Received: 14 May 2023 | Revised: 23 July 2023 | Accepted: 3 August 2023

DOI: 10.1002/ags3.12731

AGSurg Annals of Gastroenterological Surgery Open Access WILEY

ORIGINAL ARTICLE

Efficacy of lymph node dissection for duodenal cancer according to the lymph node station

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Abstract

Background: Lymph node metastasis (LNM) is associated with poor prognosis in patients with duodenal cancer (DC). However, the efficacy and optimal extent of lymph node (LN) dissection have not been thoroughly discussed.

Methods: A total of 98 consecutive patients with DC who underwent surgical resection (pancreatoduodenectomy, $n=55$; partial resection, $n=32$; pancreas-sparing total duodenectomy, n=9) were retrospectively analyzed. The LN stations located upstream of the lymphatic flow were defined as Np stations according to tumor location, whereas the others were defined as Nd stations. The association between the dissection of each LN station and survival outcome was investigated using the efficacy index (EI; percentage of metastases to lymph nodes in each station multiplied by the 5-year survival rate of metastatic cases).

Results: The survival of patients with LNM at the Nd stations ($n=6$) was significantly worse than that of patients with LNM only at the Np stations ($n=20$) (relapse-free survival, median survival time [MST], 6.0 vs. 48.4 months, $p<0.001$; overall survival, MST, 15.1 vs. 96.0 months, $p<0.001$). Multivariate analysis identified LNM at Nd stations as an independent prognostic factor for overall survival (hazard ratio 9.92; $p=0.015$). The Np stations had a high EI (range, 8.34–20.88), whereas the Nd stations had an EI of 0, regardless of the tumor location.

Conclusions: LN dissection of the Np stations contributed to acceptable survival, whereas LNM of the Nd stations led to poor survival, possibly reflecting advanced tumor progression to systemic disease in patients with DC.

KEYWORDS
duodenal neoplasms, lymph node excision, lymphatic metastasis, prognosis, survival

1 | INTRODUCTION

Previous retrospective studies of duodenal cancer (DC) have shown that lymph node metastasis (LNM) is associated with a poor prognosis, and several multivariate analyses have also indicated that LNM is an independent prognostic factor.[1–9] LNM is one of the most important factors to consider when treating patients with DCs.

The Union for International Cancer Control TNM (UICC-TNM) classification (8th edition, 2017) defines the regional lymph nodes (LNs) of the nonampullary duodenum as pancreaticoduodenal LNs (peri-pancreatic head LNs), pyloric LNs, hepatic LNs, and superior mesenteric (SM) LNs.[10] Lymphatic vessels originate from blind-ending vessels in each villus of the mucosa. The collecting trunks of the lymphatic vessels pass over the anterior and posterior duodenal wall toward the lesser curvature to enter the anterior and posterior pancreaticoduodenal LNs. These follow the veins and arteries to the nodes related to the superior mesenteric artery (Figure 1).[11] Thus, the lymphatic flow of the duodenum is complicated due to different vascular supplies according to the location and presence of peripheral organs.

Previous reports have indicated that the most frequent area of LNM differs according to the tumor location.[3,4,12–14] For instance, tumors located in the first portion are expected to be more likely to metastasize to hepatic LNs than SM LNs.[3] However, the current UICC-TNM classification defines only the number of metastatic LNs as a prognostic factor, and the association between the location of LNM and prognosis has not been verified, with the appropriate extent of LN dissection being undefined.

Thus, the present study investigated the efficacy of LN dissection for DC, focusing on the tumor location and the location of LNM.

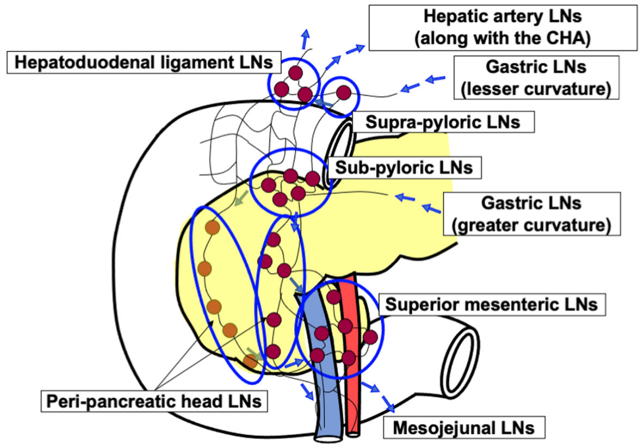

FIGURE 1 Diagrammatic presentation of duodenal lymphatics. The blue arrows indicate lymphatic flow. CHA, common hepatic artery; LN, lymph node.

2 | MATERIALS AND METHODS

2.1 | Study population

A total of 98 patients who underwent surgical resection for DC between April 2002 and December 2019 at Shizuoka Cancer Center were included in this retrospective study. Patients with ampullary cancer were excluded from this study. Clinicopathological factors, surgical results, and survival outcomes were evaluated from patients' medical records. This study was approved by the Institutional Review Board (J2021-82-2021-1).

2.2 | Surgical strategy

The preoperative work-up for DC to evaluate localization, depth of tumor invasion, and resectability was performed using upper gastrointestinal endoscopy, endoscopic ultrasonography, and multidetector-row computed tomography (MDCT). The surgical procedures depended mainly on the preoperative evaluation of tumor depth. When the tumor was deemed to be contained in the mucosa (cT1a), partial resection (PR) of the duodenum or pancreas-sparing total duodenectomy (PSD) was performed. During PR and PSD, the peri-pancreatic head (peri-Ph) LNs were sampled as needed. Classical PD with regional lymphadenectomy was generally performed in cases of cT1b or deeper DC.[10] In PD, en bloc resection of regional LNs was routinely performed in accordance with the Union for UICC-TNM classification.[10] Sampling of the para-aortic LNs and peritoneal lavage cytology are generally performed during PD. None of the patients received neoadjuvant or adjuvant therapy.

2.3 | Definition of the LN Station

In this study, dissected LN stations were classified into six regional LN stations: the supra-pyloric LN station, sub-pyloric LN station, hepatic artery (HA) LN station (along the celiac axis to the common hepatic artery), hepatoduodenal ligament (HDL) LN station, peri-Ph LN station, and SM LN station (Figure 1). Additionally, the gastric and mesojejunal LN stations were also examined[3,12,14,15] (Figure 1).

Subsequently, based on previous reports[3,4,12–14] and the anatomical features of the lymphatic flow,[11] these LN stations were categorized into two groups based on the tumor location: stations located upstream in the lymphatic flow, defined as the Np (proximal node) stations, and those located downstream, defined as the Nd (distal node) stations. The peri-Ph LN station was resolutely defined as the Np station in all cases due to its proximity to the tumor and its upstream position in the lymphatic flow,[11,13] regardless of the tumor location. In addition, for tumors in the first portion of the duodenum, the HDL LN station, as well as the supra- and sub-pyloric LN stations, were defined as Np stations because of their upstream position in the lymphatic flow.[11–13] For tumors in the third and fourth portions, the SM LN station was defined as the Np station because of its proximity to the tumor and its upstream position in the lymphatic flow.[3,11,13] Figure 2 illustrates the Np stations according to the tumor location.

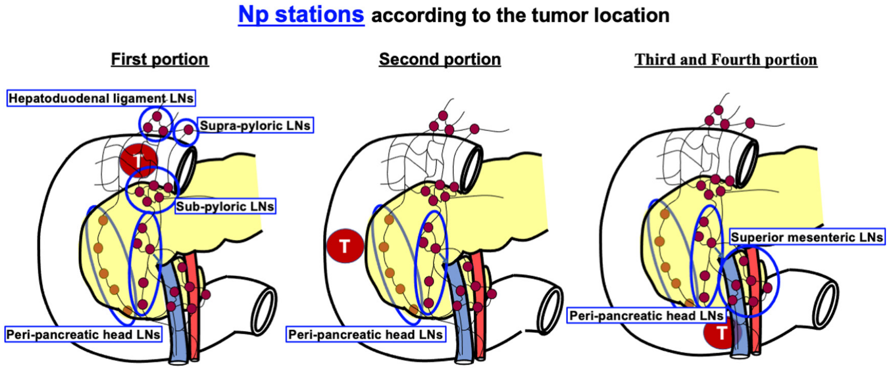

FIGURE 2 Definition of Np stations according to tumor location. Each Np station is indicated by a blue circle.

2.4 | Histopathological evaluation

The LNs were divided from the specimens as much as possible and assigned to stations by hepato-biliary-pancreatic surgeons, and all specimens were prepared in the usual manner for microscopic examination with hematoxylin–eosin staining. Pathological findings were confirmed by an experienced pathologist (K. S). Tumor size, histologic grade, microscopic lympho-vascular invasion, lymph node metastasis (LNM), and staging were recorded according to the UICC-TNM classification (8th edition, 2017).[10]

2.5 | Follow-up

Adjuvant chemotherapy was not administered in this study. All patients were followed at 3- to 6-month intervals after surgery with laboratory tests, including tumor markers (carcinoembryonic antigen and carbohydrate antigen 19-9) and imaging studies. Tumor recurrence was confirmed based on radiological findings or histological evidence, and the initial recurrence sites were recorded. Patients who did not undergo systematic LN dissection (PR/PSD) were assessed for the presence of LNM at regional LN stations during the follow-up period.

2.6 | Evaluation of the efficacy of LN dissection for each LN station

To clarify the effectiveness of the dissection of each LN station, the efficacy index (EI) was calculated by multiplying the frequency of metastasis to the LN station (%) by the 5-year survival rate (%) of patients with metastasis to the LN station and dividing by 100 as an indicator of the survival benefit.[16] The dissection frequency of each LN station, including the sampled LNs, was determined.

2.7 | Statistical analyses

Continuous data are expressed as the median and range and were compared using the Mann–Whitney U test. Categorical data were analyzed using Fisher's exact test. Overall survival (OS) and relapse-free survival (RFS) were defined as the period from the time of surgery to the time of death or last follow-up or from the time of operation to the time when the initial recurrence was recorded on the follow-up imaging study using the Kaplan–Meier method and compared using the log-rank test, respectively. Variables with a *p*-value of <0.050 in the univariate analysis were included in a multivariate Cox proportional hazards regression analysis to identify independent risk factors for OS. A *p*-value of <0.050 was considered statistically significant.

All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[17]

3 | RESULTS

The clinicopathological characteristics of the 98 patients with DC are shown in Table 1. The second portion of the duodenum was the most frequently encountered original tumor site, and was found in 70 patients (71.4%). Only two patients had tumors located in the fourth portion.

PD with regional lymphadenectomy was performed in 55 patients (56.1%), whereas PR or PSD was performed in the remaining 43 patients (23 of whom underwent peri-Ph LN sampling). Regarding the pathological T stage, 51 patients with T1a tumors, including 43 who underwent PR/PSD, did not have LNM. LNM was confirmed in one of nine patients with pT1b tumors (11.1%), in one of three patients with pT2 tumors (33.3%), in six of 12 patients with pT3 tumors (50.0%), and in 17 of 23 patients with pT4 tumors (73.9%). Five patients diagnosed with stage IV disease had a pathological diagnosis of metastatic extra-regional LNs, including two patients with metastatic para-aortic LNs. Comparisons of clinicopathological characteristics according to tumor location are shown in Supporting Information Table S1.

3.1 | Survival outcomes according to conventional *N* stage and location of LNM

The median observation period was 64.2 (range, 1.1–169.8) months in the censored cases. Figure 3 shows comparisons of RFS and OS curves according to the conventional N stage (classified according

TABLE 1 Clinicopathologic characteristics of the 98 patients with duodenal cancer.

Characteristics	Whole patients
n	98
Age at surgery (years)[a]	55 (21–84)
Sex (Male)	65 (66.3)
BMI (kg/m^2)[a]	22.3 (16.5–31.1)
CEA (ng/mL)[a]	2.3 (0.5–62.1)
CA19-9 (U/mL)[a]	8 (2–3660)
Tumor location (1st/2nd/3rd/4th)	15 (15.3)/70 (71.4)/11 (11.2)/2 (2.0)
Surgical outcomes	
Operation (PD/PSD/PR)	55 (56.1)/9 (9.2)/34 (34.7)
Mortality	0 (0.0)
Morbidity (C-D ≥ III)	45 (46.0)
Postoperative hospital stays (days)[a]	19 (7–71)
Pathological findings	
Tumor size (mm)[a]	33 (6–115)
Lymphatic invasion (+)	32 (32.7)
Vascular invasion (+)	22 (22.4)
Differentiation (pap, tub/por, other)	86 (87.8) / 12 (12.2)
Pathological T stage[b] (T1a/T1b/T2/T3/T4)	51 (52.0)/9 (9.2)/3 (3.1)/12 (12.2)/23 (23.5)
Pathological N stage[b] (N0/N1/N2)	72 (73.5)/12 (12.2)/14 (14.3)
Pathological Stage[b] (I/IIA/IIB/IIIA/IIIB/IV)	61 (62.2)/5 (5.1)/5 (5.1)/11 (11.2)/11 (11.2)/5 (5.1)
Residual tumor status = R1	3 (3.1)
Number of LNs examined[a]	17 (0–52)

Note: Values in brackets represent percentages unless otherwise indicated.

Abbreviations: BMI, body mass index; CA19-9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; C-D, Clavien-Dindo classification; PD, pancreatoduodenectomy; PR, partial resection; PSD, pancreas spearing duodenectomy.

[a]Median (range).

[b]The eighth edition of UICC classification.

to the number of LNMs). Significant differences in RFS and OS were found between the N0 (no LNM, $n = 72$) and N1 groups (LNM in 1–2 regional LNs, $n = 12$) (RFS, $p < 0.001$; OS, $p = 0.001$), and between the N1 and N2 groups (LNM in ≥3 regional LNs, $n = 14$) (RFS, $p = 0.023$; OS, $p = 0.023$). None of the 43 patients who underwent PR/PSD without systematic LN dissection experienced recurrence during the follow-up period (median observation period: 70.2 months).

Subsequently, the patients were classified into three groups according to the location of LNM: N0 group (no LNM, $n = 72$), Np group (LNM in only the Np station, $n = 20$), and Nd group (others, $n = 6$), irrespective of the M stage. Of the six patients in the Nd group, one was classified as the conventional N1 stage, and the others were classified as the N2 stage. Figure 4 shows a comparison of the RFS and OS curves according to LNM location. None of the patients in the Nd group achieved a five-year survival. Significant differences in RFS and OS were observed between the N0 and Np groups (RFS, $p < 0.001$; OS, $p < 0.001$) and between the Np and Nd groups (RFS, $p < 0.001$; OS, $p < 0.001$).

3.2 | Prognostic factors for OS

Table 2 shows the results of the univariate and multivariate analyses for identifying the prognostic factors for OS. To eliminate the confounding factors between the conventional N stage and classification according to the location of the LNM, two models were developed with these factors separately in the multivariate analysis. Multivariate model 1 identified pathological T stage of 4 (hazard ratio [HR] 14.90; $p = 0.002$), microscopic vascular invasion (HR 11.69; $p = 0.004$), positivity for peritoneal lavage cytology (HR 3.85; $p = 0.023$), and pathological M stage of 1 (HR 6.81; $p = 0.040$) as independent prognostic factors. The number of LNMs was not significantly associated with OS. In contrast, multivariate model 2 (Table 2) identified microscopic vascular invasion (HR 11.68; $p = 0.002$), pathological T stage 4 (HR 10.22; $p = 0.015$), LNM at Nd stations (HR 9.92; $p = 0.015$), and positivity for peritoneal lavage cytology (HR 3.77; $p = 0.028$) as independent prognostic factors.

3.3 | EI of each LN station

Figure 5 shows the total number of dissected LNs and the frequency of LNM at each LN station according to tumor location. In 15 patients with tumors in the first portion, LNM was found in the sub-pyloric, HDL, and peri-Ph LN stations, and the frequency of metastasis was 11.11%, 10.00%, and 16.67%, respectively. In 70 patients with tumors in the second portion, LNM was found in the supra-pyloric, sub-pyloric, HA, HDL, peri-Ph, SM, and gastric LN stations. LNM was found only in the peri-Ph LN station in 13 patients with tumors in the third or fourth portion, and the frequency of metastasis was 12.50%. LNM was not detected in SM or mesojejunal LN stations.

Table 3 shows the efficacy of LN dissection for each node station using EI according to the tumor location. In the first-portion DC, the EI values of the sub-pyloric, HDL, and peri-Ph LN stations were 11.1, 10.0, and 8.34, respectively, whereas those of the other LN stations were 0.00. In the second-portion DC, the EI value of the peri-Ph LN station was 20.88, whereas that of the other LN stations was 0.00. In the third- or fourth-portion DC, the EI value of the peri-Ph LN station was 12.50, whereas that of the other LN stations was 0.00. A table of EI values excluding T1a cases, provided for additional information, is shown in Supporting Information Table S2.

4 | DISCUSSION

The present study investigated the survival outcomes of DC patients according to the location of LNM (Np or Nd station) and the

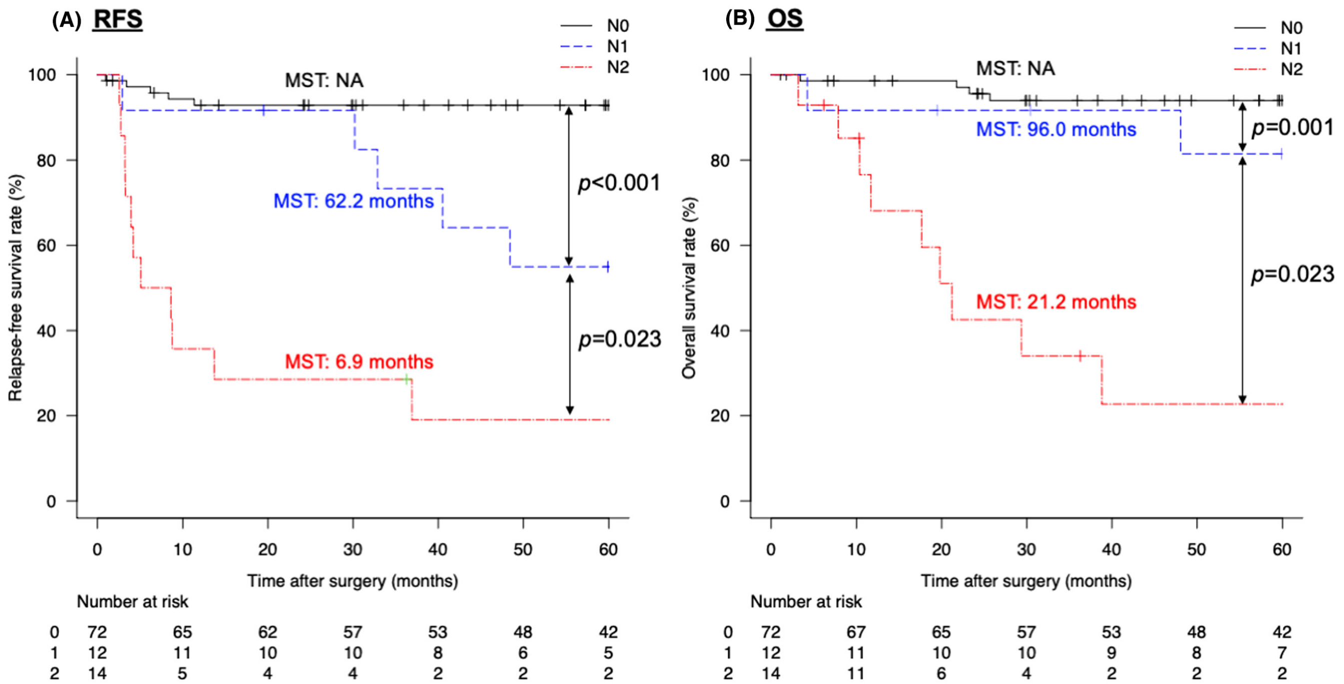

FIGURE 3 (A) Relapse-free survival curves according to N stage. (B) Overall survival curves according to N stage. MST, median survival time.

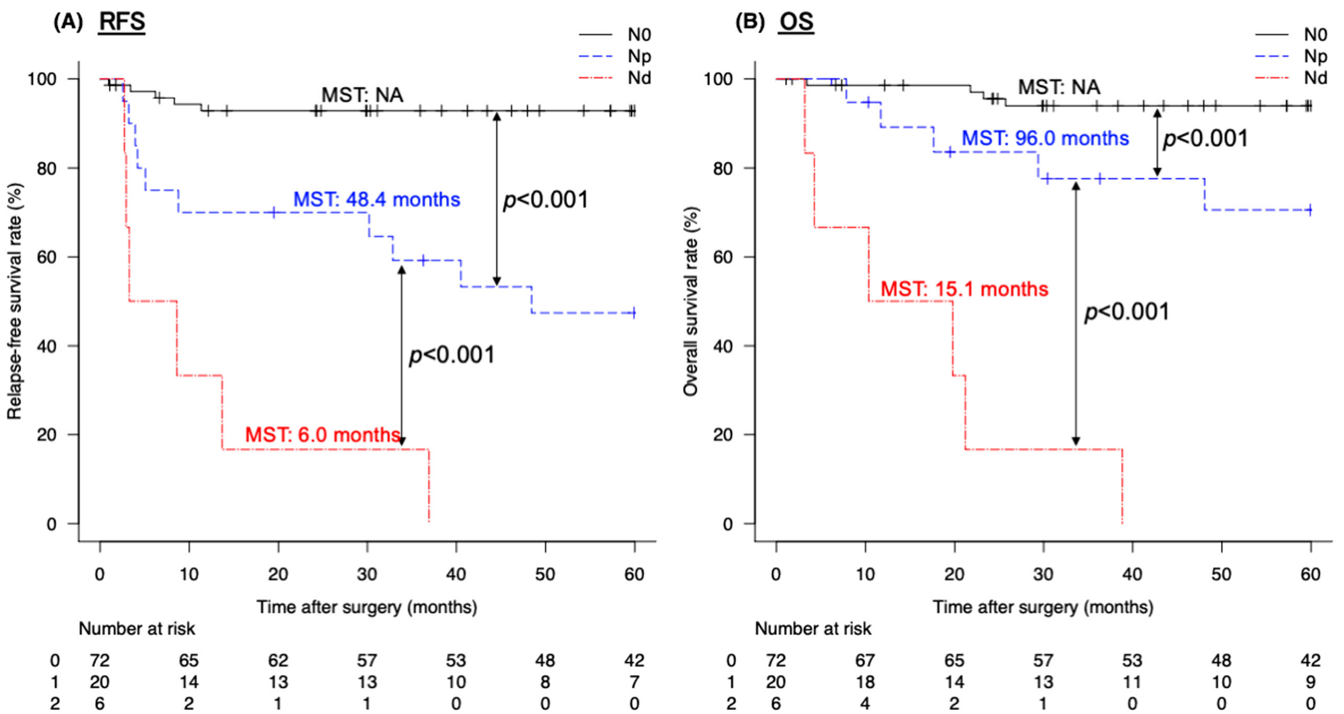

FIGURE 4 (A) Relapse-free survival curves according to the location of lymph node metastasis. (B) Overall survival curves according to the location of lymph node metastasis. MST, median survival time.

prognostic benefit of LN dissection at each LN station. The OS of patients with LNM at Nd stations was significantly worse than that of patients with LNM at Np stations. Multivariate analysis identified LNM in Nd stations as an independent prognostic factor. Regarding the prognostic impact of LN dissection using EI, the Np stations, including the peri-pancreatic head LN, had a high EI, whereas the Nd stations had an EI of 0 regardless of the tumor location. These results suggest that Np stations should be thoroughly dissected during curative resection, and LNM at Nd stations may represent advanced tumor progression to systemic disease.

Previous reports have shown that the most frequent areas of LNM differ according to the tumor location.[3,4,12] These studies

TABLE 2 Univariate and multivariate analyses of the prognostic factors for 98 patients with duodenal carcinoma.

Variable	n	Univariate		Multivariate model 1		Multivariate model 2	
		5-year OS (%)	*p*-value	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Age (years)							
≥70	28	83.8	0.383				
<70	70	82.0					
Sex							
Male	56	83.4	0.690				
Female	33	81.1					
BMI (kg/m^2) ≥21							
>21	67	88.0	0.223				
≤21	31	72.3					
CEA (ng/mL)							
>5.0	14	66.7	**0.011**	0.25 (0.05–1.27)	0.094	0.48 (0.09–2.64)	0.398
≤5.0	84	85.5					
CA19-9 (U/mL)							
>37	13	26.9	**<0.001**	1.01 (0.28–3.61)	0.990	2.02 (0.43–9.50)	0.373
≤37	85	91.0					
Differentiation							
pap, tub	86	84.0	0.252				
por, others	12	75.0					
Tumor size (mm)							
≥30	60	77.7	**0.047**	1.05 (0.23–4.83)	0.952	0.67 (0.14–3.26)	0.622
<30	38	87.9					
ly							
Present	32	50.4	**<0.001**	0.37 (0.05–2.99)	0.352	0.53 (0.09–3.16)	0.485
Absent	66	98.3					
v							
Present	22	37.7	**<0.001**	**11.69 (2.15–63.5)**	**0.004**	**11.68 (2.43–56.10)**	**0.002**
Absent	76	95.5					
Peritoneal cytology							
Positive	9	34.6	**<0.001**	**3.85 (1.20–12.3)**	**0.023**	**3.77 (1.15–12.30)**	**0.028**
Negative or not collected	89	87.5					
pT stage							
T4	23	30.5	**<0.001**	**14.90 (2.60–85.19)**	**0.002**	**10.22 (1.58–66.07)**	**0.015**
T1–3	75	75.0					
pN stage							
N2	14	22.7	**<0.001**	4.26 (0.86–21.05)	0.076		
N1	12	81.5		1.91 (0.34–10.71)	0.464		
N0	72	93.9					
N0/Np/Nd							
Nd	6	0.0	**<0.001**			**9.92 (1.55–63.42)**	**0.015**
Np	20	70.6				1.71 (0.32–9.04)	0.528
N0	72	93.9					
pM stage							
M1	5	20.0	**<0.001**	**6.81 (1.10–42.36)**	**0.040**	1.59 (0.18–14.11)	0.679
M0	93	86.6					

Note: Significant values are in bold.

Abbreviations: BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CI, confidence interval; ly, microscopic lymphatic invasion; OS, overall survival; v, microscopic vascular invasion.

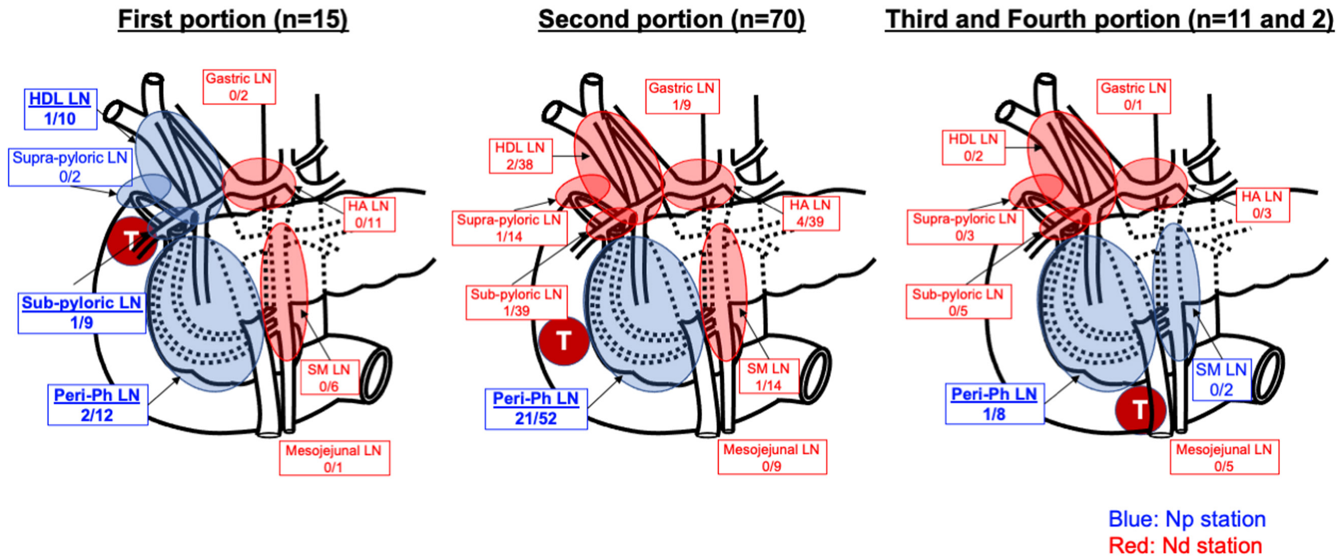

FIGURE 5 Lymph node station mapping and frequency of lymph node metastasis (number of patients with metastasis at the station/number in whom lymph node dissection of the station was performed) according to the tumor location. Np stations are shown in blue and Nd stations in red. Lymph node stations where dissection is highly effective are highlighted in bold and underlined. HA, hepatic artery; HDL, hepatoduodenal ligament; LN, lymph node; Peri-Ph, peri-pancreatic head; SM, superior mesenteric.

suggested that the sub-pyloric LN and posterior pancreatic head LN should be considered sentinel LNs among tumors in the first portion, whereas the posterior and anterior pancreatic head LNs should be considered sentinel LNs among tumors in the second portion.[12] The classification of Np stations in the present study may be consistent with previous reports on sentinel LNs. The peri-Ph LN and the SM LN were categorized as Np stations in tumors in the third and fourth portion. Although the small number of cases precluded a detailed examination, this classification is based on previous reports[3,11,13] and would be considered appropriate. The better survival outcome in the Np group than in the Nd group may reflect the feasibility of local control by surgical treatment with LN dissection of tumors with limited LNM to the Np stations. In particular, the peri-Ph LNs should be dissected regardless of tumor location because of the high EI in the present study. Therefore, the optimal procedure for DC should be PD while ensuring the removal of the peri-Ph LNs, as the feasibility of dissection of the peri-Ph LN station with preservation of the pancreatic head parenchyma has been unclear.[18]

The present study showed that LNM at Nd station was an independent prognostic factor for OS. The survival outcome of the Nd group was dismal, and no patients achieved a 5-year survival. This result suggests that LNM in Nd stations represents progression to systemic disease. Therefore, the surgical strategy for DC should be determined based on the metastatic LN station. Tumors without LNM can be treated with surgery alone, and PR without radical lymphadenectomy may be feasible in such cases. T1a tumors should be regarded as having no LNMs as demonstrated in the present study, minimally invasive procedures, such as laparoscopic endoscopic cooperative surgery,[19] may be a beneficial approach for these patients. However, relying solely on preoperative imaging studies to accurately predict patients without lymph node metastasis (LNM) may be challenging,[20,21] and sentinel node navigation surgery may therefore be useful in providing stronger evidence against LNM in such cases.[12,22] Tumors with LNM in Np stations should be treated with PD with regional LN dissection, although additional treatment is needed, as shown in previous reports.[1–9] Two large cohort studies using propensity score-matched analyses showed the efficacy of adjuvant chemotherapy for DC with LNM.[13,23] Patients with DC showing LNM at Np stations may be good candidates for adjuvant chemotherapy after surgical treatment. In contrast, tumors with LNM in Nd stations should be considered potentially unresectable DCs with systemic disease progression. Upfront resection for these lesions should be avoided, and neoadjuvant chemotherapy may be needed to improve survival.[24,25] Currently, FOLFOX (5FU + Leucovorin + Oxaliplatin)[26–29] and CAPOX (Capecitabine + Oxaliplatin)[30] are considered the most effective treatment regimens for small bowel adenocarcinoma including DC. Treatment for advanced DC should be started as soon as possible. Although FOLFOX requires the placement of a central venous port, CAPOX can serve as a beneficial neoadjuvant chemotherapy (NAC) regimen, as it can be administered immediately in an outpatient setting. The multimodal treatment of advanced DC should be established in the future.

Several limitations associated with the current study should be considered. First, it was retrospective in nature and had a single-institutional setting with a limited number of patients. The proportions of patients with DC located in the first or the third/fourth portion were especially small. In addition, the limited number of patients with LNM, coupled with the infrequency of LN dissection for the SM LN station, hindered the adequate validation of the efficacy of LN dissection, particularly in the distal duodenum. Second, there was variation in the number of cases of each T stage, with more cases of T1a and T4 than of T2 and T3. Third, the current study

TABLE 3 Index of estimated benefit from lymph node dissection.

LN station	First portion			Second portion			Third and fourth portion		
	n = 15			*n* = 70			*n* = 13 (11 and 2)		
	Frequency of metastasis	5-year OS rate	EI	Frequency of metastasis	5-year OS rate	EI	Frequency of metastasis	5-year OS rate	EI
Gastric LN	0.00 (0/2)	N.A.	0.00	11.11 (1/9)	0.00	0.00	0.00 (0/1)	N.A.	0.00
Supra-pyloric LN	0.00 (0/2)	N.A.	0.00	7.14 (1/14)	0.00	0.00	0.00 (0/3)	N.A.	0.00
Sub-pyloric LN	**11.11 (1/9)**	**100.0**	**11.11**	2.56 (1/39)	0.00	0.00	0.00 (0/5)	N.A.	0.00
HA LN	0.00 (0/11)	N.A.	0.00	10.26 (4/39)	0.00	0.00	0.00 (0/3)	N.A.	0.00
HDL LN	**10.00 (1/10)**	**100.00**	**10.00**	5.26 (2/38)	0.00	0.00	0.00 (0/2)	N.A.	0.00
Peri-Ph LN	**16.67 (2/12)**	**50.00**	**8.34**	**40.38 (21/52)**	**51.70**	**20.88**	**12.50 (1/8)**	**100.00**	**12.50**
SM LN	0.00 (0/6)	N.A.	0.00	7.14 (1/14)	0.00	0.00	0.00 (0/2)	N.A.	0.00
Mesojejunal LN	0.00 (0/1)	N.A.	0.00	0.00 (0/9)	N.A.	0.00	0.00 (0/5)	N.A.	0.00

Note: Lymph nodes stations with high EI are indicated in bold.

included patients who underwent only LN sampling or no systemic LN dissection, due to the inclusion of patients who underwent PR for T1a tumors. As a result, the frequency of metastasis and EI might have been overestimated in LNs that were not frequently dissected. An additional large-scale, multi-institutional study will be required to accurately define the Np and Nd LN stations and validate the present findings because of the rarity of DC and the limited number of cases available for review at a single institution. Furthermore, prospective studies with defined LN dissection coverage are required to validate the effects of LN dissection using the EI.

In conclusion, LN dissection of the Np stations contributed to acceptable survival, whereas LNM in the Nd stations led to poor survival. LNM at Nd stations may reflect advanced tumor progression to systemic disease in patients with DC.

AUTHOR CONTRIBUTIONS

Yuya Miura and Katsuhisa Ohgi developed the main concepts and designed the study. Ryo Ashida, Mihoko Yamada, Shimpei Otsuka, and Teiichi Sugiura were responsible for acquisition of clinicopathological data. Yuya Miura and Katsuhisa Ohgi performed the data analysis, interpretation, and drafted the manuscript. Ryo Ashida, Mihoko Yamada, Shimpei Otsuka, Keiko Sasaki, Katsuhiko Uesaka, and Teiichi Sugiura contributed to the editing and critical intellectual content. All authors have read and approved the final manuscript.

FUNDING INFORMATION

The authors declare that no external funding was received for this study.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest for this article.

ETHICS STATEMENT

The study protocol for this research project was approved by a suitable Institutional Ethics Committee and conformed to the provisions of the Declaration of Helsinki. The Institutional Review Board of Shizuoka Cancer Center approved this study (J2021-82-2021-1-3).

Informed Consent: N/A.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Miura Y, Ohgi K, Ashida R, Yamada M, Otsuka S, Sasaki K, et al. Efficacy of lymph node dissection for duodenal cancer according to the lymph node station. Ann Gastroenterol Surg. 2024;8:51–59. https://doi.org/10.1002/ags3.12731