

Benefits of Surgery for Patients with Pulmonary Metastases from Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is a common malignancy worldwide and has been difficult to treat successfully. Although surgical resection offers patients with HCC a chance for cure, the post-resectional tumor recurrence rate is high with a cumulative 5-year tumor recurrence rates ranging from 40 to 70%.¹ Tumor recurrence may be intrahepatic and/or extrahepatic. The lung is the most frequent extrahepatic metastatic site of HCC after hepatic resection.

In prolonging survival after resection of HCC, effective treatment of patients with recurrence is critical. Previous studies have demonstrated that aggressive management of patients with intrahepatic and/or extrahepatic recurrences of HCC, including repeat hepatic resection² and resection of extrahepatic recurrence, offers a chance for long-term survival. Poon *et al.*³ reported that resection of isolated extrahepatic recurrence (including the lung, diaphragm and mediastinal hilar lymph node) may offer long-term survival in selected patients. Yeh *et al.*⁴ reported resection of isolated peritoneal implantation from HCC recurrence with a median overall survival of 15.9 months.

In this issue, Chen *et al.*⁵ reported the results of surgical management in 6 patients with pulmonary metastases from HCC. Among these patients, only 1 patient had solitary pulmonary metastatic nodule, 2 patients with bilateral lungs involvement underwent sequential resection and another 2 patients received repeat pulmonary metastasectomy. In an earlier study, Lam *et al.*⁶ indicated that among 380 patients with HCC underwent hepatectomy, some 48 patients (12.6%) developed pulmonary metastases and 9 with solitary nodule were suitable for curative pulmonary resection, with a resectability rate of 18.8%. The median survivals of patients after pulmonary resection, ranging between 42-47 months, were similar in both studies.

In HCC patient, pulmonary metastases usually come from extrahepatic metastases of the tumor plugs in the hepatic venous systems secondary to vascular invasion.⁷ The tiny or microscopic tumor deposits in the lung parenchyma can be overlooked at the time of the primary operation. Another explanation for pulmonary recurrence after hepatic resection is postoperative seeding of the lungs or other sites by tumor cells present in the peripheral bloodstream at the time of the operation. These cells enter the bloodstream either before surgery or during resection as a result of the manipulation of the tumorous liver. Recurrence arising in 1 or more of these ways usually becomes evident shortly after hepatic resection, especially in patients with aggressive tumor biological behaviors. However, in some patients hematogenously spreading tumor cells may persist in a dormant state for long before growing into detectable tumor nodules.

The natural history of pulmonary metastasis of HCC remained largely undefined and spontaneous regression of multiple lung metastases has been reported.⁸ Because of limited data on the factors that affect prognosis, decision of surgical management should be made cautiously. The usual indications for resection of metastatic lung tumors include: (i) the patient being a good risk for surgical intervention, (ii) well-controlled primary malignancy, (iii) all nodules potentially resectable with planned surgery, and (iv) no evidence of metastatic disease elsewhere. The relationship is still unclear between survival and the number of metastatic tumors, unilateral or bilateral lung lobes involvement, intrathoracic lymph-node involvement, synchronous or metachronous resection, prethoracotomy α -fetoprotein level, the invasiveness and stage of the primary tumor, the effectiveness of repeat pulmonary metastasectomy, as well as other factors. It is expected that the survival rate will decrease in patients with bilateral lungs metastases even if all meta-

static nodules are macroscopically extirpated. In this issue, Chen *et al.*⁵ included 2 patients with bilateral lungs tumor involvement for pulmonary resection, and another 2 patients undergoing repeat pulmonary metastasectomy. The results are promising with 3 patients kept disease-free after a follow up period of 1-94 months. These encouraging results may support expanding selection criteria to benefit some patients who would otherwise be excluded from surgical treatment such as pulmonary metastasectomy. However, operative indications must also be considered in all aspects, as pulmonary resection still associates with morbidity and pulmonary metastasis is a distant lesion. Even when a pulmonary metastasis seems solitary, presence of occult metastases can be possible. Microscopic tumor that spreads outside the liver in other sites before surgery is undetectable, and this is also a reason for the possible usefulness of perioperative adjuvant chemotherapy.

Since there is presently no other effective treatment for HCC patients with pulmonary metastases, pulmonary metastasectomy is warranted in carefully selected patients. In order to define who will benefit from a metastasectomy, there is a heightened need in the future to perform multicenter analysis to evaluate the prognostic factors, the outcomes of pulmonary metastasis found during treatment for the primary lesion, the results of treatment for pulmonary metastases, the recurrent sites after pulmonary metastasectomy, and the significance of repeat pulmonary metastasectomy. In addition, the usefulness of perioperative adjuvant chemotherapy for HCC patients who underwent pulmonary metastasectomy could be evaluated by enrolment of those patients at risk of recur-

rence in randomized trials.

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