ELSEVIER Original Article

Hepatic Resection for Hepatocellular Carcinoma With Lymph Node Metastasis: Clinicopathological Analysis and Survival Outcome

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OBJECTIVE: Lymph node metastasis (LNM) rarely occurs in hepatocellular carcinoma (HCC). Few studies have reported the potential risk factors of LNM and the influence of LNM on the progression and prognosis of HCC. The purposes of this study were to explore the clinicopathological characteristics of operable HCC with LNM and to demonstrate the effects of LNM on HCC prognosis.

METHODS: A retrospective review of 2,034 HCC patients undergoing surgery from 1982 to 2005 was performed. The influence of LNM was assessed by clinicopathological factors, tumour recurrence, and overall survival. A total of 66 randomly selected patients matched for clinicopathological variables were used to analyse the difference in survival.

RESULTS: A total of 25 patients (1.23%) were reported to have LNM. Higher preoperative carcinoembryonic antigen levels (> 10 ng/mL) were significantly associated with a higher incidence of LNM than were low preoperative carcinoembryonic antigen levels (≤ 10 ng/mL) (15.38% *vs.* 3.79%, $p = 0.042$). Furthermore, HCC with LNM (N1 disease) was larger in size (mean, 9.44 *vs.* 5.85 cm, $p = 0.016$) and significantly associated with vascular invasion, worse histological grade, and nonencapsulation ($p = 0.002$, < 0.001, and < 0.001, respectively). Finally, patients with HCC accompanied by LNM had shorter mean disease-free survival and overall survival ($p = 0.001$ and < 0.001, respectively).

CONCLUSION: This study identified the worst prognosis of HCC in a population with LNM. HCC with LNM tends to be the infiltrating type with larger tumour size (> 5 cm), presence of microvascular invasion, and worse histological grade. Liver resection with lymphadenectomy is possibly beneficial for patients with HCC accompanied by LNM. [*Asian J Surg* 2011;34(2):53–62]

Key Words: hepatic resection, hepatocellular carcinoma, hepatoma, lymph node metastasis, prognosis

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver with an estimated annual death incidence of 598,000 worldwide. In Taiwan, it is the second most common cause of cancer death and causes more than 7,500 deaths each year.[1] Surgical resection remains the most effective therapy in selected patients, but approximately 75% of patients with HCC have advanced unresectable diseases upon presentation. In addition,

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metastasis to peri-hepatic lymph nodes noted during surgery is historically deemed to be a poor prognostic factor.[2–5] Compared with other malignancies such as lung cancer, oesophageal cancer, renal cancer, gastric cancer, and intra-hepatic cholangiocarcinoma, the incidence of lymph node metastasis (LNM) in HCC is very low, and data regarding HCC with LNM are quite limited.[6–12]

Previous reports have shown that the survival of patients with HCC accompanied by LNM matched the survival of those with major vascular invasion (T3).[2] Therefore, they proposed simplification of the fifth edition of AJCC (American Joint Committee on Cancer) Cancer Staging Manual by regrouping T3N0M0 tumours into stage IIIA and T1–4N1M0 tumours into stage IIIB. The latest seventh edition of AJCC Cancer Staging Manual has further classified N1 diseases into stage IVa because the survival of N1 disease is comparable with that of M1 disease.[13] These studies and the TNM staging system suggested that HCC with LNM is associated with a dismal prognosis. However, very few studies have reported the potential risk factors of LNM.

Recent studies revealed that higher carcinoembryonic antigen (CEA) expression can be found in patients with LNM and recurrent tumours of fibrolamellar carcinoma, a rare variant of HCC.[14] In addition, a high serum CEA level is also linked to a more advanced stage of pancreatic cancer[15] and is an appropriate marker for early detection of recurrent colorectal liver metastasis.[16] Thus, CEA expression might be associated with a more aggressive biological behaviour of HCC, such as LNM, distant metastasis, and recurrences. Nevertheless, there are no studies demonstrating the possible relationships between the CEA level and clinical characteristics of HCC, especially LNM.

Therefore, the aims of this study were to explore the clinicopathological characteristics of operable HCC with LNM and to demonstrate the effects of LNM on HCC prognosis in a large cohort of HCC patients. In addition, the predictive value of CEA levels on LNM was investigated, which may detect patients at risk of LNM and allow for the implementation of appropriate treatment.

Patients and methods

Patients

From 1982 to 2005, records of patients with histologically proven primary HCC from the Cancer Registry of the Cancer Center, Chang Gung Memorial Hospital, Linkou, Taiwan, were retrospectively reviewed. Only patients who underwent either curative hepatectomy or exploratory laparotomy for tissue diagnosis (operable HCC confirmed by imaging) by the same surgical team were included in our study. A total of 2,034 patients were evaluated, and their clinicopathological data were retrieved from the prospectively collected database. The following variables were included in the analyses: age, gender, cigarette smoking, alcohol consumption, hepatitis B virus (HBV) infection, anti-hepatitis C virus antibody (anti-HCV) level, albumin level, bilirubin level, preoperative alpha-foetoprotein level, preoperative CEA level, tumour-LNM status, tumour encapsulation, histological grade, tumour recurrence, and mortality. The study endpoint was 30 June 2010, and tumour staging was based on the 6th edition of AJCC TNM staging system for HCC.[17]

This study was conducted in a retrospective case-control manner. HCC patients with pathologically proven LNM were compared with those without LNM. Absence of LNM was confirmed by the following three criteria: (1) negative reports of preoperative computed tomography scans, interpreted by experienced radiologists; (2) no intra-operative detectable enlarged lymph nodes, proven by experienced hepatobiliary surgeons; and (3) negative postoperative pathological report of LNM in the resected specimen, examined by pathologists who were experts in hepatology.

Surgical procedures

The indications for surgery included a lack of cancerous thrombi in the main trunk of the portal vein, no distant metastasis to other organs, and a technically operable main tumour in the preoperative evaluation.[18–20] Suspected LNM restricted to the hepatoduodenal ligament, detected by a preoperative image study, was defined as HCC operable by experienced surgeons, and hepatectomy combined with lymph node dissection was performed.

If the tumour and LNM invaded or encased major vessels or if cancerous carcinomatosis was identified during surgery, the tumour was deemed unresectable and only a wedge biopsy of the liver mass was performed for a postoperative histological diagnosis. The hepatic hilum and hepatoduodenal ligament were carefully examined and palpated to detect any enlarged lymph nodes by the chief surgeons. Any enlarged lymph node was considered suspicious for metastasis, and lymphadenectomy was performed if the main tumour was resectable. Lymphadenectomy

meant complete excision of soft tissue and lymph nodes (skeletonisation) at the hepatic hilum, hepatoduodenal ligament, and common hepatic artery stations. In addition, any other enlarged lymph nodes in the vicinity of the primary tumour were removed for pathologic diagnosis. On the other hand, only an incisional biopsy of the enlarged lymph node was performed if the primary tumour was unresectable. All resected or biopsied specimens were examined by independent experienced pathologists.

Statistical analysis

The statistical analysis was performed with SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA). Fisher's exact test and Pearson's χ^2 test were used to analyse categorical data. Student's *t* test was used to analyse quantitative variables. Compared with 22 patients with LNM, a total of 66 randomised patients matched for clinicopathological variables were selected to conduct the survival analysis. Overall survival (OS) was defined by the time elapsing from the date of diagnosis to either the date of death or the date of the last contact. Disease-free survival (DFS) was calculated from the date of surgery to the date of the first documented clinical disease recurrence. Cases with surgical mortality, defined as death within one month of surgery, and patients who received only operative biopsy for tissue proof were excluded from the survival analyses. Kaplan-Meier analysis was used to determine the OS and DFS.[21] The log-rank test was applied to compare survival outcomes between or among groups. Statistical significance was defined as $p < 0.05$.

Results

Demographic data

A total of 2,034 patients with histologically proven HCC were enrolled. Among them, 1,594 (78.33%) were males and 441 (21.67%) were females. The mean age was 55 years (4–88 years). HBV infection was detected in 1,215 (63.41%) patients, and anti-HCV was detected in 533 (28.05%) patients. A total of 585 (49.65%) patients had T1 disease, 223 (12.91%) had T2 disease, 392 (22.69%) had T3 disease, and 255 (14.76%) had T4 disease according to the sixth edition of the AJCC TNM staging system for HCC.[17] Intra-operative lymphadenectomy or lymph node biopsy was performed in 170 (8.36%) patients because of a suspicious enlarged lymph node, but only 25 (1.23%) patients had pathologically proven LNM (N1 disease). A total of 50 (4.19%) patients developed distant metastases (M1 disease) until the endpoint of this study. Of 25 patients with LNM, three underwent only open biopsy for a postoperative histological diagnosis. Of the 195 lymph nodes dissected from these 25 N1 patients, 77 were neoplastic (mean, 3.08; range, 1–8). The number of metastatic lymph nodes was not related to patient survival ($p = 0.13$).

Clinicopathologic characteristics with respect to LNM

The relationship between clinical characteristics and LNM in HCC is summarised in Table 1. Age, gender, cigarette smoking, and alcohol consumption were not significantly associated with LNM. In terms of viral infection, neither HBV infection nor HCV infection were related to development of LNM (1.23% *vs.* 1.28%, $p = 0.587$, with *vs.* without HBV infection, respectively; and 0.75% *vs.* 1.44%, $p = 0.265$, with *vs.* without HCV infection, respectively). Preoperative albumin, bilirubin, alpha-foetoprotein levels, and tumour T stage were not significantly associated with LNM. However, patients with high preoperative CEA levels (> 10 ng/mL; normal is ≤ 5 ng/mL in our hospital) had a higher incidence of LNM than did those with low preoperative CEA levels (≤ 10 ng/mL) (15.38% *vs.* 3.79%, $p = 0.042$). The result was still statistically significant when the mixed tumours (combined HCC and cholangiocarcinoma) were excluded from the analysis (15.38% *vs.* 3.48%, $p = 0.031$). Furthermore, M1 disease was significantly associated with LNM compared with M0 disease (8.00% *vs.* 0.96%, $p < 0.001$).

Tumour size of greater than 5 cm, encapsulated HCC, tumours with microvascular invasion, cancerous thrombi, and worse histological grade were associated with a higher incidence of LNM. HCC with LNM was larger in size (mean diameter, 9.44 cm) compared with HCC without LNM (5.85 cm; $p = 0.016$). Nevertheless, effects of tumour rupture and daughter nodules in LNM did not reach statistical significance ($p = 0.631$ and 0.857, respectively) (Table 2).

Patient survival with respect to LNM

The overall median DFS was 15.9 months (95% CI, 13.6–18.2 months) in this study. The 2-year DFS rate was 0% in N1 disease and 34.1% in N0 disease ($p = 0.001$). The median DFS was 5.8 months (95% CI, 4.0–7.6 months) in HCC with LNM and 16.3 months (95% CI, 13.9–18.2 months) in HCC without LNM ($p = 0.001$). The DFS of HCC with and without LNM is illustrated in Figure 1.

Table 1. Relationship between clinical characteristics and lymph node metastasis (LNM) in hepatocellular carcinoma (HCC)

	Without LNM	With LNM (%)	*p*
Age (yr)			
≤60	1,149	16 (1.37)	0.514
>60	849	9 (1.05)	
Sex			
Male	1,568	21 (1.32)	0.490
Female	435	4 (0.91)	
Cigarette smoking			
Yes	776	15 (1.90)	0.208
No	1,038	10 (0.95)	
Alcohol			
Yes	563	9 (1.57)	0.496
No	1,038	10 (0.95)	
HBV			
Positive	1,200	15 (1.23)	0.587
Negative	540	7 (1.28)	
Unknown	151	3 (1.95)	
HCV			
Positive	529	4 (0.75)	0.265
Negative	888	13 (1.44)	
Unknown	458	8 (1.72)	
Preoperative AFP (ng/mL)			
>400	1,213	15 (1.22)	0.934
≤400	588	7 (1.18)	
Preoperative CEA (ng/mL)			
Including mixed tumour*			
≤10	305	12 (3.79)	0.042
>10	11	2 (15.38)	
Excluding mixed tumour			
>10	305	11 (3.48)	0.031
≤10	11	2 (15.38)	
Albumin (g/dL)			
≤2.8	67	1 (1.47)	0.776
>2.8	1,617	18 (1.10)	
Total bilirubin (mg/dL)			
≤2	1,718	20 (1.15)	0.708
>2	130	2 (1.52)	
T stage			
T1	853	5 (0.58)	0.072
T2	220	3 (1.35)	
T3	488	4 (0.81)	
T4	248	7 (2.75)	
M stage			
M0	1,131	11 (0.96)	<0.01
M1	46	4 (8.00)	

*Combined HCC and intra-hepatic cholangiocarcinoma. HBV = hepatitis B virus; HCV = hepatitis C virus; CEA = carcinoembryonic antigen.

Table 2. Relationship between pathological features and lymph node metastasis (LNM) in hepatocellular carcinoma (HCC)

	Without LNM	With LNM (%)	*p*
Tumour size (cm)			
≤ 5	981	6 (0.61)	0.011
> 5	899	17 (1.90)	
Mean tumour size (cm)	5.85	9.44	0.016
Encapsulation			
Yes	1,182	5 (0.42)	< 0.001
No	497	14 (2.73)	
Tumour rupture			
Yes	214	1 (0.47)	0.631
No	1,665	20 (1.19)	
Microvascular invasion			
Yes	454	13 (2.78)	0.002
No	1,253	5 (0.40)	
Cancerous thrombi			
Yes	516	14 (2.64)	0.003
No	1,460	5 (0.34)	
Daughter nodules			
Yes	374	2 (0.54)	0.857
No	1,303	11 (0.83)	
Edmonson and Steiner grade			
I	78	1 (5.32)	< 0.001
II	920	2 (10.53)	
III	760	4 (21.15)	
IV	162	12 (63.15)	

The median OS was 50.93 months (95% CI, 43.5–58.3 months) in this study. The 1-year, 3-year, and 5-year OS rates for N0 disease were 72.6%, 54.9%, and 38.4%, respectively. The 1-year, 3-year, and 5-year OS rates for N1 disease were 36.4%, 13.6%, and 13.6%, respectively. Five N1 patients survived for more than 2 years after the operation. The median OS was 11.0 months (95% CI, 8.4–13.6 months) in HCC with LNM and 52.3 months (95% CI, 44.6–60.0 months) in HCC without LNM ($p < 0.001$). Of patients with LNM, radical operation and lymphadenectomy resulted in significantly longer OS (median OS, 11.3 months; 95% CI, 5.4–17.3 months) compared with only open biopsy for tissue proof (median OS, 0.95 months; 95% CI, 0.64–1.3 months) ($p = 0.012$). The three patients who underwent only open biopsy for a postoperative histological diagnosis died of complications of metastatic portal vein thrombi and liver failure. The OS of HCC with and without LNM is depicted in Figure 2. The DFS and OS outcomes are summarised in Table 3.

Figure 3 shows the OS curve of 66 randomised N0 patients and 22 N1 patients. The selected N0 patients were matched with N1 patients for age, gender, viral status, T stage, M stage, and resection margins. All of these patients underwent radical operations for their primary HCC. Three N1 patients who underwent only open biopsy for a histological diagnosis were excluded from this analysis. Two of these three patients succumbed to surgical mortality. HCC with LNM was still significantly associated with worse OS than HCC without LNM when the other variables were matched ($p = 0.001$).

A total of 13 of 22 N1 HCC patients who underwent surgery developed recurrence. The recurrence rate was 59%. The most common site of recurrence was intra-hepatic (9 patients, 69.2%), followed by peritoneal (3 patients, 23.1%) and retroperitoneal (1 patient, 7.7%). The mean overall survival of the nine patients without recurrence was 6.02 months, with the longest reaching 15.5 months. Among them, one patient died of inadvertent choking

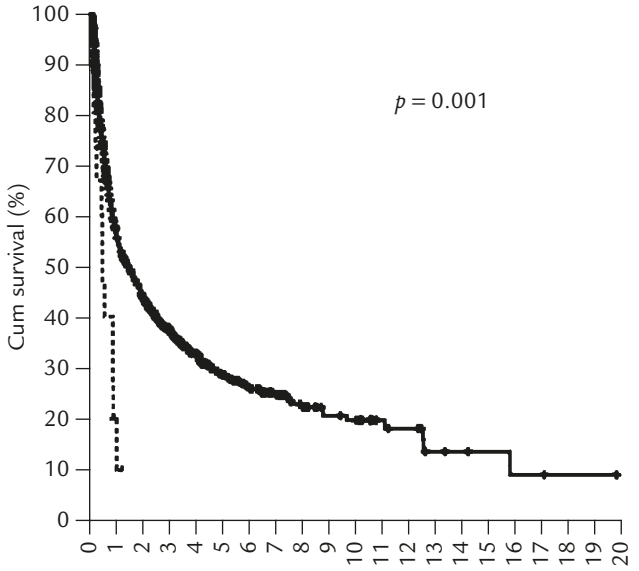

Figure 1. Disease-free survival (DFS) of hepatocellular carcinoma (HCC) with and without lymph node metastasis (LNM). The solid line represents N0 patients, and the dashed line represents N1 patients. The horizontal axis is the survival in years, and the vertical axis is the percentile cumulative survival. The median DFS was 5.8 months (95% CI, 4.0–7.6 months) for HCC with LNM and 16.3 months (95% CI, 13.9–18.2 months) for HCC without LNM ($p = 0.001$). HCC with LNM had a significantly poorer DFS. HCC = hepatocellular carcinoma; LNM = lymph node metastasis.

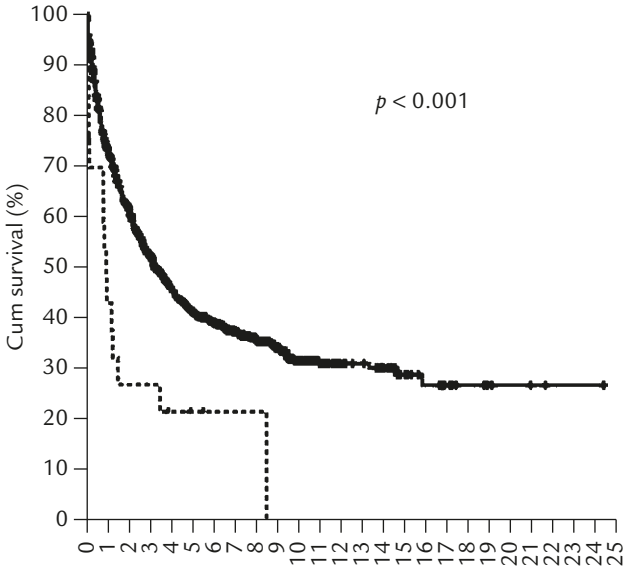

Figure 2. Overall survival (OS) of hepatocellular carcinoma (HCC) with and without lymph node metastasis (LNM). The solid line represents N0 patients, and the dashed line represents N1 patients. The horizontal axis is the survival in years, and the vertical axis is the percentile cumulative survival. The median OS was 11.0 months (95% CI, 8.4–13.6 months) for HCC with LNM and 52.3 months (95% CI, 44.6–60.0 months) for HCC without LNM ($p < 0.001$). HCC with LNM had a significantly poorer OS. HCC = hepatocellular carcinoma; LNM = lymph node metastasis.

Table 3. Survival outcomes with respect to lymph node metastasis (LNM) in hepatocellular carcinoma (HCC)

	Mean (95% CI)	Median (95% CI)	*p*
Disease-free Survival (mo)			
Without LNM	54.2 (46.8–61.6)	16.3 (13.9–18.2)	0.001
With LNM	7.2 (4.9–9.4)	5.8 (4.0–7.6)	
Operation	7.6 (5.3–9.8)	6.7 (4.9–8.6)	0.013
Biopsy only	1.7 (1.7–1.7)	1.71 (–)	
Overall	53.8 (46.5–61.2)	15.9 (13.6–18.2)	
Overall survival (mo)			
Without LNM	54.2 (46.8–61.6)	52.3 (44.6–60.0)	< 0.001
With LNM	29.7 (11.6–47.7)	11.0 (8.4–13.6)	
Operation	32.5 (12.6–52.3)	11.3 (5.4–17.3)	0.012
Biopsy only	3.9 (0.0–9.9)	0.95 (0.64–1.3)	
Overall	118.9 (108.9–128.7)	50.93 (43.5–58.3)	

and respiratory failure 2 months after surgery, two died of liver failure and ascites more than 2 months after surgery, and another patient died of gastric ulcer bleeding 1.5 months after surgery. The remaining three patients did not develop recurrences until the endpoint of this study, and the last two patients did not come to our clinic for follow-up after stabilisation of their disease.

Discussion

The incidence of LNM in operable HCC is very low. Changchien et al[22] in a hospital-based retrospective analysis in 2008, reported that 1.5% of 6,381 HCC patients developed LNM. However, 2,890 (42.3%) patients in the study were not treated, and fewer than 10% of patients

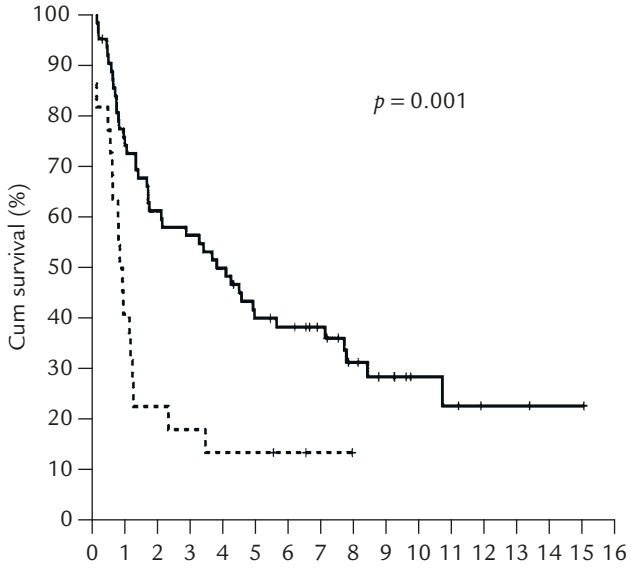

Figure 3. Survival outcomes matched for clinicopathological variables. The solid line represents N0 patients, and the dashed line represents N1 patients. The horizontal axis is the survival in years, and the vertical axis is the percentile cumulative survival. A total of 66 randomly selected N0 patients matched for age, sex, viral status, T stage, and resection margin with 22 N1 patients were analysed. Three N1 patients who underwent only biopsy for tissue proof were excluded. HCC with LNM still had a significantly poorer OS than HCC without LNM when these variables were matched ($p = 0.001$). HCC = hepatocellular carcinoma; LNM = lymph node metastasis.

underwent surgery. Thus, the results may not be appropriately applied to the operable HCC patients. In a 2007 study evaluating the value of routine complete lymphadenectomy, Sun et al[23] indicated that the incidence of LNM was 5.1% (49/968). According to the study performed by the Liver Cancer Study Group of Japan[24] in 1990, 417 of 1,374 patients had LNM (30.3%) in the autopsy series. The incidence was 1.7% to 2.2% in resectable cases. Grobmyer et al[25] sampled perihepatic lymph nodes in 100 patients undergoing resection for primary and metastatic hepatic malignancy. Eleven patients had HCC and none developed LNM (0%). In 2002, Vauthey et al[2] proposed a simplified staging system for HCC and reported that, in their series, the incidence of LNM was 3.2% (18/557). In a prospective study, Ercolani et al[26] performed routine lymphadenectomy in 120 patients undergoing liver resections for hepatic malignancies and reported that 7.5% of operable HCC patients had LNM. Being the second largest study in terms of patient number, our study showed that the incidence of LNM was 1.23% (25/2,034). This result is compatible with those of the other reports, confirming the rarity of LNM in operable HCC patients. The incidence and respective findings of HCC with LNM in the literature are summarised in Table 4.[2,22–26,30]

Table 4. Incidence and clinical pictures of HCC with LNM in the literature[2,22–26,30]

Author, yr	No. of LNM	No. of patients	Incidence (%)	Special remarks
Shen, 2010[30]	39	523	7.45	Risk factors for LNM included multiple nodules, cancerous thrombi, noncirrhotic liver, and nonhepatitis status
Changchien, 2008[22]	94	6,381	1.5	≤ 10% of total patients underwent surgery
Sun, 2007[23]	49	968	5.1	Risk factors for LNM included CA-199, satellite lesions, large tumour (> 5 cm), cancerous thrombi, no HBV/HCV infection, and absence of liver cirrhosis
Grobmyer, 2006[25]	0	11	0	Low yield when no evidence of LNM on pre-operative CT or PET scans or at the time of exploration
Ercolani, 2004[26]	3	40	7.5	Risk factors for LNM included multiple nodules
Vauthey, 2002[2]	18	557	3.2	Survival of lymph node involvement matched that of patients with major vascular invasion
Liver Cancer Study Group of Japan, 1990[24]	417	1,374	30.3	The incidence in resectable cases was 1.7–2.2%, autopsy series
Present study	25	2,034	1.23	Risk factors included tumour size, cancerous thrombi, tumour grading, tumour staging, and infiltrative growth pattern CEA may be helpful in predicting LNM

HCC = hepatocellular carcinoma; LNM = lymph node metastasis; HBV = hepatitis B virus; HCV = hepatitis C virus; CT = computed tomography; PET = positron emission tomography; CEA = carcinoembryonic antigen.

One might question the reliability of our intra-operative lymph node examination and indication for lymphadenectomy. In a retrospective review related to peri-hepatic lymph nodes, Kokudo et al[27] concluded that, "all positive nodes were macroscopically enlarged to a certain degree and palpated as firm by the surgeon." A very low rate of pathologically positive nodes among clinically unsuspicious nodes (1%) was also reported in a previous study. The incidence of definite occult metastatic disease was concluded to be very low, and routine intra-operative sampling of peri-hepatic lymph nodes without evidence of disease involvement on preoperative images or intra-operative explorations had a low yield.[25] This conclusion was echoed by another report which found a low incidence of missed LNM diagnosis and few benefits of routine complete lymphadenectomy.[23] In our experience, routine peri-hepatic lymph node dissection carried a higher risk of postoperative complications including ascites formation and may hamper further treatment such as liver transplantation. Our suggestion, therefore, was that intra-operative lymph node exploration (careful palpation and examination of the hepatic hilum and hepatoduodenal ligament), as opposed to routine lymph node dissection, should be adopted. Lymphadenectomy (skeletonisation) should be performed to remove lymph nodes with connective tissue in the hilar area, hepatoduodenal ligament, and common hepatic artery stations when suspicious enlarged lymph nodes are found intra-operatively.

Our study showed that a high preoperative CEA level (> 10 ng/mL) was significantly associated with the occurrence of LNM. This result was still statistically significant when mixed tumours (combined HCC and cholangiocarcinoma) were excluded from the analysis. Although lacking statistical significance, a recent study reported that patients with positive preoperative CA-199 (> 37 U/L) had a higher incidence of LNM (3.1% *vs.* 1.7%, $p = 0.412$).[23] However, their study did not investigate the relationship between CEA level and LNM. This relationship was mentioned in another report that showed that higher CEA expression can be found in patients with LNM and recurrent tumours of the fibrolamellar variant of HCC. They thus concluded that CEA expression might be associated with the aggressive biological characteristics of this tumour.[14] However, this conclusion was based on a case report study. In this study, a high preoperative CEA level of > 10 ng/mL is a risk factor for LNM in HCC, and HCC with LNM may be a special type that has the potential for dual differentiation into both HCC and intra-hepatic cholangiocarcinoma. Further studies, including immunohistochemical studies, are warranted to validate this hypothesis.

In addition to preoperative CEA level, a significantly higher incidence of LNM was associated with larger tumour size (> 5 cm), presence of microvascular invasion, and tumours with a worse histological grade. These findings were consistent with those of a recent report that showed that large tumours, cancerous thrombi, and satellite nodules were associated with LNM.[23] Furthermore, our study showed that HCC with LNM was usually nonencapsulated. HCC was first proposed to be classified into encapsulated and nonencapsulated in 1977. The authors suggested that encapsulated HCC was usually well differentiated with less frequent intravenous tumour invasion. They tended to have a slowly expanding growth pattern which rendered a longer survival.[28] Conversely, nonencapsulated HCC may have a more malignant behaviour. Therefore, HCC with LNM tends to be the infiltrating type that has a rapid growth pattern and invasive clinical behaviour. Altogether, our findings suggest that HCC with LNM may be a sign of advanced tumour stage, and more aggressive surgical treatment and more frequent postoperative follow-up should thus be applied whenever LNM is suspected or confirmed.

Our analyses show that HCC with LNM had a much worse DFS and OS than did HCC without LNM. After matching patients with and without LNM, OS was still significantly worse in patients with LNM. In other words, LNM was a poor prognostic factor for HCC. This corresponds with the proposal of Vauthey JN and the latest edition of AJCC on the TNM staging system of HCC in that LNM represents a more advanced stage. According to the Barcelona Clinic Liver Cancer staging classification,[29] HCC with LNM, which represents an advanced stage or stage C disease, should receive palliative treatments or new agents in the setting of phase II investigations or randomised controlled trials. In other words, radical resection is not suggested for HCC with LNM. However, our study found that hepatic resection and lymphadenectomy was associated with a better OS than only surgical biopsy for tissue proof. Although the OS of N1 disease was still significantly inferior to that of N0 disease after radical surgery, there were still five patients who survived for more than 2 years after surgery. In other words, aggressive surgical treatment is still suggested even when

LNM is noted pre- or intra-operatively. LNM was not a contraindication for curative surgery for HCC. Our result was comparable with that of the series reported by Shen et al[30] who concluded that LNM has a poor prognostic impact on HCC. The better outcome reported in that study was probably due to their routine performance of regional lymphadenectomy. Nevertheless, as discussed previously, our experience suggests that peri-hepatic lymph node dissection should only be performed when lymph node involvement is suspected pre- or intra-operatively.

This study had some limitations. First, because this study was a retrospective hospital-based analysis, incomplete data were inevitable when reviewing records from a very long time ago. Second, because the preoperative CEA level was not routinely obtained, the resulting statistical value may not be persuasive enough. Third, inconsistent surgery may be related to performance by different hepatobiliary surgeons. Therefore, a well-designed cohort study with long-term follow-up is required to further validate the results of our study.

In conclusion, this large-scale comprehensive analysis identified a low incidence of LNM in HCC and a very poor prognosis of HCC when LNM occurred. A high preoperative CEA level (> 10 ng/mL) is a significant risk factor for LNM in HCC. Patients should have their preoperative CEA level determined to evaluate the risk of LNM. HCC with LNM tends to be the infiltrating type with a larger tumour size (> 5 cm), presence of microvascular invasion, and poorer histological grade. Furthermore, liver resection with lymphadenectomy is possibly beneficial to patients with HCC accompanied by LNM. Therefore, LNM may not be a contraindication for curative resection for HCC, and more aggressive surgical treatment, including lymph node dissection, is suggested when LNM is suspected.

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