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The Clinical Significance of Lymph Node Metastases in Patients Undergoing Surgery for Hepatocellular Carcinoma

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Abstract The frequency of lymph node (LN) metastasis in patients undergoing surgery for hepatocellular carcinoma (HCC) has rarely been studied. We evaluated the clinicopathologic characteristics and outcomes of six patients with nodal metastases from HCC among a total of 504 patients who underwent hepatic resection for HCC in our department over a 16-year period. The nodal metastases were diagnosed preoperatively in two patients. The average diameter of the resected tumors was 7.8 cm and all were confirmed as poorly differentiated HCC. All of the six patients had intrahepatic metastatic nodules and five also had portal vein invasion. One patient underwent limited resection, and the other five underwent bisegmentectomy. All of the regional LNs were removed in one patient, while only enlarged LNs were removed in the other five. One patient died of postoperative liver failure and the others all died later of intrahepatic or nodal recurrence. Our findings suggest that the prognosis of patients with nodal metastasis from HCC is generally poor, even if hepatic resection with regional LN dissection is performed.

Key words Hepatocellular carcinoma · Lymph node metastasis · Hepatic resection

Introduction

According to autopsy series, the prevalence of lymph node (LN) metastasis from hepatocellular carcinoma (HCC) ranges from 25% to 33%.[1–4] In contrast, a prevalence of 2.2% was reported in a series of Japanese patients who underwent hepatic resection.[4] Therefore, the clinical significance of LN metastases in patients undergoing hepatic resection for HCC is poorly understood.[5–7,9] We analyzed the various clinical and pathologic features of six patients with LN metastasis from HCC who underwent curative hepatic resection.

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Patients and Methods

Of a total of 504 Japanese patients who underwent hepatic resection for HCC between 1981 and 1997 in our department, six underwent LN dissection for LN metastases. Of these patients, two were found to have LN enlargement by preoperative computed tomography (Figs. 1 and 2a,b), while the remaining four were found to have nodal metastases during surgery. The clinicopathologic features and outcomes of these six patients were investigated.

Results

The mean age of the six patients was 62.5 years, with a range of 56–68 years, and a male-to-female ratio of 5:1. Three patients had an abnormal elevation of serum α-fetoprotein, while the hepatitis B surface antigen was detected in two patients. The hepatitis C virus antibody was found in two of the three patients tested. None of the patients had Child-Pugh[10] class C cirrhosis. In two patients, the tumor was located in the lateral segment and in the other four it was located in the right lobe (Table 1). The tumor diameter ranged from 4.0 to 16.0 cm, with a mean diameter of 7.8 cm. Right or left bisegmentectomy was performed in five patients, while limited resection was performed in one. We resected only enlarged LNs in five patients, while the remaining patient (patient 6) underwent regional LN dissection (Table 1). All patients had poorly differentiated HCC. Intrahepatic metastatic nodules and portal vein invasion were found in six and five patients, respectively. One patient had cirrhosis of the liver.

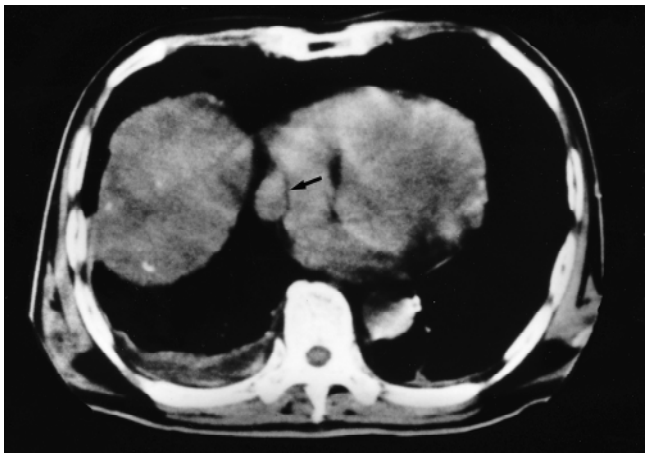


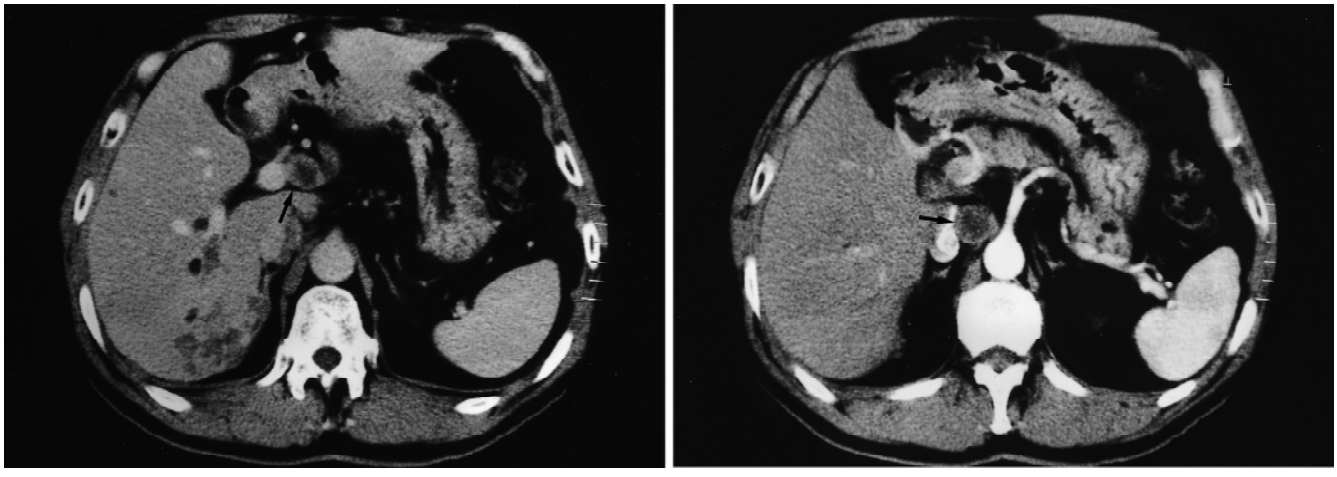
Fig. 1. Contrast-enhanced computed tomography revealed an enlarged diaphragmatic lymph node in the right thoracic cavity (*arrow*)

Hepatoduodenal LN metastases were common, whereas retropancreatic and para-aortic LN metastases were rare (Table 1). Common hepatic LN metastases were observed in both of the patients with tumors in the left lobe.

There was one perioperative death (patient 3) as a result of postoperative liver failure (Table 2). Within 14 months of surgery, the other five patients had developed either intrahepatic or LN recurrence, and all died. Four deaths resulted from multiple intrahepatic recurrences, and the other patient died of liver failure secondary to obstruction of the extrahepatic bile duct and portal vein by LN metastases.

Discussion

According to an autopsy series, LN metastases from HCC were found in 24.6% of patients with cirrhosis and 43.9% of those without cirrhosis.[1] Since the progression



a **b**

Fig. 2. Contrast-enhanced computed tomography revealed a lymph node in the hepatoduodenal ligament (**a**, *arrow*). A para-aortic lymph node (**b**, *arrow*) was also found to be enlarged

Table 1. Surgical procedures and pathologic findings

Patient	Location (segment)	Tumor diameter (cm)	Hepatic resection	Tumor invasion		Cirrhosis	Site of LN dissection[a]
				vp	im		
1	2	5.5	Limited	+	+	+	d, ch
2	5/6/7/8	11.0	A+P	+	+	−	hl
3	7	5.5	A+P	−	+	−	hh, hl
4	3	4.5	L+M	+	+	−	hl, ch
5	7/8	16.0	A+P	+	+	−	d
6	6/7	4.0	A+P	+	+	−	hh, hl, rp, pa

A+P, right bisegmentectomy; L+M, left bisegmentectomy; vp, portal vein invasion; im, intrahepatic metastatic nodules; hh, hepatic hilum; hl, hepatoduodenal ligament; d, diaphragmatic; rp, retropancreatic; ch, common hepatic arterial; pa, para-aortic

[a] All dissected LNs had tumor involvement

Table 2. Outcome after hepatic resection with lymph node dissection

Patient	Interval to recurrence (days)	Location of recurrence	Interval to death (days)	Cause of death
1	178	Liver, abdominal lymph node	424	Intrahepatic recurrence
2	22	Liver	132	Intrahepatic recurrence
3	—	—	13	Liver failure
4	163	Abdominal lymph node	204	Liver failure
5	64	Liver, para-aortic lymph node	237	Intrahepatic recurrence
6	395	Liver, cervical lymph node	423	Intrahepatic recurrence

of cirrhosis exacerbates lymphatic obstruction, cirrhosis may decrease the rate of occurrence of LN metastasis.[11–13] We previously reported that 77% of 452 patients who underwent hepatic resection for HCC in our department within a 15-year period had cirrhosis of the liver.[14] However, in the present study only one of six patients with LN metastases from HCC had cirrhosis. Moreover, LN metastasis from HCC is found much less frequently at surgery than at autopsy.[5–7,9] The apparently lower incidence of LN metastasis at surgery may incorporate such biases as the fact that LN dissection is not routinely performed at hepatectomy for HCC. An additional factor that is possibly responsible for differences in prevalence between surgical and autopsy series is the effect of known LN metastasis on decisions not to operate. Another is the timing of the operation, since many patients undergo surgery early in the course of HCC, while the opposite chronological bias applies to autopsy.

Hepatitis B and C infections are known to play important roles in the development of HCC.[4,15] In fact, four of our six patients were chronically infected with a hepatitis virus, although no clear relationship between the type of viral hepatitis and the presence of LN metastasis was observed. Tumor size and the degree of local invasion have also been shown to be related to LN metastasis in patients with HCC.[1,5] In the present study, four patients had tumors larger than 5 cm in diameter and five had both portal vein invasion and intrahepatic metastatic nodules, while one had only intrahepatic metastatic nodules. In our previously reported series, 29% of 452 patients had portal vein invasion, and 36.5% had intrahepatic metastatic nodules while the average diameter of the resected HCC tumors was 4.0 cm.[14] These intraoperative findings were the factors most predictive of local recurrence after surgery. Other authors have also reported that portal vein invasion and intrahepatic metastatic nodules are predictive of LN metastasis.[3,6]

The two main hepatic lymphatic drainage routes, namely, capsular lymphatics and intrahepatic lymphatics, are structurally defined.[11,12] Although most lymphatics course toward the hepatic hilum, other lymphatics are directed toward the triangular ligaments and communicate with the diaphragmatic lymphatics. The involvement of lymphatics in the vicinity of HCC may lead to LN metastases via either of these two routes. For left lobe tumors, common hepatic, celiac, and lesser curvature LN metastases have been reported to be most common.[7] In this study, two patients who had tumors in the left lobe were also found to have common hepatic LN metastases, while two of four patients who had LN metastasis in the hepatoduodenal ligament were found not to have hepatic hilar LN metastasis. These were cases of so-called skip metastasis.[1,5–7,9] Cirrhosis results in the formation of collateral routes of lymphatic drainage,[6] which may explain such skip metastases.

The prognosis of patients with LN metastases from HCC is generally poor.[4–8] In our previous series of 452 patients, the 1-, 3-, and 5-year survival rates after surgery for HCC were 85%, 75%, and 46%, respectively.[14] On the other hand, five of the six patients in the present study with LN metastases suffered recurrence within 395 days, and all five died within 424 days of surgery. The other patient died of postoperative liver failure.

Although external radiation therapy for abdominal LN metastasis of HCC has proven effective for relieving symptoms and inducing tumor shrinkage, it is not curative.[16] Moreover, the chemosensitivity of HCC is low.[17] Therefore, some authors have suggested that dissection of affected LN offers the only chance of long-term survival. Thus, the treatment of patients with LN metastases from HCC remains controversial. We suggest that prophylactic LN dissection is not necessary for patients with HCC, since regional LN recurrence after hepatic resection for HCC is rare and most deaths do not result from the LN metastasis.[9] In the present series, since none of our patients survived long-term after hepatectomy with LN dissection, we were unable to determine the usefulness or the indications for LN dissection for LN metastasis from HCC. Some authors consider that long-term survival may be achieved in patients with skip metastasis of the LNs by the dissection of only enlarged LNs if there are only a few.[5,6,9] Considering the potential for debilitating complications of regional LN dissection such as ascites and hepatic failure, we believe that limited lymphadenectomy of

only enlarged LNs should be performed until a more effective treatment for LN metastasis from HCC is established.

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