

Retrospective Cohort Study

Clinical characteristics of hepatoduodenal lymph node metastasis in gastric cancer

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Abstract

AIM: To assess the clinical features of hepatoduodenal lymph node (HDLN) metastasis and to clarify the optimal indication of HDLN dissection.

METHODS: We investigated a total of 276 patients who underwent gastrectomy with extended lymphadenectomy, including HDLN dissection, for gastric cancer between 1999 and 2012. Of these, 26 patients (9.4%) had HDLN metastasis. First, we investigated the clinicopathological characteristics, their perioperative clinical outcomes, such as postoperative complications, and prognostic outcomes between patients with and without HDLN metastasis. Second, we detected the prognostic factors, particularly in patients with HDLN metastasis. Third, we assessed the therapeutic value of HDLN dissection to determine its optimal indication.

RESULTS: The five-year overall survival rate of the patients with HDLN metastasis was 29%. Univariate and multivariate logistic regression analyses revealed that the tumour location (the middle or lower stomach [$P = 0.005$, OR = 5.88 (95%CI: 1.61-38.1)]) and pT category [T3 or T4, $P = 0.017$, OR = 4.45 (95%CI: 1.28-21.3)] were independent risk factors for HDLN

metastasis. Cox proportional hazard analysis identified pN3 as an independent poor prognostic factor in the patients with HDLN metastasis [$P = 0.021$, HR = 5.17 (95%CI: 1.8-292)]. For patients who underwent radical HDLN dissection, HDLN metastasis was a prognostic indicator in pN3 gastric cancer ($P < 0.0001$), but not pN1-2 ($P = 0.602$). Furthermore, the index of therapeutic value of HDLN dissection for gastric cancer in the middle or lower stomach and the upper stomach was 3.4 and 0.0, respectively.

CONCLUSION: We suggest that HDLN dissection should be indicated for pN1 or pN2 gastric cancers located at the middle or lower stomach.

Key words: Gastric cancer; Hepatoduodenal lymph node; D2 lymphadenectomy; Prognostic factor; Tumor location

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Core tip: Gastric cancer located at the middle or lower stomach is a risk factor of hepatoduodenal lymph node (HDLN) metastasis and indicates relatively high therapeutic value of HDLN dissection. N-category, in especially pN3, is an independent poor prognostic factor in gastric cancer patients with HDLN metastasis. HDLN dissection should be indicated for N1 or N2 gastric cancers located at the middle or lower stomach.

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INTRODUCTION

Gastric cancer is one of the most common causes of death from cancer worldwide^[1]. Recent advances in diagnostic techniques, less invasive treatment techniques, and perioperative management have increased the early detection of gastric cancer and decreased the mortality and morbidity^[1,2]. Patients with advanced stage disease, however, still present a poor prognostic outcome and have a high incidence of lymph node metastasis. Therefore, nodal status is the strongest predictor of the prognosis of gastric cancer patients, and treatment strategy against metastatic lymph nodes is the most important clinical issue^[3-10].

Although radical gastrectomy with lymphadenectomy is recognized as the best strategy for macroscopic tumour clearance for advanced gastric cancer, criteria for optimal lymphadenectomy are different between Eastern and Western countries,

because of differences in the number of obese patients, for whom a surgical approach is difficult, and differences in the epidemiologic characteristics of gastric cancer^[11,12]. For example, D1 lymphadenectomy, which is a dissection of the perigastric lymph nodes, is mainly performed for advanced gastric cancer in Western countries, whereas D2 lymphadenectomy, which is a dissection of the nodes along the celiac artery and its branches in addition to the perigastric lymph nodes, is routinely performed for advanced gastric cancer in Eastern countries^[12].

Recently, a 15-year Dutch trial demonstrated fewer locoregional recurrences of gastric cancer and better long-term survival benefit in patients with D2 lymphadenectomy compared with those with D1 lymphadenectomy^[13]. Therefore, the therapeutic value of D2 lymphadenectomy has started to be re-evaluated in Western countries^[14,15]. In this study, we focused on the hepatoduodenal lymph node (HDLN), especially the lymph node at station No. 12a. This node is defined as a hepatoduodenal ligament lymph node along the proper hepatic artery^[16], and the Japanese treatment guidelines^[17] recommend it to be routinely removed as a standard procedure for D2 lymphadenectomy. On the other hand, the HDLN is not removed in Western countries, and HDLN metastasis is classified as distant metastasis according to the 7th American Joint Committee on Cancer (AJCC) staging manual^[18], although a recent report indicates the inappropriateness of including the HDLN in the distant metastatic lymph node group in all gastric cancers^[19].

In this study, we hypothesized that HDLN metastasis could be an indicator of poor prognosis in some subgroups of gastric cancer and that it could also be a governor of local metastatic control in other subgroups. We aimed to verify these hypotheses and to clarify the optimal indication of HDLN dissection retrospectively from patients' hospital records.

MATERIALS AND METHODS

Study population of gastric cancer patients

A total of 276 consecutive patients that underwent gastrectomy with HDLN dissection, with curative intention, for gastric cancer in the Division of Digestive Surgery, Department of Surgery, Kyoto Prefectural University of Medicine, between January 1999 and December 2012 were retrospectively analysed from their hospital records. Surgical procedures comprised a distal gastrectomy in 211 patients, a total gastrectomy in 59 patients, a pancreaticoduodenectomy in 5 patients, and a proximal gastrectomy in 1 patient according to the preoperative stage and tumour location. Resected specimens were examined and evaluated by pathologists based on classifications of the 14th JCGC^[16] and the AJCC staging manual^[18]. As a result, 90 patients were staged as pT1, 37 as pT2, 64 as pT3, and 85 as pT4. Histological types were classified as differentiated (papillary adenocarcinoma,

Table 1 Comparison of the clinicopathological features between patients with and without hepatoduodenal lymph node metastasis *n* (%)

	<i>n</i>	HDLN metastasis		Univariate <i>P</i> value	Multivariate	
		Positive	Negative		OR (95%CI)	<i>P</i> value
Total	276	26	250			
Sex						
Male	186	16 (62)	170 (68)	0.509	-	
Female	90	10 (38)	80 (32)			
Age (yr)						
< 65	134	10 (38)	124 (50)	0.277	-	
≥ 65	142	16 (62)	126 (50)			
Tumor location						
U	64	2 (8)	62 (25)	0.029	5.88 (1.61-38.1)	0.005
M and L	212	24 (92)	188 (75)			
CA 19-9 (U/mL)						
< 10	132	9 (35)	123 (49)	0.153	-	
≥ 10	144	17 (65)	127 (51)			
CEA (ng/mL)						
< 3	195	16 (62)	179 (72)	0.295	-	
≥ 3	81	10 (38)	71 (28)			
Histopathological type						
Differentiated	135	10 (38)	125 (50)	0.260	-	
Undifferentiated	141	16 (62)	125 (50)			
Venous invasion						
(-)	173	12 (46)	161 (64)	0.072	-	
(+)	103	14 (54)	89 (36)			
Lymphatic invasion						
(-)	105	3 (12)	102 (42)	0.002	-	
(+)	171	23 (88)	148 (58)			
Tumor size (mm)						
< 45	119	5 (19)	114 (46)	0.007	-	
≥ 45	157	21 (81)	136 (54)			
T category						
T1 and T2	127	3 (12)	124 (50)	< 0.0001	4.45 (1.28-21.3)	0.017
T3 and T4	149	23 (88)	126 (50)			

HDLN: Hepatoduodenal lymph node; CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; U: Upper gastric body; M: Middle gastric body; L: Lower gastric body.

or moderately or well-differentiated adenocarcinoma) or undifferentiated (poorly differentiated or undifferentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous adenocarcinoma) based on the 14th JCGC^[16].

Of all 276 patients, 182 patients (66%) received adjuvant chemotherapy, but 94 patients (34%) did not. S-1 or 5-fluorouracil was administered as a key drug of adjuvant chemotherapy. None of the patients received adjuvant radiotherapy or chemoradiotherapy. All patients were examined in the outpatient clinic, where abdominal ultrasound, computed tomography (CT), and measurement of levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were performed every 3-6 mo after surgery. All patients gave their informed consent in writing.

Analysis of surgical outcomes and clinicopathological factors

To reconfirm the feasibility and safety of HDLN dissection, we first investigated the clinicopathological characteristics of all patients who underwent HDLN dissection (Table 1) and their perioperative clinical outcomes, such as postoperative complications (Table 2). Second, to evaluate the prognostic differences,

survival rates after surgery were compared between patients with and without HDLN metastasis (Figure 1). Risk factors for HDLN metastasis were also investigated (Table 1). Moreover, we detected the prognostic factors, particularly in patients with HDLN metastasis (Table 3 and Figure 2). Third, we assessed the therapeutic value of HDLN dissection to determine its optimal indication (Table 4). The incidence of each lymph node metastasis was calculated by dividing the number of patients with pathological lymph node metastasis by the number of the patients with the lymph node dissection. The index of therapeutic value of lymphadenectomy was calculated by multiplying the incidence of each lymph node metastasis by the five-year survival rate of the patients with metastasis at each nodal station and then dividing by 100^[20].

Statistical analysis

All continuous variables were classified into two groups based on the median value of each parameter. The χ^2 test and Fisher's exact test were used to compare clinicopathological characteristics between patients with and without HDLN metastasis. Multivariate stepwise logistic regression analysis was performed to identify the independent risk factors associated with HDLN

Table 2 Complications after gastrectomy with extended lymphadenectomy

Complications	n (%)
Anastomotic leakage	12 (4.3)
Pancreatic fistula	8 (2.9)
Intra-abdominal abscess	4 (1.4)
Surgical site infection	26 (9.4)
Pneumonia	4 (1.4)
Cholecystitis	3 (1.1)
Pancreatitis	6 (2.2)
Hepatic dysfunction	2 (0.7)
Stenosis at anastomotic site	10 (3.6)
Ileus	11 (4.0)
Post-operative hemorrhage	2 (0.7)

metastasis. Survival curves were estimated using the Kaplan-Meier method, and statistical differences were examined using the log-rank test. Univariate and multivariate survival analyses were performed using the likelihood ratio test of the stratified Cox proportional hazards model. $P < 0.05$ was considered statistically significant.

RESULTS

Clinicopathological characteristics and perioperative clinical outcomes in patients who underwent HDLN dissection

We investigated clinicopathological characteristics in the patients who underwent gastrectomy with D2 lymphadenectomy, including HDLN dissection, based on Japanese guidelines (Table 1). Tumours in the middle or lower stomach ($P = 0.029$), tumour size of 45 mm and more ($P = 0.007$), the presence of lymphatic invasion ($P = 0.002$), and T category of T3 or T4 ($P < 0.0001$) were more frequently observed in the patients with HDLN metastasis. Multivariate stepwise logistic regression analysis identified tumours in the middle or lower stomach ($P = 0.005$, OR = 5.88) and T category of T3 or T4 ($P = 0.017$, OR = 4.45) as independent risk factors of HDLN metastasis. We also analysed complications that were observed after D2 gastrectomy, including HDLN lymphadenectomy, which were defined by the Clavien-Dindo classification as type II or more^[21] (Table 2). The incidence of anastomotic leakage, pancreatic fistula, and intra-abdominal abscess was 4.3%, 2.9%, and 1.4%, respectively, and these were not as high as those in previous reports^[11,22]. One patient (0.3%) died as a result of surgery.

Long-term prognosis of patients with or without HDLN metastasis

Next, we analysed the long-term prognosis of the patients. The five-year overall survival (OS) rate of those with or without HDLN metastasis was 29% or 72%, respectively ($P < 0.0001$) (Figure 1A). Limited to node-positive patients, the five-year OS rate of

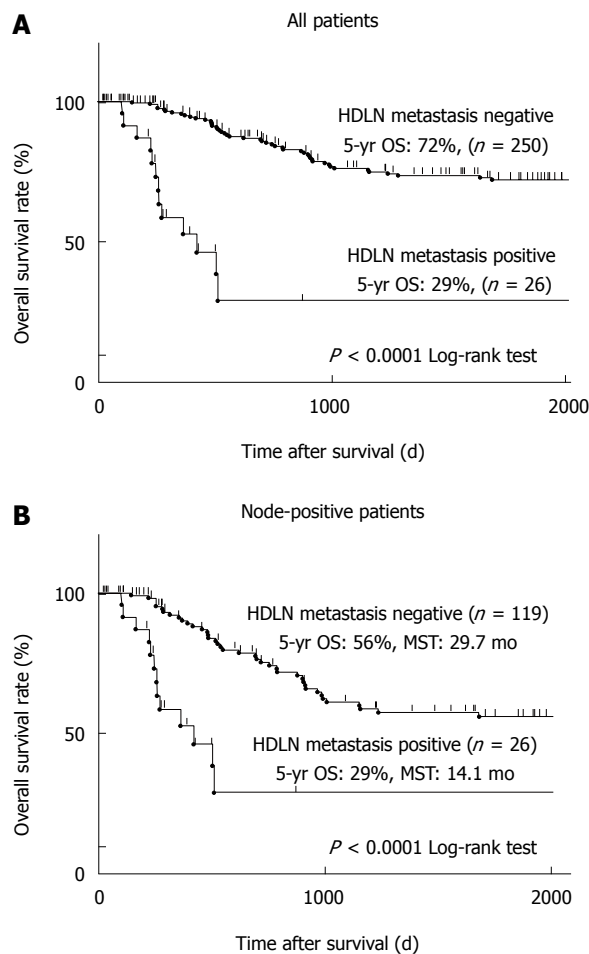


Figure 1 Five-year overall survival of gastric cancer patients based on hepatoduodenal lymph node metastasis. A: All 276 patients analysed in this study were divided into two groups based on hepatoduodenal lymph node (HDLN) metastasis. A group with HDLN metastasis ($n = 26$) and that without HDLN metastasis ($n = 250$) were compared. Kaplan-Meier survival curves were statistically analysed by the log-rank test ($P < 0.0001$); B: The patients who had lymph node metastasis ($n = 145$) were divided into two groups and analysed as described in panel a (26 patients with HDLN metastasis and 119 patients without HDLN metastasis, $P < 0.0001$).

those with or without HDLN metastasis was 29% or 56%, respectively ($P < 0.0001$) (Figure 1B). Median survival time (MST) of the node-positive patients with or without HDLN metastasis was 14.1 mo or 29.7 mo, respectively (Figure 1B).

Prognostic factors of patients with HDLN metastasis and correlation between the prognosis and nodal status

We next investigated the prognostic factors of patients with HDLN metastasis. Univariate analysis revealed that pN3 patients, whose total number of metastatic lymph nodes is seven or more, showed significantly poorer prognosis than pN1 or pN2 patients ($P = 0.002$, the five-year survival rate of pN3 or pN1-2 was 0% or 62.5%, respectively) (Table 3 and Figure 2A). Multivariate analysis using the Cox proportional hazard model showed that pN3 was an independent poor prognostic factor in patients with HDLN metastasis

Table 3 Univariate and multivariate analyses of the prognostic factors in patients with hepatoduodenal lymph node metastasis

	<i>n</i>	5-yr OS (%)	MST (mo)	Univariate <i>P</i> value	Multivariate	
					HR (95%CI)	<i>P</i> value
Sex	26	28.7	14.1			
Male	16	27.1	12.2			
Female	10	25.7	16.9	0.753	-	
Age (yr)						
< 65	10	38.1	14.1			
≥ 65	16	0	12.2	0.483	-	
CA 19-9 (U/mL)						
< 10	17	35.7	16.9			
≥ 10	9	0	12.2	0.327	-	
CEA (ng/mL)						
< 3	16	35.8	14.1			
≥ 3	10	0	9.1	0.382	-	
Tumor location						
U	2	0	8.7			
M and L	24	30.0	14.1	0.569	-	
Histopathological type						
Differentiated	10	0	16.9			
Undifferentiated	16	40.9	14.1	0.529	-	
Venous invasion						
(-)	12	0	14.1			
(+)	14	16.7	16.9	0.411	-	
Lymphatic invasion						
(-)	3	0	9.1			
(+)	23	26.9	14.1	0.624	-	
Tumor size (mm)						
< 45	5	0	9.1			
≥ 45	21	31.4	14.1	0.274	-	
T-category						
T1 and T2	3	0	9.1			
T3 and T4	23	31.5	16.9	0.222	-	
N-category						
N1 or N2	10	62.5	16.8			
N3	16	0	8.8	0.002	5.17 (1.8-292.7)	0.021

OS: Overall survival; MST: Median survival time; CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; U: Upper gastric body; M: Middle gastric body; L: Lower gastric body.

($P = 0.021$, HR = 5.17) (Table 3). Limited to pN1 and pN2 patients analysed, there was no significant prognostic difference between the patients with and without HDLN metastasis ($P = 0.602$) (Figure 2B). On the other hand, in pN3 patients, the five-year survival rate of those with or without HDLN metastasis was 0% or 32.2%, and the median survival time (MST) of those with or without HDLN metastasis was 8.8 mo or 30.2 mo (Figure 2C), suggesting that the prognosis of those patients with HDLN metastasis was significantly poorer than that of those without HDLN metastasis ($P < 0.001$).

Therapeutic value index and therapeutic benefit of HDLN dissection

Lastly, we assessed the index of therapeutic value of lymphadenectomy^[20] at each nodal station in all patients who underwent D2 gastrectomy (Table 4). The therapeutic value of lymphadenectomy of HDLN was 2.7, which was relatively low in comparison with those of the perigastric nodes at stations No. 1 to No. 7, which were in the range of 2.7 to 18.2. However,

the index of HDLN (No. 12a) for tumours in the middle or lower stomach was 3.4, which was relatively higher than that for tumours in the upper stomach, which was 0.0, suggesting that HDLN dissection could provide some advantages to patients with gastric cancer in the middle or lower stomach.

DISCUSSION

It is still unclear whether HDLN metastasis is a poor prognostic indicator or a determining factor of local metastasis such that its removal by surgery provides survival benefit. Moreover, the indication of HDLN dissection is controversial between Eastern and Western countries. In this study, we hypothesized that there are some far advanced patient subgroups for whom HDLN metastasis could be a poor prognostic indicator, and that there are other subgroups for whom dissection of HDLN with metastasis could provide an advantage. To verify these hypotheses, the clinicopathological factors and survival rates of patients who underwent HDLN dissection were analysed

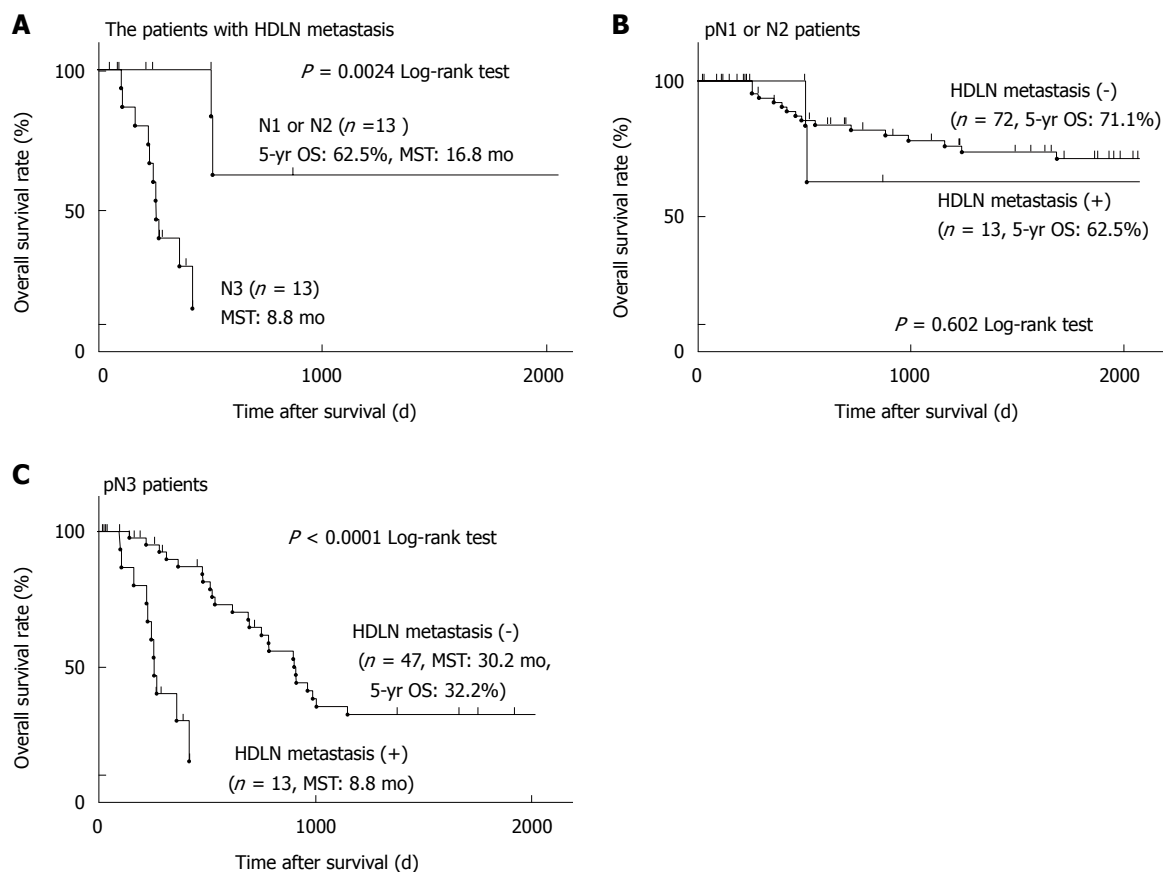


Figure 2 Five-year overall survival curves of gastric cancer patients based on the extent of lymph node metastasis. A: Twenty-six patients who had hepatoduodenal lymph node (HDLN) metastasis were divided into two groups based on the extent of lymph node metastasis. A group of pathological (p)N1 or N2 ($n = 10$) and that of pN3 ($n = 16$) were compared as described in Figure 1 ($P = 0.0024$); B: All 82 pN1 or N2 patients were divided into two groups based on HDLN metastasis and analysed as described in Figure 1 (10 patients with HDLN metastasis and 72 patients without HDLN metastasis, $P = 0.602$); C: All 63 pN3 patients were analysed as described in Figure 1 (16 patients with HDLN metastasis and 47 patients without HDLN metastasis, $P < 0.0001$).

retrospectively. Consequently, HDLN metastasis was clearly identified as a poor prognostic indicator in patients with a tumour in the upper stomach or with pN3 gastric cancer, as well as a key factor controlling local recurrence in patients with pN1 and pN2 gastric cancer.

According to the JCGC and the treatment guidelines^[16,17], the classification of regional lymph nodes and the indication of lymphadenectomy were defined by the extent of gastrectomy, regardless of tumour location. Currently, HDLN is included in the lymph nodes which are routinely removed in advanced gastric cancer patients, even when a tumour is located in the upper stomach. However, our study revealed that patients with a tumour in the upper stomach as well as HDLN metastasis had extremely poor prognosis, and that the index of therapeutic value of HDLN dissection for those patients was 0.0, suggesting it provided no advantages, which is consistent with the previous report^[20]. Thus, HDLN dissection for tumours in the upper stomach should not be recommended as a standard procedure of D2 lymphadenectomy. As described above, because the 7th AJCC staging manual^[18] defines HDLN metastasis as distant metastasis, HDLN is not removed in Western countries.

Our study, however, demonstrated that HDLN dissection provided a relatively high survival rate to the patients who had pN1 or pN2 gastric cancer in the middle or lower stomach, regardless of the presence of HDLN metastasis (Figure 2 and Table 3). Therefore, the tumour location is an important factor in making a preoperative decision about whether HDLN dissection should be performed.

There is no doubt that differences in treatment indications for gastric cancer between Eastern and Western countries are greatly influenced by the features of cancer biology, epidemiology, and surgical difficulties in those countries^[11,22-24]. Concerning tumour location, the incidence of upper gastric cancer in the United States (51%) was higher than that in Japan (17%)^[22]. This might greatly influence the treatment indication of lymphadenectomy in each country. Recently, however, the incidence of upper gastric cancer is increasing in Eastern countries, as shown in this study [23% (64/276)] (Table 1). Using the multivariate logistic regression analysis (Table 1) and the index of therapeutic values (Table 4), we revealed that the tumour location is an important factor in making a decision about HDLN dissection. Based on this, therefore, we suggest that the guidelines

Table 4 Index of estimated benefit from hepatoduodenal lymph node dissection

Nodal station	Incidence of LNM (%)	5-yr OS of patients with LNM (%)	Index
No. 1	41.0	43.9	18.0
No. 2	16.2	45.8	7.4
No. 3	32.2	56.4	18.2
No. 4sa	8.1	75.0	6.1
No. 4sb	6.6	40.6	2.7
No. 4d	22.9	59.8	13.7
No. 5	12.5	53.2	6.7
No. 6	19.2	60.6	11.6
No. 7	12.8	47.5	6.1
No. 8a	13.3	55.9	7.4
No. 9	19.7	32.1	6.3
No. 10	1.2	100.0	1.2
No. 11p	23.7	56.5	13.4
No. 11d	0.0	NA	NA
No. 12a (HDLN)	9.4	28.7	2.7
Tumor location			
No. 12a (HDLN) U	3.1	0.0	0.0
No. 12a (HDLN) M and L	11.3	30.0	3.4

The index of therapeutic value of lymph node dissection was calculated by multiplying the incidence of metastasis by the 5-year survival rate of patients with metastasis at each nodal station and then dividing by 100¹². OS: Overall survival; LNM: Lymph node metastasis; HDLN: Hepatoduodenal lymph node; U: Upper gastric body; M: Middle gastric body; L: Lower gastric body; NA: Not applicable.

should include this factor and should be standardized worldwide.

Our results indicate that HDLN dissection could salvage HDLN metastasis in patients with pN2 or lesser lymph node metastasis, because there was no significant prognostic difference between the patients with and without HDLN metastasis (*P* = 0.602) after radical HDLN dissection. Other studies, however, reported the potential survival benefit of lymphadenectomy, such as prophylactic para-aortic lymph node (PAN) dissection, for curable gastric cancer in a limited number of patients^[25,26], whereas it was not demonstrated in a randomized clinical trial (RCT) (JCOG9501)^[27]. Moreover, prospective RCTs, such as JCOG0001 and JCOG0405^[28,29], demonstrated the survival benefit of neoadjuvant chemotherapy followed by extended surgery with PAN dissection for gastric cancer patients with only PAN or bulky N2 metastasis (limited putative pN3 metastasis). Similarly to these studies, we speculate that the survival benefit may also be obtained in pN3 patients by neoadjuvant chemotherapy followed by extended surgery with HDLN dissection. For this issue, further prospective studies are warranted.

Our results indicate the significance in making a decision about HDLN dissection depending on the tumour location and pathological N-category. However, there is a major problem in diagnosing metastatic lymph nodes accurately before surgery using current imaging methods. We previously generated a simple math formula to estimate preoperative metastatic nodal counts using multidetector row computed tomography

(MDCT); Pathologic counts = 1.63 × (counts by MDCT) + 2.5^[30]. Based on this formula, 3 or more nodal counts by MDCT might be considered pN3. Therefore, for patients with less than 3 putative metastatic nodal counts by MDCT, who are considered pN1 or pN2, D2 lymphadenectomy with HDLN dissection should be performed. On the other hand, for patients with 3 or more nodal counts by MDCT, neoadjuvant chemotherapy may be considered as a treatment choice before surgical resection with extended lymphadenectomy, including HDLN dissection.

Our study, however, have some limitations. The population of the cohort was relatively small. A prospective study may be needed to validate the indication of HDLN dissection. Therefore, although the therapeutic value of HDLN dissection for gastric cancer is currently limited, we would suggest that HDLN dissection can provide a prognostic benefit to pN1 and pN2 gastric cancer patients whose tumour is located in the middle or lower stomach.

COMMENTS

Background

It is still unclear whether hepatoduodenal lymph node (HDLN) metastasis is a poor prognostic indicator or a determining factor of local metastasis such that its removal by surgery provides survival benefit. Moreover, the indication of HDLN dissection is controversial between Eastern and Western countries.

Research frontiers

This study was designed to evaluate the clinical characteristics and impact of HDLN metastasis on the clinical course and to clarify the optimal indication of HDLN dissection.

Innovations and breakthroughs

HDLN metastasis was clearly identified as a poor prognostic indicator in patients with a tumour in the upper stomach or with pN3 gastric cancer, as well as a key factor controlling local recurrence in patients with pN1 and pN2 gastric cancer.

Applications

The results indicate the significance in making a decision about HDLN dissection depending on the tumour location and pathological N-category. For patients with lesions considered as pN1 or pN2, D2 lymphadenectomy with HDLN dissection should be performed.

Terminology

Hepatoduodenal lymph node is defined as a hepatoduodenal ligament lymph node along the proper hepatic artery, and the Japanese treatment guidelines recommend it to be routinely removed as a standard procedure for D2 lymphadenectomy. On the other hand, the HDLN is not removed in Western countries, and HDLN metastasis is classified as distant metastasis according to the 7th American Joint Committee on Cancer staging manual.

Peer-review

The study is of high level, the results shown in this work could be a contribution for that the medical teams take a good decision that can help a better survival of the patient. The results could be taken in account in different hospitals in the world.

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