

Clinical Significance of Lymph Node Metastasis in Patients Undergoing Partial Hepatectomy for Hepatocellular Carcinoma

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Abstract

Background There are few detailed clinical reports about perihepatic lymph node (LN) assessment of hepatocellular carcinoma (HCC). The purpose of the present study was to evaluate the incidence, site, and impact on survival of LN metastasis in patients with HCC amenable to curative liver resection and routine regional lymphadenectomy.

Methods From January 2001 to June 2004, a total of 523 HCC patients undergoing curative hepatic resection and routine regional lymphadenectomy were included in this study. The incidence, site of LN metastasis in HCC patients, and its influence on survival were analyzed.

Results A total of 3433 lymph nodes were dissected from the 523 patients enrolled in this study and examined by pathologists. Among these patients, LN metastasis was found in 39 (7.45%) patients. Hepatic pedicle, retropancreatic space, and common hepatic artery stations were conventionally removed. The incidence of LN metastasis in the hepatic pedicle station was higher than that in the other stations ($p < 0.01$). The overall cumulative survival rate was significantly worse for patients with LN metastasis than for those without LN metastasis ($p < 0.01$). The median survival time was 28 months among the patients

with LN metastasis and 53 months among those without LN metastasis. Tumors had recurred in 82.05% (32/39) of patients with LN metastasis and in 57.64% (279/484) of those without LN metastasis ($p < 0.01$). Regional lymphadenectomy was considerably safe with a low intraoperative complication rate (0.95%).

Conclusions Lymph node metastasis in patients with HCC is closely related to a lower survival rate. Regional lymph node dissection should always be performed to determine the precise stage of the disease. Hepatic resection with regional lymphadenectomy is a safe procedure in patients with HCC.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common solid tumor in the world and accounts for about 500,000 deaths each year [1]. The highest incidence of HCC is seen in China [2, 3]. Although the overall survival rate for liver cancer patients has improved in China, the 5-year survival rate remains low [4].

Lymph node status is a definite prognostic factor in oncologic surgery and significantly affects long-term survival, as reported by the tumor staging system of the International Union Against Cancer (IUCC), which is the most widespread classification of malignant tumors worldwide [5]. The impact of lymph node (LN) metastasis on the survival rate has already been reported for lung cancer [6], esophageal cancer [7], and renal cancer [8]; and the prognostic value of LN metastasis has been strongly defined for breast carcinoma [9] and other gastrointestinal neoplasms [10–12]. However, there are few detailed clinical reports about perihepatic LN assessment of HCC and its relation to the survival rate.

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Hepatic resection remains the most effective therapy for selected patients with HCC. Regional lymphadenectomy is already the standard procedure that completes hepatic resection in the case of carcinoma arising from the extra-hepatic bile duct [13, 14]. However, the role of LN excision are still a matter of discussion, and there are no clear guidelines for patients with HCC. An increased operative risk of hepatic resection has been reported when LN dissection is performed in patients with HCC [15, 16]. The objective of this study is was to evaluate the incidence, site, and impact on survival of LN metastasis in patients with HCC amenable to curative liver resection and routine regional lymphadenectomy

Patients and methods

The participants of this study were 523 patients who underwent curative hepatic resection and routine regional lymphadenectomy for HCC at the Tianjin Medical University Cancer Center (TMUCC) from January 2001 to June 2004. A diagnosis of liver cancer was determined prior to surgery through at least two of the following four diagnostic procedures: ultrasonography (US), plain or enhanced computed tomography (CT), magnetic resonance imaging (MRI), and angiography. α -Fetoprotein (AFP) was detected in each patient. A Child-Pugh classification was used to evaluate cirrhotic patients with impaired liver function, and all selected patients were classified as Child type A. Post hoc pathology verification was performed for all cases. The diagnosis of HCC for these patients was pathologically confirmed.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Tianjin Anti-Cancer Association (TACA). Written informed consent was obtained from all individuals. No one refused to take part in the study.

Operation modalities

Curative surgery was defined as complete resection of all macroscopic and microscopic tumors. The cut surface to tumor was defined as 1 to 2 cm, and the absence of tumor cells along the parenchymal transection line (cut surface) was confirmed histologically. That there was no remaining tumor in the remnant liver was further confirmed by computed tomography (CT) 4 weeks postoperatively. The surgical technique of liver resection as performed in our center has been described elsewhere [17]. Because there is no definitive classification of regional nodes of the liver in the literature, the harvested lymph nodes were categorized on the basis of the topographic relations to the surrounding

structures, following the rules of the Japanese Society of Biliary Surgery [18].

Liver resection was performed together with regional lymphadenectomy, meaning that the lymph nodes around the hepatic pedicle (which comprises the cystic duct, pericholedochal, hilar, periportal, and periarterial lymph nodes), the retropancreatic space (posterior pancreatic station), and the common hepatic artery as far as the celiac trunk were excised. A single representative section per node was microscopically examined with hematoxylin and eosin (H&E) staining by the same group of pathologists. For nodal assessment, three to eight slides were made depending on the nodal volume.

Tumor staging was pathologically performed in accordance with the American Joint Commission on Cancer (AJCC) staging system (5th edition) [19]. In all selected patients, we obtained histopathologic information regarding histologic differentiation, tumor size and number, the size of the largest hepatic tumor, portal vein or hepatic vein invasion (gross or microscopic) and vascular embolism (gross or microscopic), and the presence of cirrhotic change in background liver. When clusters of cancer cells were present in the portal vein, hepatic vein, or microvascular embolism, vascular invasion was considered to be present.

Follow-up

Patients who underwent hepatic resection were followed up at the outpatient clinic every 3 months with a serum AFP assay and hepatic US and every 6 months with chest radiography. When recurrence was suspected, further evaluations were made by abdominal CT scans and/or angiography of the celiac trunk with Lipiodol injection and, if necessary, by US-guided biopsy to confirm the diagnosis. The study's follow-up ended on June 1, 2009 or up to the time of death. The median follow-up time was 43 months (range 4–100 months).

Statistical analysis

Medical records and survival data were obtained for all patients. Death occurring within 30 days after the surgical procedure was defined as an operative mortality. Death occurring after surgery and before discharge was defined as a hospital mortality. Survival was considered from the day of surgery to the day of death or the most recent follow-up visit. Pathologic tumor-related factors and numbers of LN metastases in different stations were analyzed by using the χ^2 test. Univariate analysis was performed to identify predictors associated with the survival rate. Cox's proportional hazards model was performed for multivariate analysis to identify factors that independently influenced

survival rates. The Kaplan-Meier method was used to estimate the cumulative probabilities of patient survival rate, and differences in the probabilities were evaluated using the log-rank test. Statistical analysis was carried out using SPSS 16.0 software. Differences associated with $p < 0.05$ were considered significant.

Results

Incidence in relation to clinicopathologic characteristics

Altogether, 449 (85.85 %) patients were hemoglobin surface antigen (HBsAg) positive, 386(73.81%) had an AFP level > 200 ng/ml, and 344 (65.77%) of patients had liver cirrhosis. No difference was found between LN metastasis(-) and LN metastasis(+) patients regarding sex, AFP status, Child-Pugh classification, or the diameter of the tumor ($p > 0.05$). On the other hand, the number of nodules, vascular invasion, cirrhosis, and hepatitis status were significantly related to the incidence of LN metastasis ($p < 0.01$) (Table 1).

Factors influencing survival

Among the eight variables, univariate analysis showed that tumor size, tumor number, vascular invasion, cirrhosis, and LN metastasis were significant factors influencing the disease-free survival of HCC patients ($p < 0.05$) (Table 2). In contrast, multivariate analysis demonstrated that only tumor number, vascular invasion, and LN metastasis were independent prognostic elements ($p < 0.05$) (Table 3).

Number of LN metastases at different stations

The lymph node stations that were constantly present were the hepatic pedicle, retropancreatic space, and common hepatic artery stations. Among the 523 patients enrolled in this study, 3433 lymph nodes were dissected and examined by the pathologist. The median number of dissected lymph nodes was 7.1 ± 2.7 per patient (range 3–25). LN metastases were found in 39 (7.45%) patients. The number of dissected LNs found in each station and overall number of LN metastases were reported. There were significant differences in the number of LN metastases among the hepatic pedicle, retropancreatic space, and common hepatic artery stations ($p < 0.01$). There was no difference in the incidence of LN metastasis between the retropancreatic space station and common hepatic artery station ($p > 0.05$).The incidence of LN metastasis in the hepatic pedicle station

Table 1 Incidence of LN metastasis in relation to clinicopathologic characteristics

Characteristic	LN metastasis (-) (n = 484)	LN metastasis (+) (n = 39)	χ^2	p
Sex				
Male	423	30	1.96	0.162
Female	61	9		
AFP status			0.09	0.767
≥ 200 ng/ml	358	28		
< 200 ng/ml	126	11		
Hepatitis status			35.54	0
Yes	428	21		
No	56	18		
Cirrhosis			9.21	0.002
Yes	327	17		
No	157	22		
No. of nodules			11.19	0
Single	295	13		
Multiple	189	26		
Diameter of the tumor			0.26	0.610
≥ 5 cm	265	23		
< 5 cm	219	16		
Vascular invasion			15.02	0
Yes	131	22		
No	353	17		

LN lymph node, AFP α -fetoprotein

The number of hemoglobin surface antigen (HbsAg)-positive patients with lymph node (LN) metastasis were significantly higher than those without LN metastasis ($p < 0.01$). There was a significant difference in the number of cases of cirrhosis regarding LN metastasis and no LN metastasis ($p < 0.01$). The number of those with multiple nodules among patients with LN metastasis was higher than among those without LN metastasis ($p < 0.01$). The incidence of vascular invasion in patients with LN metastasis was higher than in patients without LN metastasis ($p < 0.01$).

Table 2 Factors associated with survival rates of patients by univariate analysis

Factors	p
Sex (male vs. female)	0.501
HbsAg (positive vs. negative)	0.216
AFP (> 200 ng/ml vs. ≤ 200 ng/ml)	0.058
Tumor size (> 5 cm vs. ≤ 5 cm)	0.017
Tumor number (multiple vs. single)	0.011
Vascular invasion (present vs. not present)	0.0195
Cirrhosis (present vs. not present)	0.018
LN metastasis (positive vs. negative)	0.0013

Univariate analysis showed that tumor size, tumor number, vascular invasion, cirrhosis, and LN metastasis were significantly associated with the overall survival rate of hepatocellular carcinoma (HCC) patients ($p < 0.05$).

Table 3 Factors influencing survival rates of patients by multivariate analysis

Factors	β	SE	p	Exp (β)	95.0% CI for Exp (β)	
					Lower	Upper
Tumor size (>5 cm vs. \leq 5 cm)	0.319	0.233	0.179	1.376	0.759	2.199
Tumor number (multiple vs. single)	0.532	0.247	0.044	1.702	1.041	2.633
Vascular invasion (present vs. not present)	0.313	0.154	0.025	1.413	1.021	2.432
Cirrhosis (present vs. not present)	0.351	0.243	0.147	1.420	0.873	2.215
LN metastasis (positive vs. negative)	0.274	0.133	0.031	1.603	1.017	2.601

SE standard error, CI confidence interval

Multivariate analysis demonstrated that tumor number, vascular invasion, and LN metastasis were independent prognostic elements ($p < 0.05$)

Table 4 Number of dissected lymph nodes and number of LN metastases found for each station among the 523 patients with HCC

LN station	No. of patients	Total dissected LNs	No. of metastases	%
Hepatic pedicle	523	1782	311	17.45
Retropancreatic space	271	541	44	8.13
Common hepatic artery	523	1110	84	7.56
Total	523	3433	439	12.78

The numbers of LN metastases found for each station were different among the 523 patients for HCC ($\chi^2 = 72.399$, $p = 0$); retropancreatic space vs. common hepatic artery (Mantel-Haenszel, $\chi^2 = 0.093$, $p = 0.760$); hepatic pedicle vs. the other two stations (retropancreatic space vs. common hepatic artery) (Mantel-Haenszel $\chi^2 = 71.406$, $p = 0$)

was higher than that in the other two stations ($p < 0.01$) (Table 4).

Overall cumulative survival rates

The median survival time was 28 months (20.95–35.06 months) among all patients with LN metastasis and 53 months (46.91–59.09 months) among patients without LN metastasis. At the end of our study, 327 patients had died and 36 (6.88%, 36/523) were lost to follow-up. The 1-, 3-, and 5-year overall cumulative survival rates for the HCC patients with LN metastasis were 95%, 37%, and 22%, respectively; and for those without LN metastasis they were 94%, 66%, and 43%, respectively.

The Kaplan-Meier method was used to estimate overall survival rates. The log-rank test showed that significantly lower overall survival rates in the LN metastasis group compared to the group without LN metastasis ($\chi^2 = 8.564$, $p = 0.003$) (Fig. 1). Tumor recurrence had appeared in 82.05% (32/39) of patients with LN metastasis and in 57.64% (279/484) of patients without LN metastasis ($\chi^2 = 12.10$, $p = 0.0005$).

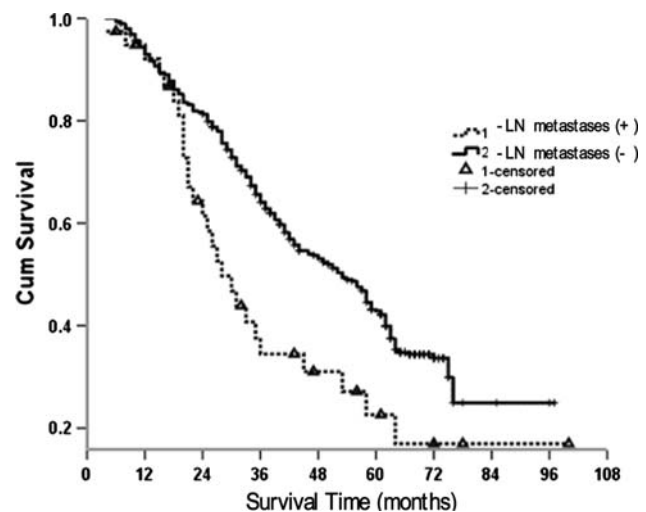


Fig. 1 Overall cumulative (*cum*) survival rate for patients with hepatocellular carcinoma undergoing curative hepatic resection and routine regional lymphadenectomy based on their lymph node (LN) status. The overall cumulative survival rate in the LN metastasis group was significantly lower than that in the group without LN metastasis (22% vs. 43% at 5 years). The overall survival rate was significantly worse in the LN metastasis-positive (+) group than that in the LN metastasis-negative (–) group ($\chi^2 = 8.564$, $p = 0.003$)

Side effects and complications

Regional lymphadenectomy was considerably safe with an associated intraoperative complication rate of 0.95% (5/523). Three patients sustained an injury to a portal vein branch and another two had an injury of the common bile duct, all of which were successfully and uneventfully repaired. Postoperative complications appeared in 19.69% (103/523) patients overall: in 94 (19.42%) of the 484 patients without LN metastasis and in 9 (23.07%) of the 39 patients with LN metastasis ($\chi^2 = 0.30$, $p = 0.581$). There was no significant difference between the two groups. The most frequency postoperative complication was ascites, which occurred in 11.28% (59/523) of patients. All postoperative complications were resolved with medical therapy, and none caused death.

Discussion

Lymph node metastasis is regarded as a poor characteristic to have during cancer progress. Using univariate analysis on our data, we demonstrated that tumor size, tumor number, vascular invasion, cirrhosis, and LN metastasis were significant factors influencing the survival rates of HCC patients, whereas the multivariate analysis demonstrated that only the tumor number, vascular invasion, and LN metastasis were independent prognostic elements. We also found a higher incidence of LN metastasis associated with multiple nodules and vascular invasion, which suggested that lymph nodes metastasis is a sign of advanced tumor stage with infiltration of the blood vessels, as reported by Abe et al. [20]. LN metastasis plays an important role in the HCC patient's prognosis. With the current data, we demonstrated that there was a trend toward a poorer survival rate for patients with LN metastasis compared to those without LN metastasis. The incidence of tumor recurrence among HCC patients with LN metastasis was higher than among those without LN metastasis.

In addition, we showed that patients who had hepatitis or cirrhosis tended to have a lower incidence of LN metastasis than those who did not. Similarly, Ercolani et al. [21] reported incidences of 6.1% and 8.3%, respectively, for patients with resectable HCC with and without cirrhosis. This suggested that the development of LN metastasis may be hindered by cirrhosis or hepatitis, which may result in hepatic architectural distortion and exacerbate lymphatic obstruction, or HCC that develops in noncirrhotic liver that may share same biological behavior with HCC.

Lymph node metastasis is reported to occur only rarely in patients with HCC. The Liver Cancer Study Group of Japan reported a prevalence of lymph node metastasis from HCC ranging from 25% to 33% in autopsy series and 2.2% in series of patients whose HCC was resected [22]. In a recent prospective study that used routine complete lymphadenectomy, Ercolani et al. [21] reported a 7.5% incidence of LN metastasis in patients with operable HCC, which was higher than in previous reports. In our current study of 523 patients who underwent regional lymphadenectomy, the incidence of LN metastasis was 7.45% (39/523), which further confirmed that LN metastasis was low among patients with operable HCC.

The common stations of LN metastasis were in the hepatic pedicle node, retropancreatic space, and common hepatic artery stations in present study. Among them, the most frequent site of LN metastasis was the hepatic pedicle station. These nodes appear to be the key stations for lymphatic spread from liver tumors toward regional and more distant nodes [21]. Our results showed that there was no difference in LN metastasis numbers in the retropancreatic space station and the common hepatic artery station. Taking these

characteristics of LN metastasis into consideration, strict operative performance and cautious pathologic diagnosis are equally important. We believe that routine regional lymph node dissection should always be performed to determine the precise stage of the disease. Furthermore, this study showed that liver resection combined with excision of lymph nodes around the hepatic pedicle, the retropancreatic space, and the common hepatic artery is a safe procedure that can be performed in all patients.

Conclusions

Patients with HCC and LN metastasis had a poorer prognosis than those without LN metastasis. Regional LN dissection should be always performed to determine the precise stage of the disease. Hepatic resection with regional lymphadenectomy is a safe procedure in patients with HCC.

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