was significantly lower in patients with recurrence (22%) vs those without (64%). Most patients (88%) with recurrent tumors had vascular invasion. Multivariate analysis indicated that the size and differentiation of the primary tumor, as well as the presence of bone metastasis, negatively affect survival from the time of transplantation. Roayaie et al note that factors associated with recurrent HCC (eg, tumor size, > 5 cm) also correlate with earlier recurrence and shorter survival.

Cumulative experience from the United Network for Organ Sharing database compared more than 900 patients who had transplantations for HCC with more than 33,000 who did not. Overall, 5-year survival was 48.2% in patients with HCC and 74.7% in patients without. Survival improved dramatically over time. Patients who had transplantations between 1987 and 1991 had a 5-year survival of 25%, while those who had transplantations between 1996 and 2001 had a 5-year survival of 61%. In the United Network for Organ Sharing database, only 75 of 985 (7.6%) patients had tumor recurrence. Unfortunately, detailed staging information and specific selection criteria were not available. A separate study from the University of Pittsburgh reported an extremely high incidence of recurrence (40%). The authors noted that macrovascular invasion was the single most influential risk factor for recurrence. Additionally, all patients with positive margins developed recurrent disease within 1 year of transplantation. Of the 71 patients who had a recurrence, 35% had recurrences in the liver and more than 90% had recurrences within 2 years of transplantation. While the actual incidence of HCC recurrence varies between centers, it is clear that several tumor-associated factors are prognostically important. Tumor size and the presence of vascular invasion have emerged as the most clinically significant characteristics for predicting recurrence. Furthermore, increasing tumor size predicts the presence of vascular invasion.

PREOPERATIVE STAGING AND IMMUNOSUPPRESSION

With the prognostic importance of tumor size and number of lesions, preoperative staging is crucial to patient selection and ultimately to organ allocation. Unfortunately, up to 60% of patients are assigned incorrect staging prior to transplantation. In the seminal article by Mazzaferro and colleagues, 48 patients with cirrhosis underwent OLT for small, unresectable tumors. The strict criteria that were used to select patients for OLT included a single tumor 5 cm in diameter or smaller or no more than 3 tumor nodules, each less than 3 cm in diameter. Overall, 4-year survival for patients meeting these criteria was 85% compared with only 50% in those exceeding the selection parameters. Importantly, even with extensive preoperative imaging, 27% of patients were assigned inappropriate staging prior to OLT.

Pathologic evaluation of the hepatic explant, with comparative findings to radiologic imaging, is currently the

Table 1. Hepatocellular Carcinoma Recurrence Following Orthotopic Liver Transplantation

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>HCC Recurrence, %</th>
<th>Study Description/Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemming et al</td>
<td>112</td>
<td>9.8</td>
<td>Vascular invasion is an independent risk factor for HCC recurrence</td>
</tr>
<tr>
<td>Leung et al</td>
<td>144</td>
<td>15.3</td>
<td>AFP of &gt; 10 ng/mL and pathologic UCSF criteria are predictors of recurrence-free survival</td>
</tr>
<tr>
<td>Margarit et al</td>
<td>103</td>
<td>14.5</td>
<td>Vascular invasion is the only independent risk factor for HCC recurrence</td>
</tr>
<tr>
<td>Zavaglia et al</td>
<td>155</td>
<td>6.4</td>
<td>HCC recurrence is associated with grade and macroscopic vascular invasion</td>
</tr>
<tr>
<td>Yoo et al</td>
<td>985</td>
<td>7.6</td>
<td>5-y survival for patients with HCC was 42.3% and 71.7% in patients without HCC (from UNOS data set)</td>
</tr>
</tbody>
</table>

Abbreviations: AFP, α-fetoprotein; HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation; TACE, transarterial chemoembolization; UCSF, University of California, San Francisco; UNOS, United Network for Organ Sharing.
gold standard in determining the accuracy of preoperative staging. Unfortunately, the sensitivity for identifying HCC preoperatively by computed tomography and magnetic resonance is only 50% and 70%, respectively. Sotiropoulos and colleagues observed that only 10 of 70 patients (14.3%) with HCC who underwent OLT had tumor diameter accurately quantified by preoperative radiologic examination. Additionally, only 34% of patients had correct identification of the number of tumors. Finally, the sensitivity of preoperative imaging for lesions smaller than 1 cm in diameter was 0%.

The adoption of strict selection criteria for patients with cirrhosis and HCC has led to improved recurrence-free survival. However, the inaccuracy of the preoperative staging may prevent achievement of the full survival benefit. Accurate quantification of tumor size and number may prevent OLT in patients exceeding the selection criteria. If this is achieved, unnecessary operations may be avoided. Currently, imaging modalities for both diagnosis and staging remain suboptimal. Interestingly, preliminary observations suggest that the use of positron emission tomography may be beneficial in evaluation of liver masses. Specifically, Ho and colleagues documented an 87% sensitivity using positron emission tomography with C-acetate tracer in HCC patients with 3 or fewer lesions. While these findings have been confirmed by other groups, the true accuracy of this new technology remains to be determined.

Liver biopsy for diagnosis as well as for further characterization of the tumor remains controversial. Unfortunately, the multifocal nature of HCC complicates the accuracy of percutaneous biopsy. As such, the false negative rates remain high in most studies, despite multiple biopsy attempts. The diagnosis remains questionable in up to two-thirds of cases. The possibility of seeding the abdominal cavity and/or disseminating malignant cells into the blood or lymphatic tissue remains a serious concern. Many centers feel that the risk of seeding far outweighs the minimal improvement in diagnostic accuracy. Finally, against the background of decompensated cirrhosis, many experts argue that the diagnosis of HCC will not change the indication for transplantation.

Effects of Immunosuppression

Attenuation of immunosurveillance was initially thought to be responsible for de novo and recurrent malignancy in transplant recipients. However, there is a growing body of evidence to suggest that some immunosuppressive agents may directly promote phenotypic changes in a variety of cell types. In 1999, Hojo and colleagues demonstrated that cyclosporine induced cellular changes in adenocarcinoma cells, promoting cellular motility and tumor invasion. In vivo, cyclosporine increased the number of pulmonary metastatic deposits in mice for several different tumors, including human bladder carcinoma. In a rat malignant hepatoma transplantation model, overall survival in cyclosporine-treated animals was significantly reduced. More importantly, the incidence of pulmonary metastasis was increased with extrapulmonary recurrence exclusive to the cyclosporine treatment group.

To date, clinical experience has not paralleled observations in the laboratory. However, data suggest a possible association between cyclosporine-based immunosuppression and HCC recurrence. Vivarelli and colleagues reported an increase in 5-year recurrence-free survival in patients treated with smaller cumulative doses of cyclosporine in the first year following OLT for HCC. Furthermore, they observed a significantly higher mean cyclosporine level in patients with HCC recurrence. Despite these findings, there is still no definitive link between cyclosporine-mediated immunosuppression and recurrent HCC following transplantation. Furthermore, these data are retrospective and based on a small number of patients.

Sirolimus, a bacterial macrolide, possesses both immunosuppressive and antineoplastic properties. Prevention of allograft rejection is mechanistically related to sirolimus binding to the mammalian target of rapamycin and subsequent inhibition of IL-2 (interleukin 2)–mediated lymphocyte proliferation. In a preclinical model, sirolimus inhibits metastatic tumor growth and decreases neovascularization in the liver. Conversely, cyclosporine promoted tumor growth and new blood vessel formation. Sirolimus was associated with a decrease in vascular endothelial growth factor expression and attenuated the response of endothelial cells to vascular endothelial growth factor stimulation. Similarly, an antiproliferative effect of sirolimus in vitro has been observed by other groups. Interestingly, drug levels at which sirolimus maintains antiangiogenic properties are compatible with immunosuppressive dosages used clinically.

Recently, a group from the University of Alberta reported a prospective series of patients with HCC undergoing OLT. The authors sought to achieve maintenance monotherapy with sirolimus within 6 months of OLT with a protocol designed to wean steroids and calcineurin inhibitors early postoperatively. Overall, 19 cases were documented as being within the Milan criteria and 21 were not. During the follow-up period, 4 tumor recurrences were observed in the extended criteria group vs only 1 recurrence in the Milan criteria group. The overall and disease-free survival was not different between the 2 groups. The authors conclude that the Milan criteria may be safely extended without compromising patient outcome. Furthermore, they suggest that sirolimus monotherapy appears to have a beneficial effect on tumor recurrence and survival. However, this study did not include a control group to compare with those treated with sirolimus monotherapy. They suggest the protocol may be beneficial by comparing HCC recurrence and postrecurrence survival in this series with that of another center. Importantly, only 25 of 35 surviving patients continued treatment with sirolimus monotherapy. Thus, preclinical data suggest that current regimens of immunosuppression may possess an undefined degree of oncologic influence in vitro. Whether these actions have a clinically significant effect on the incidence of tumor recurrence after transplantation remains unclear.

Locoregional Therapy Prior to Transplantation

Despite encouraging preliminary reports, chemotherapy for HCC has no proven benefit. As such, local ablative techniques, including transarterial chemo-

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embolization (TACE) and radiofrequency ablation (RFA), are increasingly being employed prior to OLT. Promoting tumor necrosis may control progression and thus provide a bridge to transplantation. However, the effect of ablative therapy on survival and cancer recurrence after OLT is not clear. A preliminary report from the University of California, San Francisco, notes a reduction in the drop-out rate from the transplant waiting list in patients treated with preoperative TACE or ablative therapy within the first 6 months of listing. Similar findings have been reported by other groups.

Several studies have failed to demonstrate a survival benefit of preoperative locoregional therapy. However, local ablation may positively influence outcome in a select group of patients. In a retrospective analysis of 168 patients from 2 centers, a survival advantage was observed in patients with T2 or T3 tumors who received preoperative locoregional therapy. With staging pathologically confirmed by explant, the 5-year recurrence-free survival rate was 94% in 85 patients. In contrast, 41 patients who did not receive pre-OLT ablation had a 5-year recurrence-free survival rate of 81%. This difference did not reach statistical significance.

Our experience at the University of California, Los Angeles, includes 52 patients listed for OLT who were treated with preoperative percutaneous RFA. Ultimately, 41 patients underwent transplantation. Complete tumor coagulation was achieved in 85% at postablation imaging, with only a 3% drop-out rate during the waiting period. Overall, the 3-year post-OLT survival was 76% and no recurrences were observed. This favorable effect on drop-out and recurrence was achieved despite inclusion of 10 patients whose tumor burden exceeded the Milan criteria. Unfortunately, a control group was not included to document a potential survival advantage of pre-OLT RFA. Despite these encouraging results, there has not been a prospective randomized trial comparing post-OLT outcomes. Furthermore, the treatment modalities employed (ie, TACE vs RFA) are not consistent across different series. In fact, most studies include patients who have received TACE and/or RFA.

The first prospective attempt to downstage HCC via ablative therapy was recently reported. Twenty-one patients initially assigned staging beyond Milan criteria were successfully downstaged to meet United Network for Organ Sharing T2 criteria preoperatively. Ultimately, 16 patients underwent OLT. While no recurrences were observed, 14 of the 16 patients who had transplantations had either complete tumor necrosis or met the T2 criteria by explant pathology. Although these findings are encouraging, Yao et al acknowledged that the length of follow-up is too short to accurately assess the risk of tumor recurrence.

**SALVAGE TRANSPLANTATION AND SURGICAL TREATMENT OF RECURRENT**

Cancer recurrence following surgical intervention is the major limitation to long-term survival. Several authors suggest that the incidence of HCC recurrence is significantly higher following liver resection than after transplantation. Recurrent tumor after liver resection is predominantly intrahepatic. Conversely, recurrent HCC after OLT may present at distant sites, including lung, bone, and brain, as well as the transplanted allograft. Recurrent tumor generally presents within a short interval from the time of transplantation. This suggests that preoperative or intraoperative microscopic metastasis is responsible for recurrent disease. Unfortunately, phenotypic differences between the primary tumor and metastatic lesions are not clearly defined. However, it is plausible that these recurrent lesions are poorly differentiated and/or biologically more aggressive.

**Resection as a Bridge to Transplantation**

Liver transplantation is the best treatment option for patients with HCC and decompensated liver disease. However, the optimal treatment strategy for patients with preserved liver function and small cancers is not well established. Several studies have demonstrated reasonable survival in Child-Turcotte-Pugh class A patients treated primarily by transplantation. Alternatively, several authors have concluded that overall and disease-free survival are similar after liver resection and after OLT. Given a critical shortage of cadaveric organs and extended time on waiting lists, some authors have proposed liver resection as first-line therapy in patients with preserved liver function. A product of this debate is the treatment strategy termed *salvage transplantation*. As such, primary hepatic resection followed by OLT for HCC recurrence or liver failure, has been employed by several centers.

Recently, Margaret and colleagues observed an increased recurrence rate following liver resection for single lesions smaller than 5 cm in diameter in Child-Turcotte-Pugh class A patients (Table 2). In this series, 59% of patients undergoing liver resection developed recurrences, which were predominantly intrahepatic. The recurrence rate after primary OLT was only 11% and was extrahepatic in 75% of patients. The lungs, adrenal glands, and bones were the most frequent sites of metastasis, which appeared at a mean of 16 months postoperatively. Interestingly, 5 patients were treated with salvage OLT following postresection recurrence with comparable 1- and 5-year survival in primary OLT. They conclude that liver resection may serve as a bridge to transplantation in a select group of patients with small tumors and well-compensated disease. Importantly, previous resection did not appear to jeopardize the outcome of subsequent transplantation.

The 2 largest clinical experiences with salvage OLT report conflicting results. Belghiti and colleagues reported a series of 107 patients. Seventy patients underwent primary OLT, with 18 patients treated with primary resection. Eleven of these 18 patients underwent salvage OLT for cancer recurrence. Both 3- and 5-year survival rates between primary and secondary OLT groups were similar. Conversely, Adam et al reported 17 patients undergoing secondary OLT after liver resection compared with 195 patients undergoing primary OLT. Adam and colleagues make several important observations: Of the 69 recurrences after resection, only 17 (25%) were eligible for transplantation. Fifty-four percent of patients receiving a salvage OLT had cancer recurrences,
most of which were intrahepatic. Patients undergoing hepatic resection had a higher operative mortality and blood requirement. Finally, the 5-year disease-free survival for salvage and primary OLT was 29% and 58%, respectively. Based on these findings, Adam et al57 advocate that patients who are at high risk for HCC recurrence (eg, multiple tumors and presence of vascular invasion) be excluded from a 2-stage treatment strategy.

While these data conflict with previous reports, several important differences are worth mentioning. Adam and Azoulay69 restricted secondary OLT to patients with HCC recurrence exclusively. Alternatively, the study by Belghiti et al68 extended salvage OLT to patients with deteriorating liver function and positive margins after resection. Also, operative mortality was much higher in Adam and Azoulay’s report69 than in that by Belghiti et al68 (56% vs 23.5%, respectively), which was largely attributed toportal hypertension and impaired liver function. Finally, the number of patients eligible for OLT after resection was extremely low at 17%. Thus, primary liver resection may render a large number of patients unable to undergo transplantations secondary to more biologically aggressive tumor recurrence.

Resection of Recurrent HCC After Transplantation

Few treatment options are currently available for patients with recurrent cancer after OLT. Unfortunately, most present with disseminated disease and are not candidates for local ablative therapy.70 However, aggressive surgical intervention has recently been advocated for a subgroup of patients with localized recurrence. To date, 3 groups have reported their results in a modest number of patients. A series from Milan included 132 patients who underwent OLT for HCC performed at 3 Italian hospitals.15 Overall, 21 patients (15.9%) had a recurrence at an average of 7.8 months following transplantation. Approximately 40% of patients had multiple organ involvement. Importantly, 7 patients underwent surgical resection for recurrence in the liver, lungs, bone, and skin. Four-year survival was 57%, while survival at the same time interval for 14 patients with unresectable disease was only 14%. Similar data from Hannover, Germany, described 11 patients with recurrent tumor who underwent surgical resection of isolated metastases, including 8 lung resections.5 At the time of the report, 7 of these 11 patients were alive at 4.3 years’ follow-up. Finally, the most recent series from Mount Sinai Medical Center documents 57 recurrences in 311 patients who had transplantations for HCC.16 Five patients underwent liver resection and 7 patients underwent lung resection. Survival in patients treated with radical surgical resection was significantly better than those who were not. Clearly, aggressive resection of recurrent disease is not possible in most patients. However, a survival advantage may be realized in a select group of patients with localized disease. Currently, the cumulative experience is too small to draw firm conclusions.

CONCLUSIONS

Recurrence of HCC after transplantation remains a formidable problem in approximately 20% of patients despite refined selection criteria and exhaustive preoperative staging. Attempts to identify clinical variables that may distinguish patients at a higher risk of recurrent disease have had a modest effect. With the questionable accuracy of pretransplantation radiologic imaging, identifying molecular markers and detailed genetic profiling may hold the most promise.71,72 For example, the loss of tumor suppressor gene heterozygosity combined with clinical variables, including tumor number and size, and presence of vascular invasion provides a predictive model of cancer recurrence.73 As surgical strategies continue to evolve, the true benefit of transplantation after liver resection remains unclear. With such a small number of patients currently reported, the actual incidence of secondary HCC recurrence and long-term survival rates after salvage OLT are unknown. It is plausible that risk stratification by molecular staging may identify patients who are least likely to have recurrences and thus ideal candidates for either primary or salvage OLT and resection of localized metastatic disease.

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The review by Zimmerman et al is important and timely in furthering our awareness of deficiencies in the current staging and allocation system for liver transplantation in the presence of HCC. While there is a consensus within the transplant community that the current pTNM staging system (and therefore the United Network for Organ Sharing and Milan criteria, which are based on this system) is not predictive of HCC recurrence after liver transplantation, little has been done to rectify the situation.

Put succinctly, the most demanding argument for change to current policy is that HCC is the only cancer for which, when diagnosed in its earliest and most curable stage (stage I), a biopsy is deferred and the patient is required to wait for tumor growth and possible spread before being offered potentially curative treatment (ie, liver transplantation; excluding the option of living-donor transplantation).

For diagnosis alone, we agree with the authors about the lack of necessity of a preoperative biopsy. However, given the molecular techniques currently available, so much additional information can be gained from a biopsy that we feel it should be mandatory for all lesions that are visible and accessible by imaging. The risk of bleeding and tumor seeding, while real, are sufficiently low and the potential yield is sufficiently great to warrant this approach. The information gained from HCC molecular analysis is the single strongest predictor of HCC recurrence, surpassing that of vascular invasion by 6-fold.

If a preoperative biopsy is not to be made mandatory, we feel that patients in stages other than stage I and with disease limited to the liver should at least have the option of biopsy and subsequent upgrading on the United Network for Organ Sharing waiting list if the genetic analysis proves favorable.

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