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ORIGINAL SCIENTIFIC REPORT

The Prognostic Relevance of the Number and Location of Positive Lymph Nodes for Ampulla of Vater Carcinoma

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Abstract

Background Lymph node metastasis (LNM) has been regarded as one of the prognostic factors in patients with ampulla of Vater carcinoma (AC). However, the consensus about an optimal cutoff value of the number of LNMs and the definition of the regional lymph nodes (RLNs) has not been achieved.

Methods This study included 114 consecutive patients who underwent pancreatoduodenectomy for AC between January 2002 and March 2019.

Results The minimum p value approach for the greatest difference in the overall survival classified the number of LNM into none (N0, $n = 66$), from 1 to 2 (N1, $n = 32$), and ≥ 3 LNM (N2, $n = 11$) ($p = 0.004$). Distant LNM was defined as M1 ($n = 5$). Significant differences in relapse-free survival (RFS) were found between N0 and N1 ($p < 0.001$), N1 and N2 ($p = 0.047$), and N1 and M1 ($p = 0.044$) but not between N2 and M1 ($p = 0.683$). Moreover, the patients with regional LNM were classified into two groups: Np group ($n = 35$, LNM only in pancreatic head region) and Nd group ($n = 8$, LNM in other regional location). Significant differences in the RFS were found between N0 and Np ($p < 0.001$), Np and Nd ($p = 0.004$), and Np and M1 ($p = 0.033$) but not between Nd and M1 ($p = 0.883$). A Cox proportional hazards analysis for RFS revealed that ≥ 3 LNMs (hazards ratio [HR], 3.22) and LNM except for pancreatic head region (HR, 4.27) were individually independent worse prognostic factors.

Conclusions ≥ 3 LNMs and regional LNM except for pancreatic head region were associated with poor prognosis comparable to that of the patients with M1.

Introduction

Ampulla of Vater carcinoma (AC) is rare, accounting for only 0.2% of gastrointestinal cancers and approximately 7% of all periampullary cancers [1]. AC presents with symptoms in the early phase of the disease course due to biliary obstruction; therefore, it has been known to have a comparatively favorable prognosis among periampullary malignancies, with reported 5-year OS rates of 30–70% after resection [2, 3]. However, the low incidence of AC makes it difficult to establish evidence on clinical practice and outcomes.

Lymph node metastasis (LNM) has been recognized as one of the pivotal prognostic factors [4]. LNMs are observed in 20–50% of resected AC, and survival rates of patients with LNM decrease by more than half compared to that of the patients without LNM [5–7]. Moreover, previous studies reported that the number of LNM is associated with survival; however, the cutoff values varied among these studies [8–10]. The current 8th edition of the Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) classification classified

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N-status into N0 (node negative), N1 (1 to 3 LNMs), and N2 (4 or more LNMs). However, Kang et al. reported that stratifying positive LNM as N1 (1 to 2 LNMs) versus N2 (3 or more LNMs) had significant prognostic value [11].

Other than the number of LNM, there are some reports to show the prognostic significance of the location of LNM in AC [12–14]. However, the classification of LNM according to its location has not been widely applied in clinical settings and the significance remains unclear. The reason for this is that the definitions of regional lymph node (RLN) varied among the staging systems, such as the UICC/AJCC classification and the staging systems of the Japanese Society of Hepato-Biliary-Pancreatic Surgery [15]. There is no evidence supporting the definition of RLN for AC in each classification. Furthermore, AC is not mentioned in the National Comprehensive Cancer Network guidelines [16]. Therefore, there is an urgent need to define RLN internationally and make the guideline regarding AC.

The aim of this study was to investigate the clinical relevance of the number of LNM and identified optimal cutoff value for further classification of N-status. Furthermore, to achieve consensus about RLN for AC, the prognostic impact of LNM according to its location was investigated.

Methods

Patient population

The study was approved by the institutional review board (J2019-130-2019-1), and each study subject provided their written informed consent. A retrospective review was performed of a prospectively maintained AC database. A total of 114 patients were diagnosed with AC between January 2002 and March 2019 and underwent pancreatoduodenectomy (PD). The patients diagnosed with neuroendocrine neoplasms, mucinous cystic neoplasms and unclassified tumors were excluded from the present study. The patients who underwent local resection, such as ampullectomy or pancreas-sparing duodenectomy, were also excluded.

Surgical strategy and procedures

PD with lymph nodes dissection was performed as the standard treatment for AC, as previously described [17]. Routine dissection of lymph nodes was performed in the following areas: lymph nodes along the common bile duct, common hepatic artery, portal vein, pyloric, infrapyloric, subpyloric, proximal mesenteric, posterior and anterior pancreaticoduodenal vessels, and the superior mesenteric vein and artery. In our institution, for all patients undergoing PD, para-aortic lymph node sampling procedures were routinely performed. When the frozen sections of sampled para-aortic lymph nodes were positive for cancer, we basically abandoned resection. However, PDs with para-aortic lymphadenectomies were performed in 5 patients with good performance status, and other tumor factors were relatively preferable for prognosis including negative lavage cytology.

Postoperative follow-up

All resected specimens were examined by a pathologist (K.S.) and evaluated based on the 8th UICC/AJCC staging system. In this study, RLNs were defined by UICC/AJCC staging system. The final surgical margins were considered positive if tumor cells were microscopically detectable at any of the resected margins. Para-aortic LNM was defined as M1. Adjuvant therapy after surgery was not performed as a standard treatment during the study periods, except for clinical trials. All patients were followed using computed tomographic scanning or abdominal ultrasound scans every 3–6 months after surgery.

Statistical analyses

Categorical variables were compared using Fisher's exact test. Survival curves were estimated using the Kaplan–Meier method, and statistical differences were examined using the log-rank test. The Cox proportional-hazards model was used for further evaluations of a multivariate analysis. The cutoff value for the number of LNM was evaluated based on a minimum p value approach [18]. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan)—a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). $p < 0.050$ was considered statistically significant.

Results

Clinicopathologic and treatment factors

Clinicopathologic and treatment factors in the patients are described in Table 1. All the five patients with M1 disease had para-aortic LNM. No patient received neoadjuvant therapy, and nine patients (7.9%) received adjuvant chemotherapy with S-1 according to the protocol of the clinical trials for the evaluation of the efficacy of adjuvant therapy for cholangiocarcinoma. Of these patients, 36 of them (31.6%) experienced disease recurrence during the study period. For recurrent disease, gemcitabine-based chemotherapy was generally performed. The median

Table 1 The clinicopathologic characteristics of patients who underwent pancreatoduodenectomy for ampullary carcinomas

Clinical variables			
Sex	Male	65	(57.0%)
	Female	49	(43.0%)
Age (years)		69.0	(40–85)*
Operation time (min)		395.5	(213–648)*
Blood loss (ml)		668	(77–4158)*
Number of retrieved lymph nodes		23	(6–62)*
Number of metastatic lymph nodes		0	(0–17)*
Pathologic variables			
Tumor size (mm)		23.0	(1.0–60.0)*
Histologic type	Well or moderately differentiated	105	(92.1%)
	Poorly differentiated	9	(7.9%)
T category (8th edition UICC)	T1a	35	(30.7%)
	T1b	16	(14.0%)
	T2	19	(16.7%)
	T3a	24	(21.1%)
	T3b	20	(17.5%)
N category (8th edition UICC)	N0	66	(57.9%)
	N1	40	(35.1%)
	N2	8	(7.0%)
Lymphatic invasion	Present	73	(64.0%)
Venous invasion	Present	26	(22.8%)
Perineural invasion	Present	22	(19.3%)
Surgical margin	Positive	1	(0.9%)
Peritoneal lavage cytology	Positive	0	(0.0%)
Para-aortic lymph node metastasis	Positive	5	(4.4%)

UICC; union for International Cancer Control

* Median (range)

follow-up time was 33.2 months (range 1.1–170.2). The 5-year RFS and OS rate was 62.4% and 67.4%, respectively.

Lymph node analysis

A total of 48 cases (42.1%) had LNM. The locations of LNMs are shown in Table 2. All of the patients with LNM had LNM along the posterior and anterior pancreaticoduodenal vessels (PHLN, peripancreatic head lymph node). PHLN are defined as lymph node groups 13 and 17 in the staging systems of the Japanese Society of Hepato-Biliary-Pancreatic Surgery [15]. PHLN are located on the anterior and posterior surface of the head of the pancreas. The upper borderline was the upper border of the pancreas (Fig. 1a). Patients with only PHLN metastasis are classified into the proximal node group (Np group: $n = 35$) in this study. In contrast, there were 8 cases with regional LNM that were not PHLNs. They are classified into distal node group (Nd group) in this study (Fig. 1b).

Table 2 Number of patients with lymph node metastasis in anatomic locations

Location of lymph node metastasis	
Proximal LNs	
LNs of PHLN	48 (100%)
Distal LNs (LNM except for PHLN)	
LNs along superior mesenteric artery	4 (8.3%)
LNs along common bile duct	2 (4.2%)
Mesenteric LNs	3 (6.3%)
Para-aortic LNs	5 (10.4%)

The numbers include overlap in patients

LN; lymph node, LNM; lymph node metastasis, PHLN; peripancreatic head lymph node

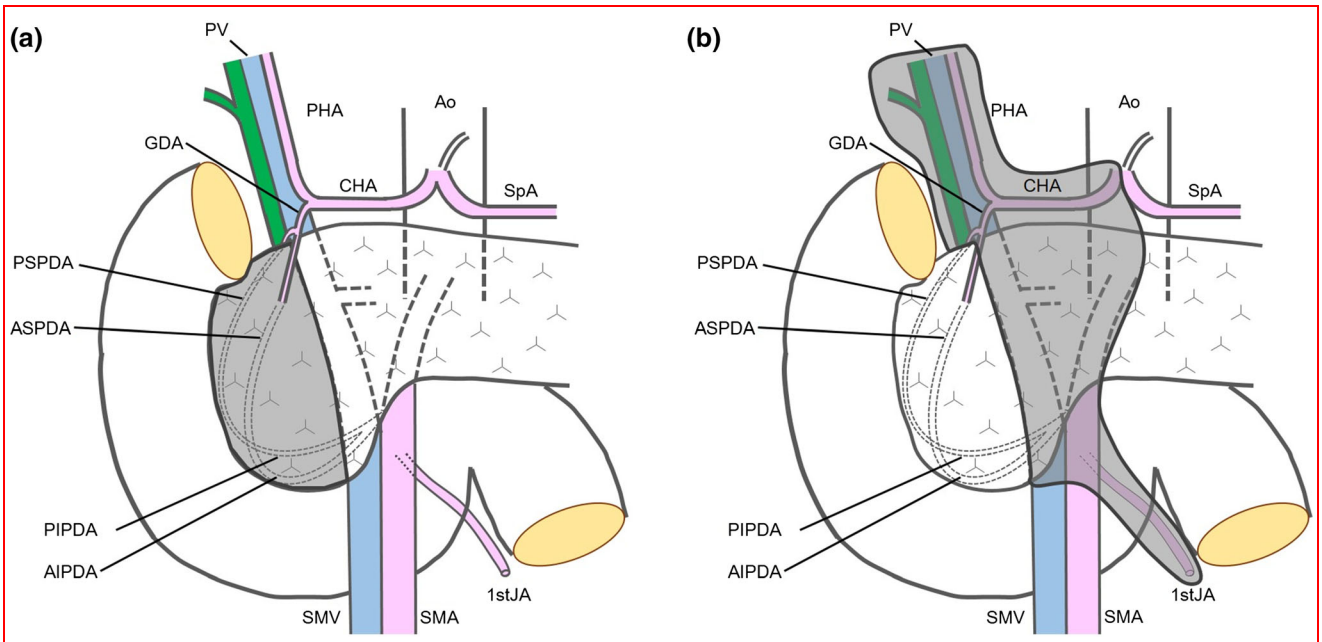

Fig. 1 Np and Nd classification **a** Np group. Peripancreatic head lymph nodes (PHLNs) are located on the anterior and posterior surface of the head of the pancreas. Moreover, the upper borderline is the upper border of the pancreas. Patients with only PHLN metastasis are classified into Np group. **b** Nd group. The patients with regional LNM that are not PHLN but are lymph nodes along the common bile duct, common hepatic artery, portal vein, pyloric, infrapyloric, subpyloric, proximal mesenteric, and the superior mesenteric vein and artery are classified into the Nd group. The lymph nodes along the pyloric, infrapyloric, and subpyloric regions are omitted in this figure. Abbreviations: AIPDA, anterior inferior pancreaticoduodenal artery; Ao, Aorta; ASPDA, anterior superior pancreaticoduodenal artery; CHA, common hepatic artery; GDA, gastroduodenal artery; PIPDA, posterior inferior pancreaticoduodenal artery; PSPDA, posterior superior pancreaticoduodenal artery; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein; SpA, splenic artery; 1stJA, first jejunal artery

A comparison of the prognosis according to the number of lymph node metastasis

The optimal number of LNM cutoff value for nodal classification was determined using the prognostic differences of 48 patients with LNM. The optimal number of LNM for dividing patients into two groups using the greatest difference in OS was 3 or more ($p = 0.004$) when using the minimum p value approach (Fig. 2). Based on this result, we proposed a new nodal classification as N0 (node negative), N1 (1–2 LNMs, n = 32), and N2 (3 or more LNMs, $n = 11$). When this proposed classification was applied, significant differences in the RFS and OS were found between N0 and N1 (RFS, $p < 0.001$; OS, $p = 0.003$), N1 and N2 (RFS, $p = 0.047$; OS, $p = 0.007$), and N1 and M1 (RFS, $p = 0.044$; OS, $p = 0.040$) but not between N2 and M1 (RFS, $p = 0.683$; OS, $p = 0.854$) (Fig. 3). On the other hand, when the 8th UICC/AJCC staging system was applied, significant differences in the RFS and OS were found between N0 and N1 (RFS, $p < 0.001$; OS, $p < 0.001$), but not between N1 and M1 (RFS, $p = 0.055$; OS, $p = 0.071$) and N2 and M1 (RFS, $p = 0.890$; OS, $p = 0.963$) (Fig. 3). As for N1 and N2, significant differences in the OS were found ($p = 0.040$), but not found in the RFS ($p = 0.069$) (Fig. 4). A multivariate analysis for RFS using the Cox proportional hazards analysis adjusted for pancreatic invasion, duodenal invasion, lymphatic invasion, venous invasion, and 3 or more LNMs identified that the presence of 3 or more LNMs was the only independent prognostic factor associated with RFS (HR, 3.22 [1.47–7.06, $p = 0.004$]) (Table 3).

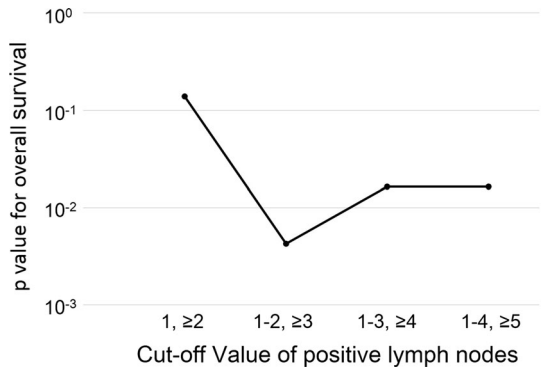

Fig. 2 The optimal lymph node metastasis number based on the prognostic differences of the patients

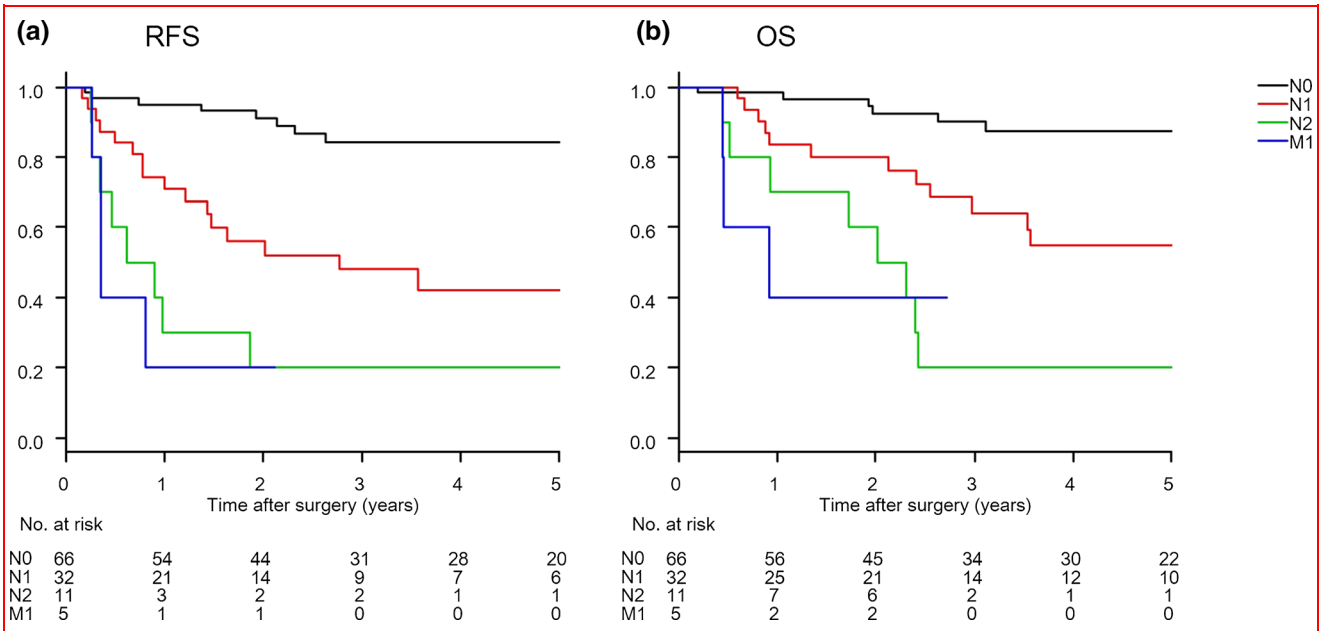

Fig. 3 Prognostic stratification according to the number of the lymph node metastasis, based on our proposal classification. **a** The RFS curves of the no lymph node metastasis group, metastasis in 1 or 2 regional lymph nodes group, metastasis in 3 or more regional lymph nodes group, and para-aortic lymph node metastasis group. **b** The OS curves of the no lymph node metastasis group, metastasis in 1 or 2 regional lymph nodes group, metastasis in 3 or more regional lymph nodes group, and para-aortic lymph node metastasis group

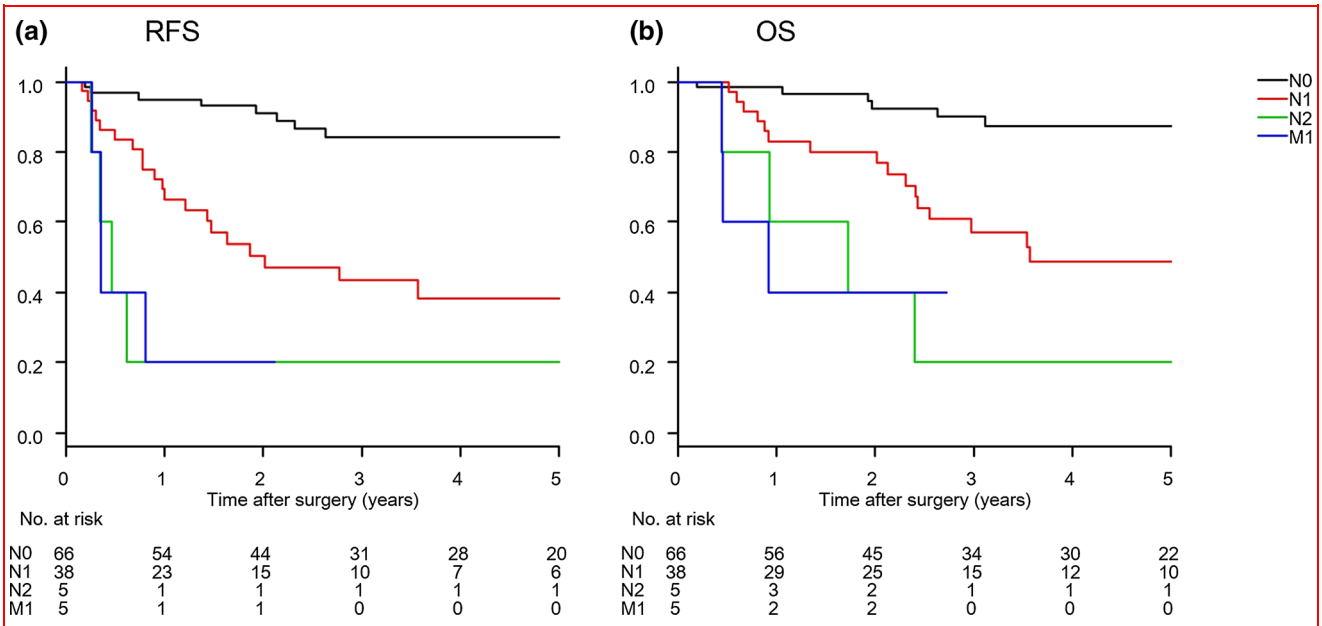

Fig. 4 Prognostic stratification according to the number of the lymph node metastasis, based on the 8th UICC/AJCC classification. **a** The RFS curves of the no lymph node metastasis group, metastasis in 1–3 regional lymph nodes group, metastasis in 4 or more regional lymph nodes group, and para-aortic lymph node metastasis group. **b** The OS curves of the no lymph node metastasis group, metastasis in 1–3 regional lymph nodes group, metastasis in 4 or more regional lymph nodes group, and para-aortic lymph node metastasis group

Table 3 Univariate and multivariate analyses for relapse-free survival of ampulla of Vater carcinoma patients using Cox proportional-hazards analysis adjusted for pancreatic invasion, duodenal invasion, lymphatic invasion, venous invasion, and 3 or more LNMs

	Variable	Number	3yRFS (%)	Univariate analysis	Multivariate analysis		*p* Value
				p Value	HR	95% CI	
Pancreatic invasion	Positive	41	41.2	<0.001*	1.48	0.70–3.12	0.304
	Negative	73	75.9		1.000		
Duodenal invasion	Positive	79	53.0	<0.001*	3.23	0.59–17.64	0.175
	Negative	35	92.3		1.000		
Lymphatic invasion	Positive	73	50.9	<0.001*	2.15	0.62–7.48	0.230
	Negative	41	87.7		1.000		
Venous invasion	Positive	26	49.2	0.044*	1.13	0.55–2.30	0.744
	Negative	88	68.8		1.000		
The number of LNM	≥3	14	15.4	<0.001*	3.22	1.47–7.06	0.004*
	≤2	100	71.2		1.000		

* statistical significance

3yRFS 3-year relapse-free survival, HR hazard ratio, CI confidence interval, LNM lymph node metastasis

A comparison of the prognosis according to the location of lymph node metastasis

The patients were classified into four groups with respect to the location of LNM, i.e., N0 group (node negative, $n = 66$), Np group ($n = 35$), Nd group ($n = 8$), and M1 group ($n = 5$). When this proposed classification was applied, significant differences in the RFS and OS were found between N0 and Np (RFS, $p < 0.001$; OS, $p = 0.002$), and Np and Nd (RFS, $p = 0.004$; OS, $p = 0.004$), but not between Nd and M1 (RFS, $p = 0.883$; OS, $p = 0.826$). As for Np and M1, significant differences in the RFS were found ($p = 0.033$), but not found in the OS ($p = 0.0568$) (Fig. 5). A multivariate analysis for RFS using the Cox proportional hazards analysis adjusted for pancreatic invasion, duodenal invasion, lymphatic invasion, venous invasion, and LNM except for PHLN identified that LNM except for PHLN was the only independent prognostic factor associated with RFS (HR, 4.27 [1.92–9.48, $p < 0.001$]) (Table 4).

Discussion

The purpose of this study was to propose an optimal classification of LNM according to the number of LNM and to define RLN of AC based on clinical relevance. The results of this study could propose an alternative classification of N-status into N0 (none), N1 (1–2 LNMs), and N2 (3 or more LNMs). The prognosis of patients with 3 or more LNMs was comparable with that of patients with distant metastasis. Moreover, all of the patients with LNM had PHLN metastasis, while there were only 8 cases (7.0%) in the Nd group. The prognostic outcome in patients in the Nd group was significantly worse than that of Np group and comparable to that of the patients with M1.

For AC, as well as other digestive system tumors [19–22], the number of LNM has been regarded as a prognostic factor [8–10, 23]. However, the cutoff value varied among studies [8–10]. Lee et al. [24] noted the factor of 3 or more LNMs had the independent power in predicting a poor outcome in patients with AC after resection. Meanwhile, Sierzega et al. [25] reported that 4 or more LNMs was the independent prognostic factor in patients with AC. In this study, the presence of 3 or more LNMs was identified as a best cutoff value, and the prognostic stratification of our classification was better than that of UICC/AJCC classification; however, an absolute LNM cutoff value is still contentious. Larger sample sizes are needed to prove the optimal cutoff value of LNM.

There is no consensus on the extent of lymphadenectomy for AC. Therefore, the number of nodes retrieved is different between institutions. AJCC recommends 12 or more lymph nodes evaluated for accurate nodal staging. In this study, the median number of lymph nodes examined was 23. Therefore, staging in this study might be qualifiable. The different number and different extent of examined lymph nodes potentially caused stage migration and resulted in the different cutoff value among studies. Therefore, unification of the definition of RLN for AC is a priority issue.

The prognostic significance of the location of LNM has also widely accepted in AC [12–14]. In this study, only 7.0% of the patients had Nd LNM and the prognosis with

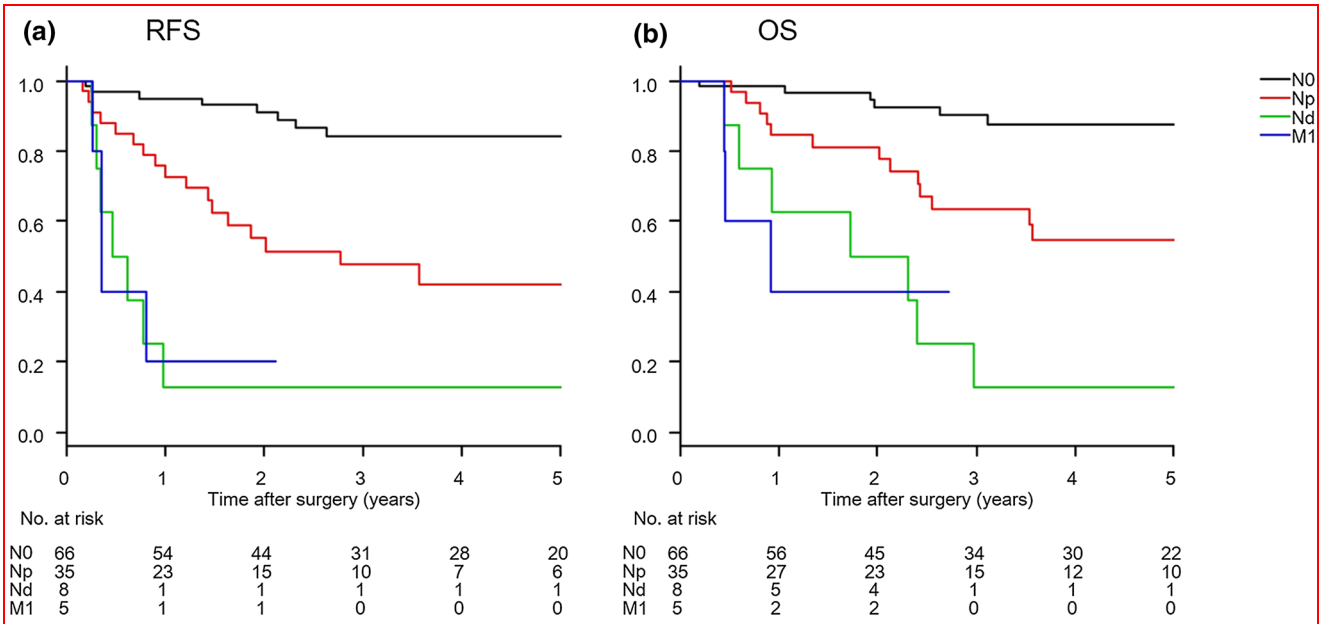

Fig. 5 Prognostic stratification according to the location of the lymph node metastasis. **a** The RFS curves of the no lymph node metastasis group, Np group (metastasis along posterior and anterior pancreaticoduodenal vessels), Nd group (metastasis in other regional areas), and para-aortic lymph node metastasis group. **b** The OS curves of the no lymph node metastasis group, Np group (metastasis along the posterior and anterior pancreaticoduodenal vessels), Nd group (metastasis in other regional areas), and para-aortic lymph node metastasis group

Table 4 Univariate and multivariate analyses for relapse-free survival of ampulla of Vater carcinoma patients using Cox proportional-hazards analysis adjusted for pancreatic invasion, duodenal invasion, lymphatic invasion, venous invasion, and LNM except for PHLN

	Variable	Number	3yRFS (%)	Univariate analysis	Multivariate analysis		*p* Value
				p Value	HR	95% CI	
Pancreatic invasion	Positive	41	41.2	<0.001*	1.56	0.75–3.24	0.235
	Negative	73	75.9		1.000		
Duodenal invasion	Positive	79	53.0	<0.001*	3.41	0.63–18.34	0.154
	Negative	35	92.3		1.000		
Lymphatic invasion	Positive	73	50.9	<0.001*	2.11	0.61–7.28	0.237
	Negative	41	87.7		1.000		
Venous invasion	Positive	26	49.2	0.044*	1.08	0.52–2.26	0.840
	Negative	88	68.8		1.000		
LNM except for PHLN	Positive	13	15.4	<0.001*	4.27	1.92–9.48	<0.001*
	Negative	101	71.1		1.000		

*Statistical significance

3yRFS 3-year relapse-free survival, HR hazard ratio, CI confidence interval, LNM lymph node metastasis, PHLN peripancreatic head lymph node

Nd LNM was comparable with distant metastasis. The findings might suggest that the dissection of Nd LNM may provide little clinical benefit of upfront surgery. In fact, it has been reported that the involvement of the superior mesenteric nodes indicates a poor outcome after resection [13]. Lymphatic invasion of AC is considered toward superior mesenteric artery along the posterior pancreaticoduodenal vessels because ampulla of Vater is derived embryologically from ventral pancreas [26]. Therefore, the invasion may be unlikely to be toward the gastric duodenal artery, common hepatic artery, and pyloric, infrapyloric, and subpyloric vessels [26]. In this series, five patients had

para-aortic LNM at the time of PD, and three of them died of the disease within a year after resection. De Castro et al. also reported similar results [27]. These results suggest that only PHLNs were defined as RLN and the other nodes might be suitable to be excluded from RLN for AC.

There is also no consensus on the best chemotherapy for patients with advanced AC because of the rarity of this disease. In our institution, adjuvant therapy was not performed in any patients regardless of the staging of the AC, except for clinical trials, because of the lack of data from randomized trials proving a survival advantage. A meta-analysis of 14 studies found no associated survival benefit for adjuvant therapy in the treatment of periampullary cancer [28]. In the systematic review, a total of 1671 patients (904 in the control group and 767 who received adjuvant therapy) were included. The median 5-year OS rate was 37.5% in the control group, while it was 40.0% in the adjuvant group (HR, 1.08 [0.91–1.28, $p = 0.067$]) [28]. Based on the results from the ABC-02 trial, it is considered that the combination of gemcitabine and cisplatin is a reasonable approach [29]. Similarly, there is no consensus regarding the optimal management of patients after curative resection. However, some studies show that adjuvant chemotherapy was associated with improved survival in patients with resected AC, especially with advanced stage disease [2, 30–32]. The patients will likely be treated with a fluorouracil- or gemcitabine-based regimen as extrapolated using data from other cases of periampullary cancers [2, 30, 31]. Because the prognosis of the patients with 3 or more LNM and/or Nd LNM was comparable with that of the patients with distant metastasis after curative resection, systemic chemotherapy is preferable for the patients that are preoperatively suspected of having 3 or more LNM and/or Nd LNM.

This study is associated with some limitations, including its retrospective nature, short follow-up period, and the fact that it was conducted in a single center. In particular, N2, Nd, and M1 patients were only 11 (9.6%), 8 (7.0%), and 5 (4.4%), respectively. From the viewpoint of LNM, the population in each subgroup is biased and relatively small in some subgroups, potentially leading to a statistical type II error. Therefore, larger sample sizes are needed in order to prove that the stratification of the prognosis in the 8th edition is insufficient. Further prospective studies are required to precisely evaluate the clinical significance of LNM in the treatment of AC.

Reconsidering the N category based on the prognostic impact, it can be reasonable that only PHLN would be defined as RLN, and the optimum cutoff value was 3 or more. Surgical indications may be carefully determined in patients with suspected Nd LNM or 3 or more LNMs based on the preoperative images. After surgery, for the patients with Nd LNM or 3 or more LNMs confirmed by pathologic examination, addition of chemotherapy may need to be considered to improve survival.

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Compliance with ethical standards

Conflict of interest :The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all participants included in the study.

Statement of human rights The study was approved by the institutional review board (J2019-130-2019-1), and each study subject provided their written informed consent.

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