Resection of Metachronous Lymph Node Metastases from Hepatocellular Carcinoma after Hepatectomy: Report of Four Cases

Masashi Utsumi*, Hiroaki Matsuda, Hiroshi Sadamori, Susumu Shinoura, Yuzo Umeda, Ryuichi Yoshida, Daisuke Satoh, Masaaki Hashimoto, Takahito Yagi, and Toshiyoshi Fujiwara

*Department of Gastroenterological Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan, and 
+Department of Surgery, Fukuyama Daichi Hospital, Fukuyama, Hiroshima 721-0873, Japan

We report 4 cases of surgical resection of metachronous lymph node (LN) metastases from hepatocellular carcinoma (HCC) following hepatectomy. Clinico pathological features and results of LN dissection were investigated in the 4 patients. One patient was found to have a single metastasis in the mediastinal LNs, another had multiple metastases in the mediastinal and abdominal LNs, and the other 2 had single metastases in the abdominal LN. The locations of the abdominal LN metastases were behind the pancreas head in 2 patients and around the abdominal aorta in 1 patient. They all underwent surgical resection of metastatic LNs and had no postoperative complications. The 3 patients whose LN metastases were solitary have been alive for more than 2 years after LN resection, and one of them is free from recurrence. The patient with multiple LN metastases died 13 months after LN resection due to carcinomatosis. With the expectation of long-term survival, a single metachronous LN metastasis from HCC after hepatectomy should be resected in patients without uncontrollable intrahepatic or extrahepatic tumors.

Key words: hepatocellular carcinoma, lymph node metastasis, hepatectomy

Heptocellular carcinoma (HCC) is the most frequent primary malignant tumor of the liver, but the incidence of extrahepatic metastasis in HCC is lower than that in other hepatic cancers [1]. Hematogenous metastasis from HCC is well known to occur, with the most frequent site being the lung, followed by the adrenal gland and skeleton [2, 3]. Autopsy studies have clarified that the frequency of lymph node (LN) metastasis from HCC was 23.5–43.9% [3–6]. However, LN metastasis after treatments has been described as uncommon (11.6%), accounting for only 1.0% of hepatectomy cases [4]. Although there have been many reports on the patterns and treatment of intrahepatic recurrence of HCC, the modality of treatment for LN metastasis of HCC has not been fully discussed. We herein report the clinical features of 4 patients who developed LN recurrence of HCC after hepatectomy, and discuss the effects of resection of the metastatic LNs.
Case Report

Between January 2000 and January 2011, 554 patients with HCC underwent hepatectomy in our department. Four patients having isolated LN metastasis without intrahepatic and other extrahepatic recurrence were selected for surgical removal of LN. Further resection of a metastatic LN was performed for one patient with the reappearance of a solitary LN metastasis following the initial resection of a metastatic LN (Case 3). There was no postoperative mortality. The clinicopathological features and prognosis of all 4 patients after LN resection are shown in Table 1.

Case 1. A 58-year-old woman had undergone percutaneous ethanol injection therapy (PEIT) and radiofrequency ablation therapy (RFA) for HCC in the right lobe for 4 years at another hospital. Subsequently, we performed right hemihepatectomy for HCC recurrence. Two years later, a single intra-abdominal tumor adjoining the posterior surface of the pancreas head was detected by follow-up ultrasonography. Dynamic computed tomography (CT) showed a swollen solitary mass 45 mm in diameter with early enhancement (Fig. 1A). She was diagnosed with LN metastasis of HCC by fine needle biopsy under endoscopic ultrasonography. Because there were no other distant metastases, pancreaticoduodenectomy (PD) was performed for resection of the LN metastasis (Fig. 1B). Histopathological examination of the resected mass

<table>
<thead>
<tr>
<th>Case</th>
<th>Primary tumor</th>
<th>Maximal size (cm)</th>
<th>Number</th>
<th>Differentiation</th>
<th>Underlying liver pathology</th>
<th>Hepatectomy</th>
<th>Interval from hepatectomy (month)</th>
<th>Location</th>
<th>Number</th>
<th>Surgical treatment</th>
<th>Survival after LN resection (month)</th>
<th>Recurrence after LN resection</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Multiple</td>
<td>1.2</td>
<td>Multiple</td>
<td>Undifferentiated</td>
<td>Normal</td>
<td>Right hemihepatectomy</td>
<td>24</td>
<td>Peripancreatic</td>
<td>Single</td>
<td>PD</td>
<td>Alive (27)</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Multiple</td>
<td>1.1</td>
<td>Multiple</td>
<td>Moderately</td>
<td>Hepatitis C</td>
<td>Right trisegmentectomy</td>
<td>19</td>
<td>Paraaortic Mediastinal</td>
<td>Multiple</td>
<td>LN dissection</td>
<td>Dead (13)</td>
<td>LN</td>
</tr>
<tr>
<td>3</td>
<td>Single</td>
<td>5.2</td>
<td>Single</td>
<td>Moderately</td>
<td>Hepatitis B</td>
<td>Right hemihepatectomy</td>
<td>21</td>
<td>Mediastinal</td>
<td>Single*</td>
<td>LN dissection</td>
<td>Alive (41**)</td>
<td>Bone</td>
</tr>
<tr>
<td>4</td>
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<td>2.3</td>
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<td>Normal</td>
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<td>Left hemihepatectomy</td>
<td>31</td>
<td>Peripancreatic</td>
<td>Single</td>
<td>PD</td>
<td>Alive (25)</td>
<td>Liver</td>
</tr>
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LN lymph node, PD pancreaticoduodenectomy; *The first and second lymph node metastasis; **After the first lymph node dissection.

Fig. 1  A, Dynamic computed tomography findings of case 1. A solitary enlarged lymph node metastasis at the posterior pancreaticoduodenal site can be seen, having marked enhancement during the arterial phase (arrow); B, Gross appearance of the resected lymph node. The cut surface of this tumor revealed a yellow-brownish tumor, 45 × 25 mm in diameter, with a capsule.
revealed metastatic HCC. The patient’s postoperative course was uneventful. She is doing well without recurrence, 27 months after LN resection.

**Case 2.** A 72-year-old woman with hepatitis C infection presented with HCC in the right anterior superior segment (S8) in 1996 and underwent PEIT and RFA several times at another hospital, but suffered from HCC recurrence in the right lobe with hepatic infarction. In March 2007, she underwent right trisegmentectomy of the liver for HCC recurrence at our hospital. Nineteen months later, mediastinal and abdominal paraaortic lymphadenopathies, 18 mm and 36 mm in diameter respectively, were found by CT (Fig. 2A, B). Because there were no other distant metastases, thoracolaparotomy was performed to dissect these lymph nodes. Histopathological examination of the dissected LNs revealed metastasis of HCC. Six months later, aortic LN metastases were detected again. She died of carcinomatosis 13 months after the second operation.

**Case 3.** A 59-year-old man with hepatitis B infection presented with HCC in the right superior segment (S8, S7) and underwent right hepatic lobectomy in November 2005. Twenty-one months later, lymphadenopathy in the mediastinum above the diaphragm was found by enhanced CT (Fig. 3A). Because there were no other distant metastases, thoracolaparotomy was performed to dissect this LN after transcatheter arterial embolization (TAE). Histopathological examination of the dissected LN revealed metastasis of HCC. Eighteen months after the second operation, LN recurrence adjacent to the

![Fig. 2](image1.jpg) **Fig. 2** Dynamic computed tomography findings of case 2. A, An enlarged mediastinal lymph node above the left diaphragm (arrow) demonstrated moderate enhancement during the arterial phase; B, A paraaortic lymph node (arrow) with marginal fat deposition was also found to be enlarged, having mild enhancement during the arterial phase.

![Fig. 3](image2.jpg) **Fig. 3** Dynamic computed tomography (CT) findings of case 3. A, CT revealed a swollen mediastinal lymph node 35 mm in diameter along the esophagus (arrow). After TAE, it had Lipiodol accumulation partially with little contrast material enhancement; B, A mediastinal lymph node adjacent to the right atrium (arrow) enhanced mildly during the arterial phase.
right atrium in the mediastinum was detected by CT (Fig. 3B), and repeated LN dissection was performed as a third operation. Three months after the third operation, bone metastasis was detected. The patient remains alive 41 months after the second operation.

**Case 4.** A 79-year-old man underwent left hemihepatectomy of the liver, with a diagnosis of HCC in the medial segment (S4) in June 2006. Thirty-one months after the heptectomy, a solitary metastatic tumor 40 mm in diameter was detected in the pancreaticoduodenal LN by follow-up CT (Fig. 4A), and he was diagnosed with LN metastasis of HCC. Because there were no other distant metastases, PD was performed to resect the mass (Fig. 4B). He had no postoperative complications. The histopathology of the mass showed a metastatic LN from HCC. Seventeen months after PD, intrahepatic recurrence was detected and controlled by PEIT. He is alive at 25 months after the second surgery.

**Discussion**

LN metastasis from HCC is not rare, and autopsy studies have clarified that the frequency of LN metastasis from HCC is 23.5–43.9% [3–6]. Nonetheless, surgeons rarely find LN metastasis during operations for HCC, unlike for other cancers. The prevalence of LN metastasis in patients who have undergone heptectomy for HCC was reported to be only 1.0% [4]. The cause of the discrepancy is associated with the following. Most synchronous LN metastases usually occur in patients with advanced and poorly differentiated HCC [6], and most such patients do not receive surgical treatments. Moreover, we do not routinely perform LN dissection during surgery for HCC, because of the risk of lymphatic leakage and coagulopathy caused by poor liver function and because of the low incidence of LN metastasis from HCC in the operable-stage disease [1, 7].

The hepatic lymphatic system has been well elucidated [8]. Much of the lymph flow towards the hepatic hilum runs into the intra-abdominal lymphatic system through the hepatoduodenal ligament; however, some of the lymph flow communicates with the diaphragmatic and intrathoracic lymphatic system through bilateral triangular ligaments. It is very important that some HCC exhibits so-called skip metastasis, which means there are no LN metastases in the proximal hepatoduodenal ligament but rather at distant sites [1, 9]. The prevalence of LN metastasis has been reported to be higher in patients without cirrhosis than with cirrhosis [6, 8]. Since the progression of cirrhosis leads to lymphatic obstruction, advanced cirrhosis may reduce the rate of LN metastasis; however cirrhosis leads to the formation of collateral routes for lymphatic drainage and these may produce skip metastasis [6]. Although no patient in this series had cirrhosis, 3 patients had skip metastasis of paraaortic or retropancreatic LN; therefore, attention should be given to the possibility of skip LN metastasis in HCC patients.

LN metastasis of HCC is associated with a poorer prognosis, and a standard treatment modality has not
been established. Retrospective studies regarding radiotherapy to target LN recurrence of HCC agreed that LN metastasis from HCC was sensitive to radiation therapy [10–12], but Park et al. [10] demonstrated that radiotherapy for metastatic LN from HCC could have survival benefit only to patients without other distant metastases or uncontrollable primary HCC and that the median survival time under the condition was 15 months.

Clinical researches employing surgical treatments for LN metastasis from HCC have been reported as small retrospective series [1, 5, 7, 9, 13, 14]. Kobayashi et al. [7] reported that selective lymphadenectomy, in which only lymph nodes suspected of metastasis by preoperative radiologic imaging diagnosis were resected, could improve the prognosis of selected patients who developed single LN metastasis without uncontrollable intrahepatic tumor or other extrahepatic metastases, and that the median survival time was 29 months after surgery, a period almost twice as long as the survival time after radiotherapy demonstrated by Park et al. Other surgical series for synchronous and metachronous LN metastasis also recommended selective use of LN dissection for solitary LN metastasis cases because the presence of multiple metastatic LNs implied the systemic nature of the disease, and the alteration of lymphatic flows by regional lymphadenectomy could lead to postoperative refractory ascites in cirrhotic patients. [5, 9, 13, 14]. As for the site of LN recurrence, a good prognosis was mainly achieved in patients with locoregional LN metastases in the hepatoduodenal ligament and/or on the posterior surface of the pancreatic head [1, 5, 9, 13], but Hashimoto et al. reported 2 patients surviving for more than 2 years after resection of paraaortic LN metastasis [13].

In our case series, which focused on surgical treatments of metachronous LN metastases in the absence of intrahepatic or extrhepatic lesions, the patient with multiple distant LN metastases at the mediastinal and paraaortic sites died of carcinomatosis about a year after surgery while the others with a single LN metastasis survived for more than 2 years. Concerning the performed surgeries, 2 patients who developed a solitary retropancreatic LN metastasis with normal liver function underwent pancreaticoduodenectomy uneventfully to complete regional LNs dissection. Consequently, one of them survived 27 months after surgery without recurrence; however, the case was considered to be rare and limited among the population suffering from HCC, which usually originates from injured livers.

The efficacy of Sorafenib, a newer molecular targeting agent, has been recently verified for prolonging survival in patients with advanced HCC [15, 16]. The American Association for the Study of Liver Disease guidelines on the management of HCC recommend the use of Sorafenib for advanced-stage HCC with lymph node metastasis [16]. However, the survival benefits have not yet been demonstrated in a subgroup analysis of patients with extrahepatic metastasis.

We concluded that long-term survival could be expected after surgical resection of metachronous LN metastasis of HCC following hepatectomy, especially in patients developing a solitary metastatic LN without concurrent uncontrolled intrahepatic or extrahepatic tumors.

References

10. Park YJ, Lim do H, Paik SW, Koh KC, Lee JH, Choi MS, Yoo