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Significance of Hepatic Lymph Node Metastasis in Patients With Unresectable Synchronous Liver Metastasis of Colorectal Cancer

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The frequency and significance of hepatic lymph node (HLN) metastasis were retrospectively evaluated in 43 patients with unresectable synchronous liver metastasis of colorectal cancer who underwent resection of the primary tumor and histopathologic evaluation of HLNs between March 1997 and August 2007. HLN metastasis was detected in 12 patients (27.9%). No significant correlations were observed between the presence of HLN metastasis and any of the 12 clinicopathologic factors examined. On multivariate analysis using the Cox proportional hazards model, the presence of HLN metastasis ($P = 0.002$), along with a large number (≥4) of regional lymph node metastases ($P = 0.003$), and nonuse of oxaliplatin-based chemotherapy ($P = 0.005$) were identified as independent risk factors for shorter survival. To establish a new therapeutic strategy for initially unresectable liver metastasis of colorectal cancer, HLNs should be examined histologically in patients undergoing resection of hepatic lesions when they are rendered resectable by effective chemotherapy.

Key words: Hepatic lymph node – Liver metastasis – Colorectal cancer

Hepatic lymph node (HLN) metastasis, known to be a re-metastasis[1] from liver metastasis in cases of colorectal cancer, is considered to be a poor prognostic factor following potentially curative hepatic metastatectomy.[2,3] Recent advances in effective chemotherapy[4–8] have increased the resection rate of liver metastases of colorectal cancer that are considered unresectable at initial diagnosis. How-

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ever, little has been reported about the frequency and significance of HLN metastasis in such cases. This retrospective study was performed to examine the status of HLN metastasis in patients with initially unresectable synchronous liver metastasis of colorectal cancer, and to highlight the significance of HLN metastasis in the era of effective chemotherapy.

Patients and Methods

This study was approved by the local ethical committee of Saitama Medical University.

Patients

Data on 43 patients with unresectable synchronous liver metastasis of colorectal cancer who underwent resection of the primary lesion and histologic examination of HLNs between March 1997 and August 2007 were retrospectively evaluated. In terms of the level of lymph node dissection, along with resection of the primary lesion, D3-level dissection, including removal of pericolic, intermediate, and main lymph nodes, according to the Japanese Classification of Colorectal Carcinoma,[9] was performed in 41 patients, and D2-level dissection, which included removal of the same lymph node groups as above, except the main lymph nodes, was performed in the remaining 2 patients. No patients had peritoneal dissemination, paraaortic lymph node involvement, or distant metastasis other than liver metastasis. During this period, we defined 5 or more hepatic lesions located in both lobes, lesions infiltrating all 3 hepatic veins, and lesions associated with massive infiltration of the inferior vena cava as ''unresectable.''

HLN examination

Systematic lymph node dissection of the hepatoduodenal ligament was not performed. Instead, lymph nodes along the common hepatic and/or proper hepatic artery were routinely examined. When the common hepatic artery was absent (substituted by the replaced hepatic artery), lymph nodes in contact with the superior border of the pancreas, if present, were regarded as lymph nodes along the common hepatic artery and were biopsied. Additional sampling of other hepatic lymph nodes that were considered to be significantly hard in consistency or swollen (>10 mm) was also performed during surgery. Cholecystectomy was routinely undertaken in patients in whom hepatic arterial infusion chemotherapy was scheduled as postoperative treatment. Written informed consent was obtained from each patient for both the hepatic lymph node examination and cholecystectomy. The sites of hepatic lymph nodes were classified according to the Classification of Biliary Tract Carcinoma.[10]

Postoperative treatment

The postoperative treatment modality has undergone many changes over the years. Within the present study period, from 1997 to 2005, hepatic arterial chemotherapy was considered one of the useful treatment modalities for unresectable liver metastasis, and was a rather common clinical practice in Japan. From September 1999, 5-fluorouracil (FU)/leucovorin (LV); from October 2003, one of the oral fluoropyrimidines called UFT (Tegafur/Uracil) and LV; and from January 2004, another oral fluoropyrimidine called S-1 were approved for use against metastatic colorectal cancer. Thus, all of these treatments were offered as options at our institution, just as hepatic arterial chemotherapy was another option. For hepatic arterial chemotherapy, weekly high-dose 5-FU infusion (WHF)[11] or bolus infusion of mitomycin C and doxorubicin was used. For WHF, intravenous LV was sometimes used concomitantly, as appropriate. Also, along with bolus infusion of mitomycin C and doxorubicin, one of the oral fluoropyrimidines was used. Modified FOLFOX6 (mFOLFOX6), one of the oxaliplatin-based chemotherapeutic regimens, has been used as the first-line regimen since May 2005, when oxaliplatin first became available in Japan.

Factors evaluated

Factors evaluated included (1) patient-specific information: age, sex, serum carcinoembryonic antigen (CEA) level (cutoff, 6.7 ng/mL), types of operations performed, and postoperative chemotherapy; (2) characteristics of the primary tumor: location, macroscopic appearance, maximal diameter, and pathologic features of the tumor such as the number of metastatic regional lymph nodes, depth of invasion, differentiation, and lymph-vascular invasion [The macroscopic appearance, differentiation, and lymph-vascular invasion were described according to the Japanese Classification of Colorectal Carcinoma.[9] Specifically, lymphatic/venous invasion was classified into 4 categories—ly0/v0, ly1/v1, ly2/v2, and ly3/v3—representing no, minimal,

moderate, and severe invasion, respectively. The depth of invasion and the number of metastatic regional lymph nodes were categorized according to the tumor-node-metastasis (TNM) classification[12]; and (3) characteristics of the liver metastases: location, number, and volume of liver metastases. The volume of liver metastasis was calculated on serial contrast-enhanced computed tomography (CT) images.

The site and frequency of HLN metastasis were evaluated, and the relationships between HLN metastasis and the aforementioned factors were examined. Prognostic factors were assessed by univariate and multivariate analyses.

Statistics

Distributions of continuous variables were expressed as median and range. Data were compared by Mann-Whitney *U*-test or χ^2 test, as appropriate. The cumulative survival rate was calculated by the Kaplan-Meier method, and differences in survival curves were determined by the log-rank test. Multivariate regression analysis by Cox proportional hazards model was used to identify independent risk factors for overall survival. Continuous variables were dichotomized before they were entered into univariate and multivariate analyses. Variables with $P < 0.10$ by univariate analysis (log-rank test) were entered into the multivariate analysis. *P* values < 0.05 were considered to denote statistical significance. All statistical analyses were performed using a statistical software package (StatView, version 5.0, SAS Institute, Cary, North Carolina, USA).

Results

Patient characteristics

Patient characteristics are shown in Table 1. A total of 26 men and 17 women, with a median age of 60 years (range, 33–85 years), were included. The distribution of the liver metastasis was bilobar in all patients. The hepatic lesion was considered unresectable in 41 cases with 5 or more sites of liver metastasis, because even with preoperative portal vein embolization, it would have been difficult to achieve a remnant liver volume greater than 40% in these cases. In 2 cases with only 2 metastatic foci, hepatic lesions were considered unresectable, because these cases exhibited invasion of all 3 hepatic veins. The primary tumor was located in the right colon in 15 patients, in the left colon in 15 patients, and in the rectum in 13 patients. The type of resection of the primary lesion was right hemicolectomy in 11 patients, transverse colectomy in 2 patients, left hemicolectomy in 3 patients, sigmoidectomy in 10 patients, anterior resection in 10 patients, abdomino-perineal resection in 2 patients, Hartmann's procedure in 2 patients, and other segmental colectomies in 3 patients. With regard to

Table 1 Patient characteristics

Characteristics	
Age, y[a]	60 (33–85)
Sex	
Male:Female	26:17
Location of the primary tumor	
Right colon	15
Left colon	15
Rectum	13
Type of surgery	
Colectomy	29
Anterior resection	10
Hartmann's procedure	2
Abdomino-perineal resection	2
Macroscopic appearance	
Type 1 (polypoid type)	2
Type 2 (ulcerated type with clear margin)	30
Type 3 (ulcerated type with infiltration)	11
Maximal diameter of the primary tumor, mm[a]	50 (17–140)
Differentiation	
Well differentiated	13
Moderately differentiated	28
Poorly differentiated	2
Depth of invasion	
pT2	3
pT3	15
pT4	25
Number of harvested regional lymph nodes[a]	16 (4–54)
Number of metastatic regional lymph nodes[a]	4 (0–18)
Regional lymph node metastasis	
pTN0	5
pTN1	22
pTN2	16
Carcinoembryonic antigen level, ng/mL[a]	72.3 (1.5–22880)
Number of liver metastases	
≥5	41
2	2
Volume of liver metastases, cm^{3a}	120 (28–1546)
Postoperative first-line chemotherapy	
Best supportive care	5
Hepatic arterial chemotherapy	22
Systemic chemotherapy other than mFOLFOX6	9
mFOLFOX6	7

[a]Median (range).

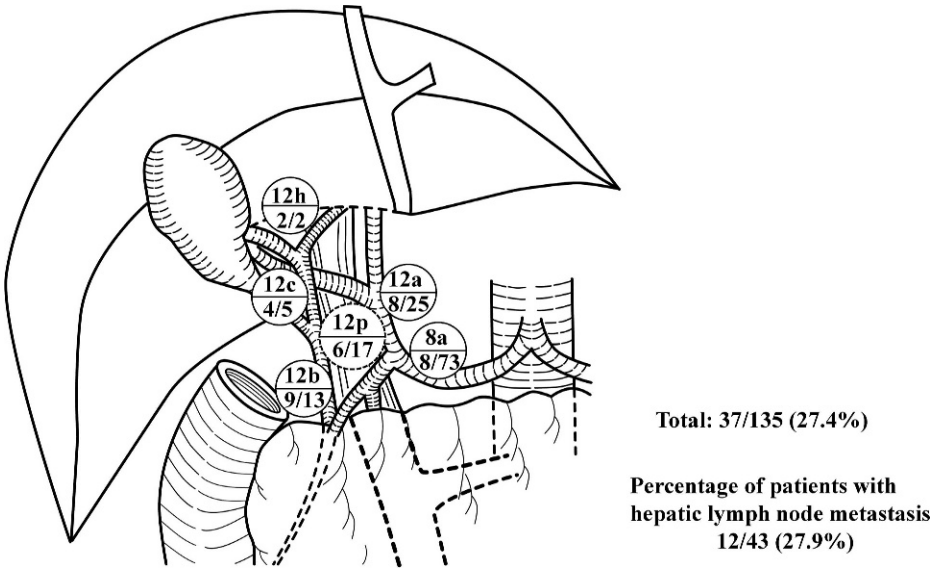

Fig. 1 Distribution of harvested hepatic lymph nodes and percentage of positive nodes. Lymph nodes are classified according to the Classification of Biliary Tract Carcinoma.

the macroscopic appearance of the primary lesion, the tumor was type 1 (polypoid type) in 2 patients, type 2 (ulcerated type with clear ulceration) in 30 patients, and type 3 (ulcerated type with infiltration) in 11 patients. The median maximal diameter of the primary tumor was 50 mm (range, 17–140 mm).

Histologic examination revealed well-differentiated adenocarcinoma in 13 patients, moderately differentiated adenocarcinoma in 28 patients, and poorly differentiated adenocarcinoma in 2 patients. The depth of tumor infiltration was pT2 in 3 patients, pT3 in 15 patients, and pT4 in 25 patients. The median number of harvested regional lymph nodes was 16 (range, 4–54), and the median number of metastatic lymph nodes was 4 (range, 0–18). The lymph node metastasis was categorized as pTN0 in 5 patients, pTN1 in 22 patients, and pTN2 in 16 patients. The median preoperative serum CEA level was 72.3 ng/mL (range, 1.5–22,880 ng/mL). The median metastatic tumor volume was 120 cm^3 (range, 28–1545 cm^3).

As for postoperative treatment, 5 patients received best supportive care with no chemotherapy. The type of chemotherapy given as first-line therapy included hepatic arterial chemotherapy in 22 patients, systemic chemotherapy in 9 patients (intravenous in 3 patients and oral in 6 patients), and mFOLFOX6 in 7 patients.

HLN metastasis

No postoperative complications were associated with resection of the primary lesion or removal of the HLNs. In only 1 case, HLN metastasis was suspected from preoperative CT images. The harvested HLN sites are shown in Figure 1: No. 12a (lymph nodes along the proper hepatic artery), No. 12p (lymph nodes behind the portal vein), No. 12b (lymph nodes along the common bile duct), No. 12h (lymph nodes in the hepatic hilum), No. 12c (lymph nodes near the cystic duct), and No. 8a (anterosuperior group of lymph nodes along the common hepatic artery). A total of 135 HLNs were harvested, and 37 (27.4%) were positive for metastasis. HLN metastasis was detectable in 12 patients (27.9%), including 1 in whom HLN involvement was suspected on preoperative CT images. The median number of HLNs harvested was 3 (range, 2–14) in patients with HLN metastasis and 1 (range, 1–15) in patients without HLN metastasis. The median number of positive HLNs in patients with HLN metastasis was 3 (range, 1–8).

Demographic and clinicopathologic variables according to the presence/absence of HLN metastasis

Relationships between the presence of HLN metastasis and the 12 clinicopathologic factors examined are shown in Table 2. No significant differences were noted between patients with (n = 12) and without (n = 31) HLN metastases with regard to age, sex, or tumor characteristics such as location, maximal diameter, macroscopic appearance, depth of invasion, differentiation, lymph-vascular invasion, metastatic regional lymph node metastases,

Table 2 Patient characteristics according to the presence/absence of hepatic lymph node metastasis

Characteristics	Hepatic lymph node metastasis (+) (n = 12)	Hepatic lymph node metastasis (-) (n = 31)	*P* value
Age, y[a]	60 (33–65)	60 (34–81)	0.34
Sex (male:female)	8:4	18:13	0.86
Location (colon:rectum)	8:4	22:9	> 0.99
Maximal diameter, mm[a]	60 (30–80)	50 (17–140)	0.50
Macroscopic appearance (type 1:type 2:type 3)	0:8:4	2:22:7	0.55
Depth of invasion (pT2:pT3:pT4)	1:2:9	2:13:16	0.30
Regional lymph node metastasis (pTN0:pTN1:pTN2)	0:7:5	5:15:11	0.30
Differentiation (well:moderately/poorly)	2:10	11:20	0.29
Lymphatic invasion (ly2/ly3:ly1/ly0)	6:6	10:21	0.31
Venous invasion (v2/v3:v1/v0)	8:4	15:16	0.46
Carcinoembryonic antigen level, ng/mL[a]	102.5 (21.2–22,880.0)	68.8 (1.5–1633.9)	0.09
Volume of liver metastases, cm^{3a}	184 (23–924)	117 (28–1546)	0.22

[a]Median (range).

and metastatic tumor volume, although the serum CEA level tended to be higher in patients with HLN metastasis ($P = 0.09$) (Table 2).

Prognostic factors

The median follow-up period was 13 months (range, 2–54 months). Cumulative 1-, 2-, and 3-year survival rates were 45.5%, 21.3%, and 12.5%, respectively. In January 2011, only 2 patients were alive, and the remaining 41 had died of the disease. There were no patients in whom liver metastases were rendered resectable by postoperative chemotherapy. Two patients with HLN metastasis developed obstructive jaundice postoperatively; 1 of these patients died of the disease with no additional treatment 2 months later, and the other patient, who showed partial response to hepatic arterial chemotherapy, successfully underwent percutaneous transhepatic biliary drainage and stenting, followed by reintroduction of hepatic arterial chemotherapy.

The median survival period (days) and the cumulative 1-year and 2-year survival rate according to the factors examined are shown in Table 3. On univariate analysis by the log-rank test, hepatic lymph node metastasis (present versus absent, $P = 0.01$), number of metastatic regional lymph nodes (≥4 versus 0–3, $P = 0.09$), and oxaliplatin-based chemotherapy (mFOLFOX6) (use versus nonuse, $P = 0.03$) were selected as the covariables associated with survival (Table 3); these factors were included in the Cox multivariate regression analysis. The latter also identified the 3 variables as independent significant factors associated with survival. The hazard ratio (95% confidence interval) for shorter survival was 3.68 (1.65–8.20) for hepatic lymph node metastasis ($P = 0.002$), 3.00 (1.40–6.45) for a large number (4 or more) of metastatic regional lymph nodes ($P = 0.003$), and 6.12 (1.85–20.22) for nonuse of oxaliplatin-based chemotherapy ($P = 0.005$), respectively (Table 4).

Discussion

HLN metastasis is considered to be a re-metastasis[1] from liver metastases via lymphatic flow. The lymphatics drain the liver by several routes[13,14]: (1) through the porta hepatis caudad along the hepatic artery to the HLNs, and then to the celiac axis and to the lymph nodes located between the aorta and the infrarenal vena cava before reaching the thoracic duct, (2) along the falciform ligament to the supradiaphragmatic right phrenic lymph nodes, and then to the mediastinal or internal mammary lymph node chains, (3) through the esophageal hiatus, the caval foramen, and, transdiaphragmatically, to the supradiaphragmatic right phrenic and mediastinal lymph nodes, (4) along the superior border of the lesser omentum to the pericardial upper gastric lymph nodes, and (5) along the phrenic arteries directly to the celiac axis. HLN metastasis is believed to occur via the first route described. Most surgeons regard HLN metastasis as extrahepatic disease and would not proceed with hepatectomy because the presence of extrahepatic disease implies a dismal prognosis.[2,3]

According to a systematic review[2] of surgery for colorectal liver metastasis with HLN metastasis, 5-year survivors among patients with HLN metastasis were rare (3.4%). However, several recent studies[15,16] have suggested that hepatectomy may not be contraindicated even in such cases, because long-

Table 3 Median survival time and cumulative survival rate according to demographic and clinicopathologic factors

Factors	Median survival time, days	Survival rate, %		*P* value
		1-year	2-year	
Age, y				
≥65 (n = 22)	358	50.0	18.2	0.67
<65 (n = 21)	470	71.1	17.4	
Sex				
Male (n = 26)	371	53.6	16.5	0.32
Female (n = 17)	486	70.6	20.2	
Location of the primary tumor				
Colon (n = 30)	395	59.5	19.7	0.57
Rectum (n = 13)	455	61.5	15.4	
Maximal diameter of the primary tumor				
≥50 mm (n = 24)	474	66.4	24.6	0.2
<50 mm (n = 19)	371	52.6	10.5	
Depth of invasion				
pT2/pT3 (n = 18)	462	72.2	16.7	0.93
pT4 (n = 25)	387	51.4	19.3	
Number of metastatic regional lymph nodes				
0–3 (n = 27)	474	73.7	23.3	0.09
≥4 (n = 16)	395	37.5	8.3	
Differentiation				
Well differentiated (n = 13)	484	76.9	36.8	
Moderately/poorly differentiated (n = 30)	371	52.9	12.1	0.18
Lymphatic invasion				
ly2/ly3 (n = 16)	304	66.7	18.5	0.22
ly0/ly1 (n = 27)	474	42.9	21.4	
Venous invasion				
v2/v3 (n = 23)	404	60.6	14	0.84
v0/v1 (n = 20)	372	60	23.3	
Carcinoembryonic antigen level				
≥100 ng/mL (n = 19)	462	68.4	24.1	0.42
<100 ng/mL (n = 24)	372	53.6	13.4	
Hepatic lymph node metastasis				
Presence (n = 12)	251	33.3	0	0.01
Absence (n = 31)	462	67.7	19.4	
Metastatic volume				
≥120 cm^3 (n = 22)	387	54.2	14.8	0.61
<120 cm^3 (n = 21)	455	66.7	21.8	
Postoperative treatment				
mFOLFOX6 (n = 7)	576	57.1	42.9	0.03
Other chemotherapy/best supportive care (n = 36)	395	57.9	12.9	

term survivors have been reported following hepatectomy combined with effective preoperative chemotherapy. The frequency of HLN metastasis has been reported to be 1% to 20%[2] among patients undergoing hepatic metastatectomy of colorectal cancer; when the analysis was restricted to patients undergoing *en bloc* resection of the HLNs, the frequency was reported to be 13% to 28%.[2] To the best of our knowledge, this is the first report describing the site and frequency of HLNs in detail in patients with unresectable synchronous liver metastases.

Table 4 Independent risk factors for shorter survival by multivariate analysis

Factors	Hazard ratio (95% confidence interval)	*P* value
Hepatic lymph node metastasis		
Positive	3.68 (1.65–8.20)	0.002
Negative	1	
Number of regional lymph node metastases		0.003
≥4	3.00 (1.40–6.45)	
0–3	1	
mFOLFOX6 therapy		0.005
Nonuse	6.12 (1.85–20.22)	
Use	1	

No general consensus has been reached regarding the extent of involvement of the HLNs because the search area seems to differ among reports. Jaeck *et al*[17] dissected HLNs systematically in patients with resectable colorectal liver metastasis and reported that survival was significantly better in patients with HLN metastasis limited to the hepatoduodenal ligament and the retropancreatic portion than in those with HLN metastasis extending over the common hepatic artery and celiac axis. Kokudo *et al*[18] and Nakamura *et al*[19] performed *en bloc* dissection of HLNs according to the Classification of Biliary Tract Carcinoma.[10] Specifically, Kokudo *et al*[18] examined, in detail, the frequency and sites of HLN metastasis in 75 patients undergoing hepatic metastatectomy. We classified the distribution of HLNs in accordance with the method of Kokudo *et al.*[18] There may be criticism that the frequency of HLN metastasis (27.9%) in the present study might be an underestimate because our method of HLN harvesting was not *en bloc* dissection. During this study period, we harvested HLN metastasis, not based on evidence, but to avoid obstructive jaundice secondary to rapid growth of HLN metastasis after primary resection of the tumor. Such a consequence would surely hinder the continuation of postoperative chemotherapy. Therefore, it was a feasible method to look for HLN metastasis without significant complications.

Because lymph nodes of the major lymphatic pathways between liver and porta hepatis, along the proper hepatic artery and the common hepatic artery,[13,14] were routinely harvested, there should be no concern that sufficient lymph node dissection was not performed. Furthermore, the median number of lymph nodes that we harvested was 3 per patient (range, 2–4), and Kokudo *et al*,[18] who performed *en bloc* HLN dissection, had an average of 2.4 per patient (range, 1–11). Thus, the results were comparable.

Only a few studies[20,21] have focused on prognostic factors for survival in patients with unresectable synchronous liver metastasis because such aggressive disease has remained outside surgeons' interest for a long time. The present study has clearly shown that HLN metastasis, along with 4 or more regional metastatic lymph nodes and nonuse of oxaliplatin-based chemotherapy (mFOLFOX6), was an independent prognostic factor for shorter survival. In addition, it is notable that HLN metastasis is a poor prognostic factor, just as in previously reported resectable cases. The reasons for the negative impact of HLN metastasis on survival are unclear: one possible explanation is that HLN metastasis is merely a reflection of other lymphatic spread, for example, to the mediastinal lymph nodes, even though we did not detect such metastases in this series. The other explanation pertains to the aggressiveness of the tumor itself, even though biomarkers associated with such a nature of the tumors have not been clarified yet and deserve further investigation. The negative impact of HLN metastasis on survival is in agreement with the report by Chang *et al*,[22] who demonstrated significantly shorter survival in patients with HLN metastasis (n = 8) than in patients without HLN metastasis (n = 18), all of whom were given hepatic arterial chemotherapy. To the best of our knowledge, their report is the only one available discussing the impact of HLN metastasis on the survival of patients with unresectable liver metastasis colorectal cancer.

Various clinicopathologic factors examined were found to be not predictive of the presence of HLN metastasis; therefore, the development of new diagnostic markers to predict such metastasis is needed. HLN metastasis was suspected on preoperative CT images in only 1 case. The only method for definitive diagnosis of metastasis is actual histologic examination of the lymph nodes.

We previously examined the sizes of HLNs on paraffin-embedded slides and demonstrated that it is difficult to discriminate between the presence and absence of metastasis in HLNs by their size alone.[23] In a recent meta-analysis,[24] both the sensitivity and the specificity of FDG-PET imaging for the detection of extrahepatic lesions exceeded 90%, as compared with only 60.9% and 91.1%, respectively, for CT. Furthermore, a systematic review[25] of FDG-PET imaging results in patients with colorectal liver metastasis has revealed that FDG-PET may detect extrahepatic disease not identified by other modal-

ities in 10% to 32% of patients. Adam *et al*[15] reported that among 47 patients undergoing hepatic metastatectomy with systematic HLN dissection, PET-CT was performed in 6 patients, and HLN metastasis was detected in 4 patients, suggesting the usefulness of PET-CT. However, additional cases are needed to validate the diagnostic usefulness of FDG-PET for predicting the presence of HLN metastasis.

In the past, almost all initially unresectable patients were treated by systemic or locoregional chemotherapy, which yielded 5-year survival rates less than 5%.[26–28] The introduction of new anticancer drugs (oxaliplatin or irinotecan) combined with molecular targeting agents, such as bevacizumab or cetuximab, as standard treatments for metastatic colorectal cancer has resulted in better outcomes. For example, oxaliplatin-based regimens, mainly FOLFOX, produced a reduction in the sizes of initially unresectable liver metastases and allowed hepatic metastatectomy in 16% to 47%[4,6,7] of such patients. However, the frequency and clinical significance of HLN metastasis in such patients have not yet been clarified. Adam *et al*[15] partly addressed the issue: they reported that combined hepatectomy and HLN dissection are justified when metastatic HLNs respond to or are stabilized by preoperative chemotherapy in young patients; however, their report has limitations in that all eligible patients received preoperative chemotherapy regardless of the resectability of hepatic lesions at initial diagnosis.

In conclusion, the frequency of HLN metastasis (27.9%) seems to be rather high in patients with synchronous ''unresectable'' liver metastasis at initial diagnosis, and the presence of HLN metastasis was an independent poor prognostic factor. To establish a new therapeutic strategy for ''initially unresectable'' liver metastasis of colorectal cancer in the era of effective chemotherapy, HLNs should be examined histologically in patients undergoing hepatectomy for initially unresectable lesions can be detected when they are rendered resectable by effective chemotherapy.

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