# Immunology

# Clinicopathological factors and long-term outcome comparing between lung and peritoneal metastasectomy after hepatectomy for hepatocellular carcinoma in a tertiary institution

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***Background.*** *Recurrence after liver resection for hepatocellular carcinoma (HCC) is common. Resection of extrahepatic recurrences such as lung metastasectomy (LM) has been well documented. Conversely, reports on the long-term outcomes of peritoneal metastasectomy (PM) are lacking. In this study, we compared the outcome of lung and peritoneal metastasectomy after hepatectomies for HCC in a tertiary institution.*

***Methods.*** *We reviewed retrospectively the data of 1,222 patients who underwent hepatectomies for HCC in Samsung Medical Center in Korea from January 2006 to August 2010. We studied the clinicopathologic factors between resected lung metastasis (LM) and peritoneal metastases (PM) and the long-term outcome of patient survival. Kaplan-Meier analysis was used to study the survival outcome.*

***Results.*** *The recurrence rate of resected HCC in this cohort was 41.6% (n = 508). Thirty-two patients with lung metastasis (23% of all lung metastasis) underwent LM whereas 13 patients (36% of all peritoneal metastasis) with peritoneal metastasis underwent PM. Two patients underwent PM and LM sequentially. Demographic and clinical data between the LM and PM groups were comparable. The mean prehepatectomy PIVKA-II level was greater in the LM group compared with the PM group (P = .029). On univariate analysis of pathologic factors, the median tumor size (P = .005), proportion of patients with tumor >75 mm (P = .005) and rate of microvascular invasion (P = .047) were greater in the LM group. The median time-to-recurrence in the LM group was 12 (4–45) months compared with 18 (1–102) months in the PM group (P = .896). The 1-year, 3-year, and 5-year overall survival of patients in the LM group was 92%, 55%, 55% (4-year) whereas that in the PM group was 90%, 75%, and 75%, respectively. The mean overall survival in the LM was comparable with that in the PM group (P = .578).*

***Conclusion.*** *Twenty-three percent of patients with lung metastasis and 36.1% of patients with peritoneal metastasis could be considered for metastasectomy. The long-term survival of patients with PM and LM was comparable in this study. Although resection of LM improves survival in patients with resected HCC, we demonstrated favorable outcomes for PM as well, which in the past would have been considered palliative. (Surgery 2015;157:645-53.)*

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Hepatocellular carcinoma (HCC) is the second-leading cause of death by malignancy in Korea after lung cancer, accordingly to the nationwide statistics reported in 2010. The age-adjusted incidence of primary HCC is 40.2 per 100,000 persons in men.[1] Worldwide, more than half a million people are affected by HCC.[2] Chronic hepatitis B is endemic in many regions in East and Southeast Asia. In Korea, chronic hepatitis B represents the most important risk factor, constituting approximately 70% of all the HCC.[3,4] Resection with curative intent for HCC is the main treatment modality that provides reasonable outcomes. Liver transplantation for HCC has become an attractive option for the treatment of selected patients, altering the natural history of this disease.[5-9]

Recurrence of HCC after liver resection is high. A cumulative 5-year recurrence rate of 75–100% has been reported.[10-14] The majority of recurrences appear in the liver remnant, especially in the background of cirrhosis. Extrahepatic recurrences, however, are not uncommon and are reported to range from 13 to 30% at 5 years.[15-17] The common sites of extrahepatic recurrence include lungs, bones, and brains. Other systemic sites, such as adrenal glands, spleen, pancreas and ovaries, usually are not detected until autopsy.[18-20] Peritoneal implantation of HCC after resection of the primary cancer is uncommon, with reported incidence ranging from 2 to 16%.[21-24] The incidence in our institution was 3%.[25] There are increasing reports on the resection of lung metastasis in HCC in the literature with encouraging long-term survival.[26-30] In contrast, peritoneal recurrence in HCC generally has been considered incurable and a terminal disease.

Selected patients with lung and peritoneal recurrences after liver resection have undergone resection of metastatic lesion(s) in our institution. In this study, the primary aim was to investigate the long-term outcome of patients with isolated recurrent HCC undergoing lung metastasectomy (LM) and peritoneal metastasectomy (PM). The secondary aim is to study the clinicopathologic factors between the 2 groups.

## PATIENTS AND METHODS

A retrospective data collection of all patients who underwent liver resection for HCC in Samsung Medical Center in South Korea from January 2006 to September 2010 was performed. After we excluded patients lost to follow-up after liver resection, there were 1,222 patients who were suitable for analysis. During process of data collection, 36 patients with peritoneal recurrence documented on imaging studies (13 underwent PM) were identified. Similarly, 138 patients with lung recurrence documented on imaging studies (32 underwent resection of lung metastases) were identified. Two patients had both PM and LM sequentially.

Demographic details (including the presumed etiology of HCC) and prehepatectomy tumor markers ($\alpha$-fetoprotein [AFP] and protein induced by vitamin K absence/antagonist-II [PIVKA-II]) and other treatment modalities (such as radiofrequency ablation and transarterial chemoembolization) were collected from the electronic medical record. Surveillance of patients with HCC after liver resection was performed at 3-month intervals. During the visit, tumor markers, such as AFP and PIVKA-II, were performed. Increased serum levels of tumor markers prompted the suspicion of tumor recurrence, and further investigations were performed to ascertain the diagnosis. Imaging modalities included computed tomography scan of the thorax, abdomen and pelvis, magnetic resonance imaging, and/or positron emission tomography scan and bone scan.

The aims of the investigation for peritoneal recurrence were 2-fold. First, the investigations would help to determine the location(s) of recurrence(s), number of lesions, and whether they were resectable. Second, the presence of extra-abdominal metastases that would preclude further curative resection was to be ascertained. In the absence of other systemic metastasis, if the peritoneal lesions were resectable without compromising essential anatomic structures such as major vasculature, operative resection would be offered to the patient. Preoperative assessment was performed to ensure that the patients were fit for general anesthesia and suitable for the operation. A midline incision was used to facilitate exploratory laparotomy. Locations and number of lesions were confirmed with the preoperative scans. Resection of the peritoneal lesions was performed to ensure adequate operative margins. En bloc resection of the lesion with its surrounding structures, such as small bowel, was required occasionally. In situations in which the malignant nature of the lesion was uncertain, excision for frozen section histology was performed intraoperatively. Careful hemostasis and selective placement of abdominal drain(s) at surgical site(s) were performed.

For patients with potentially resectable lung metastases, consultation with the thoracic operative team was made. In a study published by our institution on lung metastasectomy in HCC, the