Editorial

Long-Term Disease-Free Survival After Resection of Hepatocellular Carcinoma: Both Tumor Behavior and Surgeon's Performance Are Important Determinants

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Hepatocellular carcinoma (HCC) is the fifth most common malignancy in the world, with the highest incidence in Asian countries.¹ The management of HCC is challenging because it is an aggressive tumor with a propensity for vascular invasion and, in most patients, it is associated with cirrhosis. Hepatic resection is the mainstay of "curative" treatment for HCC in patients with preserved liver function. Resection of HCC, however, is associated with a 5-year recurrence rate of 70% to 100% in most centers.² The high recurrence rate is a result of either intrahepatic metastasis or multicentric hepatocarcinogenesis in the liver remnant. In a strict sense, hepatic resection for HCC can barely be considered curative with such a high rate of postoperative recurrence. The prolonged survival after resection of HCC depends largely on an aggressive management of recurrence.^{3,4} Liver transplantation is an alternative curative treatment for HCC, which could potentially solve the problem of multicentric recurrence in the liver remnant. The indication for liver transplantation, however, is restricted to early HCC (<5 cm in diameter), without macroscopic vascular invasion, and its application is severely limited by the shortage of organ donors.⁵

Long-term, recurrence-free survival after resection of HCC is rare but not impossible. In this issue, Yeh et al.⁶ reported 46 patients (4.5%) who survived disease free for >5 years in a series of 1092 patients having resection of HCC. The long-term survival data from this large series of patients with actual follow-up of >5 years after re-

section of HCC represent an important contribution to the literature. The results confirm the poor disease-free survival found by actuarial survival analysis in previous studies.² With their large number of patients, Yeh et al.⁶ were able to identify the prognostic factors for 5-year disease-free survival despite the small proportion of 5-year disease-free survivors. In this study, absence of satellite lesions and an uneventful postoperative course were identified as the two independent predictors of 5-year disease-free survival in a multivariate analysis. The prognostic significance of satellite lesion is in accordance with numerous previous studies that have demonstrated a higher risk of recurrence in patients with more aggressive tumors. The presence of venous invasion instead of satellite lesion, however, was the more commonly identified pathologic prognostic factor in previous studies.² The finding of an uneventful postoperative course as a favorable factor for long-term, disease-free survival is an interesting one that had not yet been reported. Yeh et al.⁶ suggest that this might be related to the slightly younger age and probably less severe cirrhosis in the group of patients with uneventful postoperative course. No significant difference was seen in the age between 5-year disease-free survivors and those who died or developed recurrence within 5 years after hepatic resection. Although a lower incidence of cirrhosis was found in the 5-year disease-free survivors, associated cirrhosis itself was not a significant prognostic factor in the multivariate analysis. The exact reason for the association between postoperative complications and disease-free survival remains unclear. Nonetheless, the finding of a better long-term, disease-free survival among patients who had hepatic resection without complications is important because this demonstrates that the surgeon's performance not only affects the perioperative outcome, but it also has an impact on the long-term prognosis of the patients. It is intuitive to speculate that

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patients who developed postoperative complications might be immunosuppressed, which could have enhanced the development of recurrent tumors.

The contention that the surgeon's performance could influence the long-term prognosis of patients having resection of HCC is not a new one. Most published studies, however, have emphasized the aggressive biological behavior of HCC as the main culprit in the high incidence of tumor recurrence after resection of HCC, and paid much less attention to the role the surgeon's performance played. Hepatic resection is often associated with substantial blood loss and can require blood transfusion. Some authors have demonstrated a significant adverse influence of perioperative blood transfusion on disease-free survival after resection of HCC, which presumably was caused by suppression of the host's immune mechanism that results in early postoperative recurrence from intrahepatic or extrahepatic metastasis.⁷⁻⁹ We have observed a significant improvement in disease-free survival after resection of HCC at our institution in recent years. Reduced perioperative blood transfusion was identified as a significant factor that contributed to the improved results.¹⁰ In the study by Yeh et al.,⁶ blood transfusion was not a significant factor for 5-year disease-free survival. The reason for the discrepancy between their study and others is unclear. Nevertheless, their finding of adverse influence of postoperative complications on long-term, disease-free survival is in line with the emphasis on the surgeon's role in the long-term prognosis of the patients. Hepatic resection can now be performed with low mortality in most specialized centers, yet, a high complication rate of 25% to 45% is still observed.¹¹⁻¹³ In this context, much room still remains for further improvement.

Intraoperative tumor cell dissemination is another surgical factor that may influence the risk of recurrence. We have reported that iatrogenic tumor rupture, caused by excessive compression of a large HCC, resulted in a significantly shortened disease-free survival and an increased risk of peritoneal metastasis.¹⁴ For resection of a large right lobe HCC, the conventional approach of mobilizing the right lobe before hepatic transection carries a risk of tumor cell dissemination through the venous system because it entails a lot of compression and retraction on the tumor. For such cases, the anterior approach may reduce the risk of tumor cell dissemination. In the latter approach, hepatic transection is performed after division of ipsilateral inflow vessels without prior mobilization of the right lobe. The right lobe is mobilized only after completion of transection and division of the right hepatic vein and the venous branches connecting the inferior vena cava and the posterior aspect of the right

lobe. Hence, the tumor is mobilized only when all the vascular connections of the right lobe have been divided. In a retrospective study comparing the outcomes of patients with right lobe HCC (>5 cm in diameter) resected using the anterior approach and the conventional approach, respectively, we found a significantly better disease-free and overall survival among patients with HCC resected by the anterior approach.¹⁵

Undoubtedly, tumor biology of HCC plays a crucial role in determining the prognosis of the patients. No effective adjuvant therapy exists that could influence the tumor behavior and thus prevent recurrence.² Some encouraging results have come from studies on novel approaches of adjuvant therapy (e.g., polyphenolic acid and adoptive immunotherapy).^{16,17} The efficacy of such adjuvant therapies has not yet been validated by other studies. It is imperative that further research be conducted to identify an effective adjuvant therapy to prevent recurrence after resection of HCC. In the meantime, the best hope of improving disease-free survival of HCC patients lies in the surgeon's capability to perform hepatic resection with minimal tumor manipulation, no blood transfusion, and no postoperative complications.

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