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ORIGINAL ARTICLE—ALIMENTARY TRACT

Clinicopathological features and risk factors for lymph node metastasis in early-stage non-ampullary duodenal adenocarcinoma

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Abstract

Background Management strategies for primary non-ampullary duodenal adenocarcinoma (NADAC) in early stage are not well established given its low incidence. This study aimed to elucidate clinicopathological features of early NADAC, including risk for lymph nodal metastasis (LNM).

Methods In total, 166 patients with early NADAC underwent initial treatment at our institution between 2006 and 2019, of whom 153 had intramucosal (M-) and 13 had submucosal (SM-) NADAC. These endoscopic and pathological features were retrospectively analyzed. Risk factors for LNM were evaluated in 46 early NADAC patients who underwent surgery with lymph node dissection.

Results Compared with M-NADAC, SM-NADAC was significantly more frequently located at the proximal side of the papilla, with mixed elevated and depressed macroscopic type, histologically poorly differentiated tumor and lymphovascular invasion (LVI) (85% vs. 47%, $P = 0.009$; 54% vs. 5%, $P < 0.001$; 23% vs. 0%, $P < 0.001$; and 46% vs. 0%, $P < 0.001$, respectively). The frequency of LNM was significantly higher in SM-NADAC than in M-NADAC (5/12, 42% vs. 0/34, 0%; $P < 0.001$). In SM-NADAC, the frequency of LNM was higher in poorly differentiated than in well to moderately differentiated tumors (3/3, 100% vs. 2/9, 22%) and higher in tumors with LVI than in those without LVI (3/5, 60% vs. 2/7, 29%). Regarding invasion depth, 2 of 4 patients with SM invasion ($400 \leq \times < 500$ μm) showed LNM. However, in this study, no patients developed very shallow SM invasion ($0 < \times < 400$ μm).

Conclusions SM-NADAC showed high LNM risk. Surgical treatment with regional lymph node dissection is recommended as a treatment strategy for SM-NADAC.

Keywords Duodenum · Non-ampullary duodenal adenocarcinoma · Submucosal invasive cancer · Lymph node metastasis · Clinicopathological features

Introduction

The prevalence of non-ampullary duodenal epithelial tumors is extremely low, as per autopsy studies (0.02–0.5%) [1–3], and primary non-ampullary duodenal adenocarcinoma (NADAC) accounts for only 0.5% of all gastrointestinal malignancies [4]. Owing to the rarity of its occurrence, information regarding NADAC is still lacking. The number of treatment cases for NADAC has recently increased owing to the widespread use of routine esophagogastroduodenoscopy, which is usually performed on the duodenum during regular medical check-ups. Early NADAC is further classified into intramucosal NADAC (M-NADAC; T1a) and submucosal invasive NADAC (SM-

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NADAC; T1b) based on the depth of tumor invasion, as per the TNM classification of malignant tumors [5]. With regard to the risk for lymph node metastasis (LNM), an analysis of M-NADACs showed no incidence of LNM [6, 7]. Therefore, M-NADACs can be treated with local resection without lymph node dissection, with techniques such as endoscopic resection (ER) and organ-preserving surgical procedures such as transduodenal local excision and wedge resection. In contrast, the incidence of LNM in SM-NADAC has been reported only in small case series to date [6, 8]. Therefore, at present, the standard treatment method for SM-NADAC is radical surgery with regional lymph node dissection, including pancreaticoduodenectomy [9, 10]. Thus, it is crucial to diagnose early NADAC invasion depth accurately in preoperative examinations to select the suitable treatment method. However, the endoscopic characteristics of SM-NADAC have not been investigated in detail, and the diagnostic criteria for SM invasion have not been established. Furthermore, even though there is an established consensus on the risk factor for LNM in other SM invasive gastrointestinal tract cancers such as gastric cancer (GC) [11–14] and colorectal cancer (CRC) [15–17], no studies have investigated the risk for LNM in SM-NADAC. Thus, this study aimed to clarify endoscopic features in determining the invasion depth of early NADAC and to evaluate risk factors for LNM.

Methods

Patients

At our institution, 166 patients with early NADAC, including 153 and 13 patients with M-NADAC and SM-NADAC, respectively, underwent initial treatment between September 2006 and December 2019. Among all 166 patients, 46 (34, M-NADAC and 12, SM-NADAC) received surgical resection with lymph node dissection, and 120 (119, M-NADAC; 1, SM-NADAC) received local resection without lymph node dissection. The exclusion criteria were tumors involving the papilla and tumors arising in the setting of familial adenomatous polyps.

This single-institutional retrospective observational study was conducted to analyze the following: (1) the endoscopic and pathological features used in determining the depth of invasion were analyzed in all 166 patients with M-NADAC and SM-NADAC, (2) the LNM rate according to the depth of invasion was analyzed in 46 patients with early NADAC who underwent surgical resection with lymph node dissection, including 34 and 12 patients with M-NADAC and SM-NADAC, respectively, and (3) in a subgroup analysis, the risk factors for LNM were analyzed in 12 patients with SM-NADAC.

This study was approved by the Institutional Review Board of the Cancer Institute Hospital of Japanese Foundation for Cancer Research (IRB No. 2018-1114).

Clinical and endoscopic characteristics

Preoperative clinical data, including patient age, sex, and endoscopic characteristics, such as tumor size, location, macroscopic type, and color were obtained from medical records. The macroscopic types of NADACs were categorized according to the Paris endoscopic classification [18] into the following groups: elevated type (0-Ip, 0-Is, and 0-IIa), flat type (0-IIb), depressed type (0-IIc), and mixed elevated and depressed type (0-IIa + IIc). The color was described as reddish, whitish, or isochromatic based on the color covering the largest area in the tumor. The location was divided in two ways: (i) into three sections (first, second, and third part) and (ii) into two areas (proximal and distal sides of the papilla).

Histopathological evaluation

All ER specimens were sectioned at 2- to 3-mm intervals, while surgical specimens were sectioned at 5-mm intervals. Subsequently, they were embedded into paraffin blocks. From each block, 4-μm-thick sections were stained with hematoxylin and eosin, and the following were evaluated: tumor size, tumor differentiation (histological grade), tumor invasion depth, lymphovascular invasion (LVI), and LNM. Based on tumor differentiation, NADACs were categorized into the following groups according to the WHO classification [19]: well differentiated (low grade), moderately differentiated (intermediate grade), and poorly differentiated (high grade). In SM (T1b) tumor, the extent of the SM invasion was assessed by measuring the distance from the muscularis mucosa to the invasive front, according to the recommendation by the Japanese Gastric Cancer Association [20]. For evaluating LNM, regional lymph node dissections were performed according to the TNM staging system of the Union for International Cancer Control (UICC) 8th Edition [5], and patients were diagnosed as pathological N0 if all lymph nodes were negative for cancer.

Immunohistochemistry

To determine the tumor immunophenotype, immunohistochemical staining was performed on sections from all 12 SM-NADAC lesions using the following antibodies: MUC5AC glycoprotein (MUC5AC; clone CLH2, Leica Biosystems Nussloch GmbH, Nussloch, Germany, diluted 1: 500), MUC6 glycoprotein (MUC6; clone CLH5, Leica Biosystems, diluted 1: 300), MUC2 glycoprotein (MUC2;

clone Ccp58, Leica Biosystems, Bond ready to use reagent), and CD10 protein (CD10; clone 56C6, Leica Biosystems, diluted 1:100). The BOND III autostainer (Leica Biosystems) was used according to the protocol recommended by the manufacturer. In accordance with previous publications, the tumor was defined as being positive for each marker when $> 10\%$ of the neoplastic cells were stained [21, 22]. Immunophenotype features were categorized into the following: gastric type (expression of gastric markers, MUC5AC and/or MUC6), intestinal type (expression of intestinal markers, MUC2 and/or CD10), mixed type (expression of both gastric and intestinal markers), and null type (no expression of markers) [21, 23]. The immunohistochemical staining was assessed by three evaluators, including an expert gastrointestinal pathologist.

Statistical analysis

Statistical analyses were performed using SPSS software version 24.0 (SPSS, Chicago, IL). We compared categorical parameters using the Wilcoxon signed-rank test and the Chi squared test and continuous parameters using a Mann–Whitney U test. P values < 0.05 were considered statistically significant.

Results

Comparison of clinicopathological features between M-NADAC and SM-NADAC in all patients

A comparison of the clinicopathological features between M-NADAC and SM-NADAC is shown in (Table 1). Proximal side tumor location, mixed elevated and depressed macroscopic type, histologically poorly differentiated tumor, and the presence of LVI were significantly more frequent in SM-NADAC than in M-NADAC (85% vs. 47%, $P = 0.009$; 54% vs. 5%, $P < 0.001$; 23% vs. 0%, $P < 0.001$; and 46% vs. 0%, $P < 0.001$, respectively). In terms of the operative procedure, a large proportion of M-NADAC cases had undergone ERs, while a large proportion of SM-NADAC cases had undergone surgical resections with lymph node dissection, and the difference was significant ($P = 0.001$). No significant differences were found in age, sex, tumor size, and color between the two groups.

Clinicopathological profiles of SM-NADAC

The clinicopathological characteristics and endoscopic features of the 13 patients with SM-NADAC are summarized in (Table 2, Fig. 1). The median age was 67 (range: 49–83) years, and there were six male and seven female patients. The median tumor size was 12.0 (range, 6–70) mm; four patients (31%) had a small tumor size of ≤ 10 mm. Moreover, 11 (85%) had tumors located in the proximal side of the papilla. On assessing the macroscopic type, all lesions were elevated or mixed elevated and depressed type, such as 0-Is, 0-IIa, and 0-IIa + IIc. A high proportion of patients had reddish color lesions (9 patients, 69%). With regard to the operative procedures, surgical treatment and ER were performed in 11 and 2 patients, respectively. Regarding tumor differentiation (Fig. 2), 5, 5, and 3 patients were classified has having well-, moderately, and poorly differentiated tumors, respectively. Regarding tumor immunophenotype (Fig. 3), the mixed immunophenotype was the most frequent (seven patients), followed by gastric (five patients) and intestinal (1 patient) types; gastric marker expression was identified in 12 patients (92%). The median (range) SM invasion depth was 1100 (400–3000) μm. According to the UICC 8th edition of TNM staging system [5], 8, 4, and 1 patient corresponded to stages I, IIIA, and IIIB, respectively. Recurrence by metachronous metastasis developed in three patients (23%) during the 31 months (median) of postoperative observation period. Of the three patients with metastatic recurrence, one developed local and lymph node recurrence and died of SM-NADAC at 11 months, and another patient developed lung, bone, and brain metastasis and died of SM-NADAC at 31 months. The remaining one patient developed mesenteric lymph node recurrence and received chemotherapy; this patient was alive at the last follow-up, with an estimated survival period of 77 months.

Comparison of the frequency of LNM between M-NADAC and SM-NADAC patients undergoing surgical resection with lymph node dissection

The frequency of LNM in patients who underwent surgical resection with lymph node dissection was significantly higher in SM-NADAC than in M-NADAC (5/12, 42%, 95% CI: 15–72% vs. 0/34, 0%, 95% CI: 0–10%; $P < 0.001$). M-NADACs showed no incidence of LNM (Table 3).

Risk for LNM in SM-NADAC

As LNM is found only in those with SM-NADAC, the risk for LNM was evaluated for patients with SM-NADAC that received surgical resection. The relationship between LNM and histopathological factors in SM-NADAC is shown in Table 4. LNM was more frequent in histologically poorly differentiated tumors and in tumors with LVI than in well- to moderately differentiated tumors and in tumors without LVI, respectively. Regarding the invasion depth, none of

Table 1 Comparisons of clinicopathological features between M-NADAC and SM-NADAC in all patients

	M-NADAC (n = 153)	SM-NADAC (n = 13)	P value
Age, median (range), years	64 (36–86)	67 (49–83)	0.19
Sex, n (%)			0.18
Male	99 (65)	6 (46)	
Female	54 (35)	7 (54)	
Location, n (%)			0.009
Proximal side of the papilla	72 (47)	11 (85)	
Distal side of the papilla	81 (53)	2 (15)	
Macroscopic type, n (%)			< 0.001
Elevated	116 (76)	6 (46)	
Depressed	29 (19)	0 (0)	
Mixed (elevated and depressed)	8 (5)	7 (54)	
Color, n (%)			0.71
Reddish	98 (64)	9 (69)	
Whitish or isochromatic	55 (36)	4 (31)	
Tumor size, median (range), mm	18.0 (3.0–92.0)	12.0 (6.0–70.0)	0.40
Operative procedure, n (%)			0.001
Endoscopic resection	94 (61)	2 (15)	
Surgical resection	59 (39)	11 (85)	
Lymph node dissection, n (%)			< 0.001
Done	34 (22)	12 (92)	
Not done	119 (78)	1 (8)	
Tumor differentiation, n (%)			< 0.001
Well to moderately	153 (100)	10 (77)	
Poorly	0 (0)	3 (23)	
LVI, n (%)			< 0.001
Absent	153 (100)	7 (54)	
Present	0 (0)	6 (46)	

LVI lymphovascular invasion; *M-NADAC* intramucosal non-ampullary duodenal adenocarcinoma; *SM-NADAC* submucosal invasive non-ampullary duodenal adenocarcinoma

the patients developed very shallow SM invasion ($0 < \times < 400$ μm). We found that two of four patients developed LNM in the group with shallow SM invasion ($400 \leq \times < 500$ μm). One of these patients had a histologically poorly differentiated tumor with LVI (case A, Table 2), and the other patient had a histologically moderately differentiated tumor without LVI (case G, Table 2). LNM incidence according to the immunophenotype was 2 of 4, 3 of 7, and 0 of 1 in the gastric, mixed, and intestinal phenotypes, respectively.

Discussion

This study analyzed the endoscopic and pathological features in determining the depth of invasion of SM-NADAC through comparisons with that in M-NADAC. The study also evaluated the risk factors for LNM in SM-NADAC for those who underwent surgical resection with regional lymph node dissection. To the best of our knowledge, this study is the first to report the clinicopathological features of early NADAC in detail, including risk factors for LNM.

In this study, in contrast to the absence of LNM in M-NADAC, SM-NADAC showed LNM in 42% of the patients. Hence, local resection without lymph node dissection could be considered for those with M-NADAC, while surgical treatment with regional lymph node dissection could be considered for those with SM-NADAC. Owing to the differences between the standard treatment choice for M-NADAC and SM-NADAC, a precise diagnosis of the invasion depth before treatment is important. In this study, compared with M-NADAC, SM-NADAC is found more frequently in proximal side tumors, with mixed elevated and depressed macroscopic type such as 0-IIa + IIc, and histologically poorly differentiated tumors; these could be an important ancillary feature for suspecting SM invasion before treatment decision.

Niwa et al. [24] reported that in the case of NADAC, tumors located at the proximal and distal sides of the papilla had different pathogeneses. Studies demonstrated

Table 2 Clinicopathological characteristics of 13 patients with SM-NADAC

Case	Age/sex	Location	Relationship with papilla	Macroscopic type	Color	Operative procedure	Tumor size (mm)	Tumor differentiation	Immuno phenotype	SM invasion depth (μm)	LVI	LNM	TNM Stage	Metastatic recurrence	Survival time (months)	Outcome
A	60 s/F	2nd	Proximal	0-Is	Reddish	SSPPD	10	Poor	G	400	+	+	IIIB	+	11	Died
B	40 s/F	2nd	Proximal	0-IIa + IIc	Reddish	SSPPD	15	Poor	G	1800	−	+	IIIA	+	77	Alive
C	70 s/M	2nd	Proximal	0-IIa + IIc	Reddish	SSPPD	10	Mod	G	2000	+	−	I	−	31	Alive
D	50 s/M	2nd	Proximal	0-Is	Isochromatic	ER	13	Mod	G	3000	+	NA	I	−	30	Alive
E	70 s/F	1st	Proximal	0-IIa + IIc	Reddish	DG	12	Mod	G	1500	−	−	I	−	6	Alive
F	60 s/F	1st	Proximal	0-IIa + IIc	Reddish	DG	33	Well	M	700	+	+	IIIA	+	31	Died
G	80 s/M	1st	Proximal	0-Is	Isochromatic	DG	70	Mod	M	400	−	+	IIIA	−	9	Alive
H	70 s/M	2nd	Proximal	0-IIa + IIc	Reddish	SSPPD	7	Poor	M	2200	+	+	IIIA	−	6	Alive
I	80 s/M	2nd	Proximal	0-IIa	Isochromatic	SSPPD	7	Mod	M	400	−	−	I	−	83	Alive
J	50 s/M	2nd	Distal	0-IIa + IIc	Reddish	WR	12	Well	M	450	−	−	I	−	38	Alive
K	60 s/F	2nd	Proximal	0-IIa + IIc	Reddish	SSPPD	12	Well	M	700	−	−	I	−	36	Alive
L	60 s/F	1st	Proximal	0-Is	Reddish	ER	15	Well	M	3000	+	−	I	−	13	Alive
M	50 s/F	3rd	Distal	0-Is	Isochromatic	WR	28	Well	I	1500	−	−	I	−	59	Alive

DG distal gastrectomy; *ER* endoscopic resection; *F* female; G, gastric phenotype; *I* intestinal phenotype; *LNM* lymph node metastasis; *LVI* lymphovascular invasion; *M* male; *M* mixed phenotype; *Mod* moderately differentiated; *NA* not assessed; Poor, poorly differentiated; *SM* submucosal; *SM-NADAC* submucosal invasive non-ampullary duodenal adenocarcinoma; *SSPPD* subtotal stomach-preserving pancreaticoduodenectomy; *Well*, well-differentiated; *WR*, wedge resection

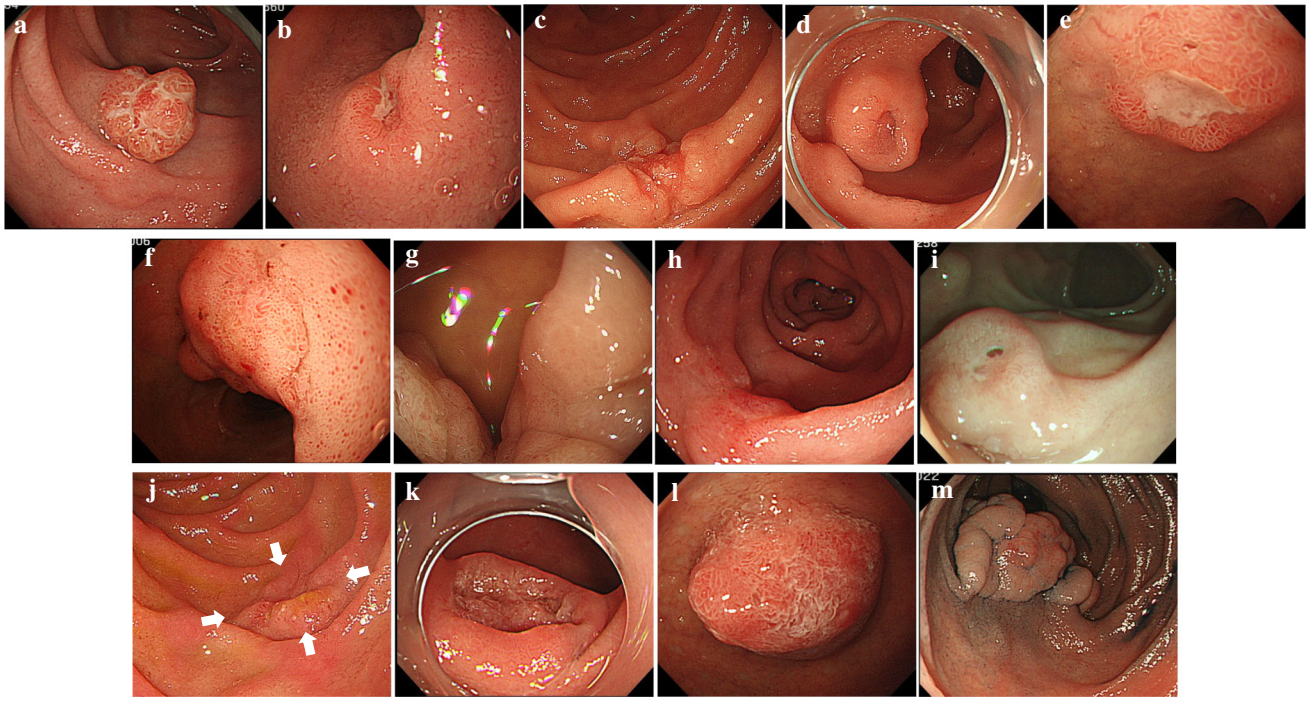

Fig. 1 Endoscopic features of 13 patients with submucosal invasive non-ampullary duodenal adenocarcinoma. The median tumor size was 12.0 mm, and four cases (**a**, **c**, **h** and **i**) showed a small tumor size of $\leq$ 10 mm. The tumors were frequently located in the proximal side of the papilla in 11 cases (**a**-**i**, **k** and **m**). Six (**a**, **d**, **g**, **i**, **l**, and **m**) were macroscopically elevated type, such as 0-Is or 0-IIa, and seven (**b**, **c**, **e**, **f**, h, **j** and **k**) were mixed elevated and depressed type, such as 0-IIa + IIc. Nine (**a**–**c**, **e**, **f**, **h**, and **j**–**l**) were reddish and 4 (**d**, **g**, **i**, and **m**) were isochromatic

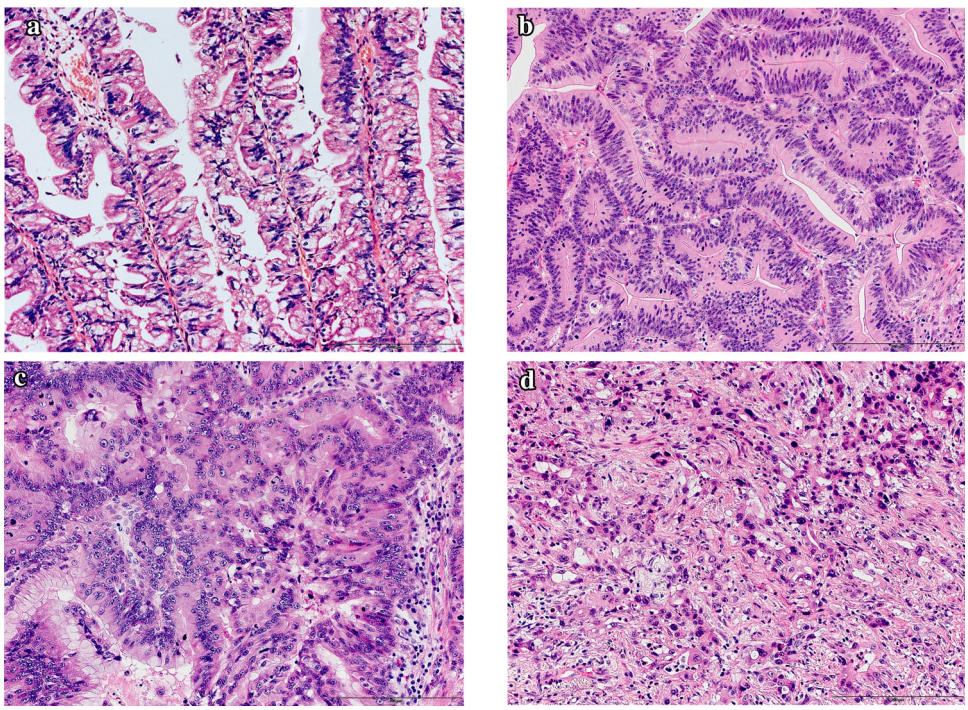

Fig. 2 Representative micrographs of each type of tumor differentiation (histological grade) of submucosal invasive non-ampullary duodenal adenocarcinoma. **a** Well-differentiated papillary adenocarcinoma (low histological grade). **b** Well-differentiated tubular adenocarcinoma (low histological grade). **c** Moderately differentiated adenocarcinoma (intermediate histological grade). **d** Poorly differentiated adenocarcinoma (high histological grade)

that NADACs with gastric marker expression in the proximal side of the papilla originated from the gastric metaplasia, Brunner's gland, or ectopic gastric mucosa [25, 26]. In addition, NADACs with gastric marker expression was reported to occasionally correlate with a higher grade of malignant potency [23, 27]. Ushiku et al.

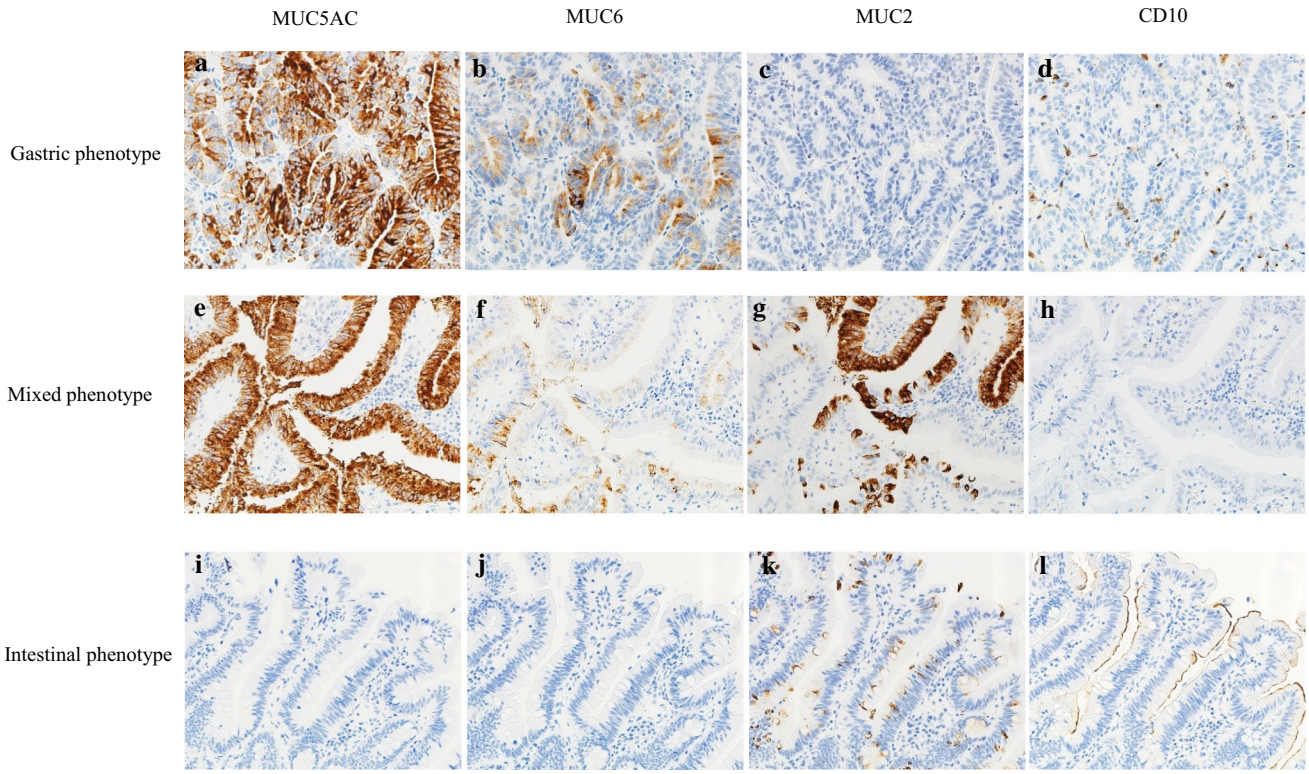

Fig. 3 Representative examples of each tumor immunophenotype of submucosal invasive non-ampullary duodenal adenocarcinoma. Gastric phenotype: tumor cells are positive for MUC5AC (**a**) and MUC6 (**b**) but negative for MUC2 (**c**) and CD10 (**d**). Mixed phenotype: tumor cells are positive for MUC5AC (**e**), MUC6 (**f**), and MUC2 (**g**) but negative for CD10 (**h**). Intestinal phenotype: tumor cells are negative for MUC5AC (**i**) and MUC6 (**j**), but positive for MUC2 (**k**) and CD10 (**l**).

Table 3 Comparison of the frequency of LNM between M-NADAC and SM-NADAC patients undergoing surgical resection with lymph node dissection

	Total	LNM positive	%	95% CI
M-NADAC	34	0	0*	0–10
SM-NADAC	12	5	42*	15–72

*$P < 0.001$

CI confidence interval; *LNM* lymph node metastasis; *M-NADAC* intramucosal non-ampullary duodenal adenocarcinoma; *SM-NADAC* submucosal invasive non-ampullary duodenal adenocarcinoma

[21] analyzed 38 cases of NADAC, including tumors of various stages such as 14 T1, 3 T2, 11 T3, and 10 T4 tumors. They demonstrated that almost all NADACs with the gastric phenotype developed in the proximal duodenum, and the gastric phenotype was associated with poorer overall survival than the intestinal phenotype [21]. In the present study, the proportion of SM-NADAC with gastric marker expression (gastric and mixed phenotypes) was 92% (12 of 13 patients), and 85% of those (11 of 13) were located at the proximal side of the papilla, which is consistent with previous reports [24]. Therefore, early NADACs with gastric marker expression in the proximal side of the papilla may have a higher malignancy potential and should be prioritized for treatment.

In many other digestive tract cancers, there is an established consensus on the risk factor for LNM. Consequently, inclusion of the differentiated phenotype (lower histologic grade) GC involving infiltration into the SM $<$ 500 μm, measuring $\leq$ 30 mm, and without LVI is currently widely accepted as an indication for ER in Japan [14], thereby reflecting the negligible risk for LNM. In addition, the inclusion of well- to moderately differentiated CRC involving infiltration into the SM layer $<$ 1000 μm, with neither LVI nor tumor budding, is also widely accepted as an indication for ER [17]. In this study, the analysis of SM invasion depth revealed that SM-NADAC, even in cases with infiltration of only the relatively shallow SM layer ($400 \leq \times < 500$ μm), showed LNM in 50% (2 of 4) of patients. Therefore, at present, we believe that conventional surgery with regional lymph node dissection is suitable as the standard treatment method for SM-NADAC. However, in this study, there was no case of very shallow SM invasion ($0 < \times < 400$ μm). Thus, whether the indication criteria for local resection without lymph node dissection can expand for SM-NADAC, in cases

Table 4 Relationship between lymph node metastasis and histopathological factors in SM-NADAC

	Total, *n*	Status of LNM, *n* (%)	
		Negative	Positive
Tumor differentiation			
Well to moderately	9	7 (78)	2 (22)
Poorly	3	0 (0)	3 (100)
LVI			
Absent	7	5 (71)	2 (29)
Present	5	2 (40)	3 (60)
SM invasion depth (μm)			
$0 < \times < 400$	0	–	–
$400 \leq \times < 500$	4	2 (50)	2 (50)
$500 \leq \times < 1{,}000$	2	1 (50)	1 (50)
$1{,}000 \leq \times < 2{,}000$	3	2 (67)	1 (33)
$2{,}000 \leq \times$	3	2 (67)	1 (33)
Immunophenotype			
Gastric phenotype	4	2 (50)	2 (50)
Mixed phenotype	7	4 (57)	3 (43)
Intestinal phenotype	1	1 (100)	0 (0)

LNM lymph node metastasis; *LVI* lymphovascular invasion; *SM* submucosal; *SM-NADAC* submucosal invasive non-ampullary duodenal adenocarcinoma

where the infiltration is limited to very shallow invasion ($0 < \times < 400$ μm), is a topic to be investigated in the future. The analyses of the risk for LNM in SM-NADAC based on the histopathological features revealed that 22% of the patients with histologically well- to moderately differentiated tumors (low-intermediate histological grade) showed LNM. Meanwhile, all patients with histologically poorly differentiated tumors (high histological grade) showed LNM; thus, higher histological grade may be a risk factor for LNM. Gotoda et al. [12] reported that the rates of LNM were higher in patients with poorly differentiated early GC than in well to moderately differentiated early GC; these findings may also extend to NADAC, because histological and genetic similarities between gastric tumors and duodenal tumors of the gastric phenotype have been reported [28]. With regard to LVI, 60% of patients with LVI showed LNM. The presence of LVI in other areas of the gastrointestinal tract has been demonstrated to be a strong independent risk factor for LNM [11–17]. Therefore, in the duodenum, LVI positivity could be a risk factor for LNM, although the results from our study may not have enough statistical power owing to the small sample size.

We believe the results of our study will help establish treatment strategies for early NADAC. For that purpose, an adequate assessment of curability for endoscopic resection in comparison with long-term surgical treatment outcomes is necessary. Further studies with a larger number of patients will be needed to reveal long-term outcomes of early NADAC. In addition to these outcomes, by investigating the surgical mortality rates, we will be able to improve the treatment strategies for patients with early NADAC. This current study may lay a foundation for this needed process.

This study has several limitations. First, this was a retrospective, single-center study. Second, given the rarity of the disease, the sample size was small. Large-scale multicenter trials and multivariate analyses to identify independent risk factors for LNM are needed to evaluate the clinicopathological features as well as the risk factors for LNM in SM-NADAC and to provide further evidence. Third, we analyzed only early NADAC cases. Future research should focus on advanced NADAC invading the muscularis propria or deeper to further clarify the risk for LNM.

In conclusion, this study demonstrated that SM-NADAC was significantly more frequently located at the proximal side of the papilla, with mixed elevated and depressed macroscopic type, and histologically poorly differentiated tumors. Because of the high LNM rate (42%, 95% CI: 15–72%), especially in tumors with poorly differentiated type and with LVI, surgical treatment with regional lymph node dissection is recommended as a treatment strategy for SM-NADAC.

Author contributions SY: conception and design; analysis and interpretation of the data; drafting of the article. HK: conception and design; analysis and interpretation of the data; drafting of the article. YY: critical revision of the article for important intellectual content. KN: critical revision of the article for important intellectual content. YH: critical revision of the article for important intellectual content. AI: critical revision of the article for important intellectual content. TT: critical revision of the article for important intellectual content. TH: critical revision of the article for important intellectual content. HI: critical revision of the article for important intellectual content. JF: critical revision of the article for important intellectual content; final approval of the article.

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Compliance with ethical standards

Conflict of interest None declared.

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