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Case Report

Surgical Resection of Metachronous Lymph Node Metastasis From Hepatocellular Carcinoma: Three Case Reports and Review of the Literature

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The prognosis for hepatocellular carcinoma (HCC) patients with lymph node (LN) metastasis is generally poor, and no consensus has yet been reached on the optimum treatment strategy. We observed 3 cases involving patients with HCC and associated metachronous LN metastasis, who benefited from surgical resection of the metastatic LNs. Each of the 3 patients had solitary LN metastasis for which selective LN resection was performed, and all had C-type cirrhosis as a background disease. There were no other uncontrolled lesions at the time of LN resection. However, additional treatments were required in cases 1 and 3 to control intrahepatic lesions that recurred following the lymphadenectomy. The overall survival in cases 1 and 3 has been >5 years, with case 1 still under observation. Case 2 also remains under follow-up at 6 months after surgery. Surgical resection could be a beneficial strategy for treatment of metachronous LN metastasis arising from HCC in some cases, particularly those involving a solitary LN metastasis with no other uncontrolled lesions.

Key words: Hepatocellular carcinoma – Lymph node metastasis – Resection of lymph node – Prognosis

Hepatocellular carcinoma (HCC) is one of the most common malignancies and claims about 598,000 deaths annually worldwide.[1,2] There are 2 types of metastases from HCC: intrahepatic and extrahepatic. In the extrahepatic form, hematogenous metastasis from HCC is a well-known pattern, with the most frequent sites being the lungs, adrenal glands, and bones.[3,4] In contrast, lymphogenous

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Table 1 Background of the 3 cases in the present study

Characteristics	Case 1	Case 2	Case 3
Age (years)	62	62	65
Sex	Female	Male	Male
Infection	HCV	HCV	HCV
Medical history (related to HCC)	2007∼2009: RFA × 4 2009: LNR 2009∼2014: TACE × 1 RFA × 3 2014: LAP-H	2011: LAP-H 2011: TACE × 1 2014: LNR	2002: Hepatectomy 2003: TACE × 2 2004: LNR 2004∼2009: TACE × 10

LAP-H, laparoscopic hepatectomy; LNR, lymph node resection.

metastasis is very rare, with the prevalence of lymph node (LN) metastasis accounting for 0.0% to 7.5% of operable HCC cases.[3,5–11]

On the other hand, there are cases of metachronous LN metastasis from HCC without intrahepatic recurrence; the incidence in a retrospective study by Tomimaru *et al*[12] was 9 in 961. Regarding metastases arising from carcinomas of other digestive organs, para-aorta metachronous LN metastasis is a systemic disease and is therefore a contraindication to surgery.[13] However, no consensus has yet been reached on the optimal treatment strategy for metachronous LN metastasis from HCC. We herein report 3 cases involving patients who underwent surgical resection for metachronous LN metastasis from HCC, review the existing literature, and discuss the significance of surgical resection of metachronous LN metastasis from HCC.[12–20]

Case 1

A 62-year-old woman was referred to our hospital in February 2004 because of liver dysfunction [alanine transaminase (ALT), 250 IU/L] that was identified by an annual health checkup. She was diagnosed with liver cirrhosis due to hepatitis C virus (HCV) on the basis of findings from blood tests, abdominal computed tomography (CT), and ultrasonography (US). She had undergone blood transfusions at 20 and 28 years of age because of dysmenorrhea and during delivery, respectively.

In January 2007, an abdominal CT scan revealed 25- × 21- and 10- × 10-mm HCCs in segments (S)4/8 and S4, respectively, for which radiofrequency ablation (RFA) was performed. Until 2009, the patient had undergone RFA 4 times for intrahepatic recurrence of HCCs (Table 1). In January 2009, an abdominal CT scan revealed an enlarged 20- × 40-mm para-aortic LN, which was diagnosed as LN metastasis from HCC, lying beneath the renal artery and vein and sandwiched between the abdominal aorta and inferior vena cava (Fig. 1a). She was admitted to our hospital, and surgical resection of the LN was performed in March 2009. The postoperative course was uneventful, and she was discharged on postoperative day (POD) 6. A 35- × 28- × 15-mm retroperitoneal LN was dissected (Fig. 1b). Histopathologically, the LN was consistent with a metastasis from HCC. The serum concentration of α-fetoprotein (AFP) decreased from 2217.6 ng/ml (normal, <10 ng ml) to 408.9 ng/ml and to 67.6 ng/ml after lymphadenectomy (Table 2).

Following the lymphadenectomy, the patient underwent transcatheter arterial chemoembolization (TACE) once and RFA 3 times. In July 2014, an abdominal CT scan detected HCC recurrence in S2. No other uncontrolled intrahepatic or extrahepatic lesion was detected; therefore, surgical intervention (laparoscopic hepatectomy) was chosen as the treatment. The operation was performed in August 2014; there were no postoperative complications, and she was discharged on POD 5. She is doing well at present, with no evidence of recurrence.

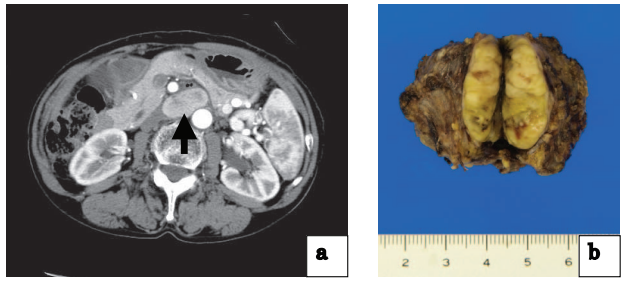

Fig. 1 (a) Abdominal CT scan showing an enlarged para-aortic LN beneath the renal artery and vein and sandwiched by abdominal aorta and inferior vena cava (↑ arrow). (b) Resected retroperitoneal LN. A 35- × 28- × 15-mm lymph node with a yellowish cut section encapsulated by fibrous tissue.

Table 2 Clinical data of the 3 cases in the present study

	LNM		AFP (ng/ml)		PIVKA-2 (mAU/ml)	
Case	Site	Size (mm)	Pre-LNR	Post-LNR	Pre-LNR	Post-LNR
Case 1	Ao	35 × 28 × 15	2217.6	67.6		
Case 2	H	37 × 32 × 24	2.2	3.2	537	17
Case 3	P	70 × 40 × 32	47.1	41.7	168	42

Ao, para-aortic LN; H, hepatic hilar LN LNM, lymph node metastasis; P, peri-pancreatic LN.

Case 2

A 62-year-old man was admitted to our hospital in January 2011 because of HCCs in S2 and S6. He had liver cirrhosis due to HCV infection yet had no history of surgical operation or blood transfusion. Laparoscopic hepatectomy was performed for HCC in S2 and S6. During the observation period, HCC recurred in S7, for which TACE was performed in November 2011 (Table 1).

In September 2014, an abdominal CT scan revealed enlargement of an abdominal LN to 22 mm in diameter in the hepatoduodenal ligament (Fig. 2a). No other intrahepatic or extrahepatic metastatic lesions were detected. Therefore, surgical dissection of the LN was performed. The postoperative course was uneventful, and the patient was discharged on POD 6. A 37- × 32- × 24-mm hepatoduodenal ligament LN was dissected (Fig. 2b). Histopathologically, the LN was consistent with metastasis from HCC. There was no change in the serum concentration of AFP (2.2 to 3.2 ng/ml) before and after the lymphadenectomy; however, protein induced by vitamin K antagonist-2 (PIVKA-2) decreased to normal after the operation (537 to 17 mAU/ml; normal, <37 mAU/ml; Table 2). The patient is doing well at present, without any evidence of recurrence.

Case 3

A 65-year -old man was referred to our hospital in 2002 because of a 35-mm HCC in S3 detected by abdominal US. He had undergone a blood transfusion at the age of 35 years due to undergoing a gastrectomy for a gastric ulcer. He was diagnosed as having liver cirrhosis due to HCV at 50 years of age.

In November 2002, an S3 hepatectomy was performed. In 2003, recurrence of HCC was identified, for which TACE was performed twice (Table 1). In 2004, a CT scan revealed an LN metastasis in the retro-pancreatic space. No other extrahepatic metastasis was detected, and the intrahepatic lesions were controlled by TACE. Therefore, the LN was resected in August 2004. The patient was discharged with no postoperative complications on POD 4. A 70- × 40- × 32-mm retro-pancreatic LN was dissected (Fig. 3). Histopathologically, the LN was compatible with a metastasis from HCC. There was no significant change in the serum concentration of AFP before and after the lymphadenectomy; however, PIVKA-2 decreased from 168 to 42 mAU/ml after the operation (Table 2).

The patient had intrahepatic recurrence of HCC after resection of the metastatic LN, for which TACE was performed 10 times in total until August 2009, when he was referred to another hospital for palliative care.

Discussion

The common sites of LN metastases from HCC are the hepatic pedicle, retro-pancreatic space, and common hepatic artery. These are the sites of regional LN metastasis from HCC.[9] However, synchronous LN metastasis from HCC is very rare, and the incidence of LN metastasis in patients with operable HCC ranges from 0% to 7.5%.[3,5–11] Therefore, complete and prophylactic dissection of LN metastasis, which is commonly performed in carcinomas of other digestive organs, is not commonly

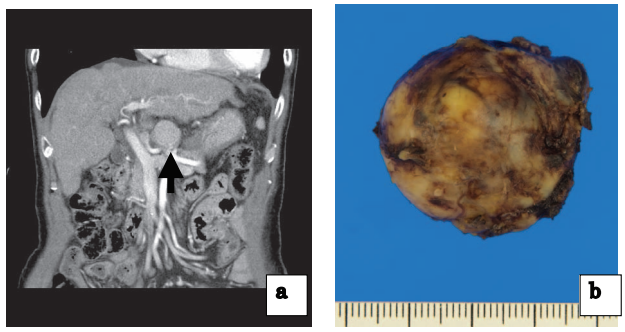

Fig. 2 (a) Abdominal CT showing an enlarged abdominal LN in the hepatoduodenal ligament (↑ arrow). (b) Resected 37- × 32- × 24-mm hepatoduodenal ligament LN.

Fig. 3 A resected 70- × 40- × 32-mm retro-pancreatic LN.

performed to treat HCC. On the other hand, the risk of intra- and postoperative complications (*e.g.*, lymphatic leakage, hepatic failure) due to complete LN dissection in patients with HCC with liver cirrhosis is high in most cases, and the postoperative prognosis remains poor, even if hepatic resection with regional LN dissection is performed.[21,22]

According to Tomimaru *et al*,[12] 22 of 961 patients who underwent surgical resection for HCC had metachronous LN metastasis, and 9 had no active lesions, other than the LNs. Intrahepatic metastasis can be well controlled by re-hepatectomy, TACE, or RFA. However, there are no established effective treatment modalities, including TACE or RFA, for LN metastasis from HCC. Therefore, surgical resection of metastatic LNs remains the only modality for the potential curative treatment of HCC. However, resection is not an established treatment strategy, and the role of the surgical resection of LN metastases in HCC remains controversial. Some researchers have previously reported that long-term survival could be expected after the surgical resection of metachronous LN metastases of HCC, particularly in patients who develop a solitary metastatic LN without concurrent uncontrolled intrahepatic or extrahepatic tumors.[15–17]

In a recent retrospective study of 961 patients who underwent surgical resection for HCC, 38 patients displayed LN metastasis (synchronous:-metachronous = 16:22).[12] Twenty-two of these 38 patients had complete resection of metastatic LNs, whereas the remaining 16 had either incomplete removal or did not undergo surgery for the metastatic LNs. The overall survival rate of the completely removed group was significantly higher than that of the other group. This finding suggests the benefit of surgical resection of LN metastasis from HCC regardless of the time of occurrence (synchronous or metachronous), as long as complete resection is expected and there are no viable lesions other than the LN metastases.[12]

Each of our 3 patients had a solitary LN metastasis that was metachronous. All 3 patients had C-type liver cirrhosis as a background disease. The initial treatment for HCC was hepatectomy in cases 2 and 3, whereas RFA was used in case 1. The intervals of LN recurrence from the initial treatments were 24, 44, and 21 months in cases 1, 2, and 3, respectively. Case 1 had a disease-free survival of 5 years and 4 months after surgical resection of the LN. Intrahepatic recurrence of HCC was later identified, for which RFA was performed 3 times and TACE and hepatectomy were performed once each. The patient is still under observation with no evidence of recurrence. After resection of the metastatic LN in case 2, the period of postoperative observation was 6 months, and the patient remains disease free today. Case 3 survived 5 years after resection of the metastatic LN, although he underwent TACE 10 times to control intrahepatic recurrence during that period. The overall survival rates in our 3 cases are consistent with those in previous reports, which also described the benefits of surgical resection of metachronous LN metastasis (Table 3).

Most HCCs are encapsulated, a significant characteristic that differentiates it from carcinomas of other digestive organs. This means HCC grows by expanding the capsule, whereas other carcinomas grow by infiltrating the organs surrounding the primary tumor.[18] There are also cases of so-called "skip LN metastasis" in HCC, which is a less common pattern of lymphogenous metastasis at distant sites without metastases in the hepatoduodenal ligament.[23,24] These LNs are often solitary, which is extremely rare in gastric or colon cancers. Therefore, para-aortic LN metastasis may not indicate systemic spread of the tumor in cases of HCC, and the outcome appears to be improved compared to those in malignancies of other gastro-

Table 3 Summary of the literature related to metachronous LN metastasis from HCC

Literature	No. of patients	HCV: HBV: non-B/C	LNM		Interval (months)	OS (years)	Recurrence after LN resection
			Site(s)	So: Mu			
Tomimaru *et al*[12]	9	5:3:1	Ao5, M1, P2, CHA2, G1, H1	6:3	18.56 (2∼82)	3.24 (0.6∼8.1)	3+ (8 alive)
Utsumi *et al*[15]	4	1:1:2	Ao1, M2, P2	3:1	23.75 (19∼31)	2.2 (1.1∼2.4)	3+ (3 alive)
Kobayashi *et al*[17]	13	B/C:non-B/C	Ao3, M3, G4, P4, H3, CHA1	13:5	36 (4∼124)	2.42 (1.7∼3.2)	12+
	18	= 13:5					
Hashimoto *et al*[13]	8	8:0:0	Ao4, P7, G2, CHA1	4:4	30.25 (1∼82)	2.36 (0.7∼6.1)	2+ (4 alive)
Kakisaka *et al*[20]	1	HBV	H1	So	9	7.42	+ (alive)
Ueda *et al*[19]	1	HBV	Ao	So	6	0.5	− (alive)
Kurokawa *et al*[16]	1	Non-B/C	G	So	19	5	− (alive)
Akamoto *et al*[18]	1	HCV	Ao	So	18	2	+ (alive)
Ochiai *et al*[14]	1	HCV	H	So	45	7	+ (alive)
Present study	3	HCV	Ao1, H1, P1	So	30 (21∼44)	3.83 (0.5∼6)	2+ (2 alive)

Kobayashi *et al*'s report represents the data of metachronous and synchronous LN metastasis combined. CHA, common hepatic artery LN; HBV, hepatitis B virus; M, mediastinal LN; Mu, multiple; non-B/C, non-HBV, non-HCV; OS, overall survival; So, solitary.

intestinal organs.[13,19] The LNs in cases 1 and 3 were regional LNs, but case 2 exhibited skip LN metastasis.

All 3 of our patients had C-type liver cirrhosis, although no clear relationship between the type of viral infection and presence of LN metastasis has been reported.[5] However, cirrhosis appears to have an effect on skip LN metastasis. The progression of cirrhosis leads to the obstruction of lymphatic flow and then to the formation of collateral lymphatic drainage, which may produce so-called skip metastases.[23] The initial treatment of HCC may also alter lymphatic and blood flow around the liver to produce skip metastasis.

Conclusion

There is no established effective treatment modality for metachronous LN metastasis from HCC. Selective resection could be the only beneficial strategy in the treatment of metachronous LN metastasis from HCC. However, it should be restricted to cases with particularly solitary LN metastasis and with no other uncontrolled lesions. Nonetheless, a multi-institutional study comprising a large number of patients is necessary to make any definitive conclusion on the feasibility and efficacy of surgical resection for LN metastasis arising from HCC.

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