

The clinicopathological features of submucosal invasive non-ampullary duodenal carcinoma

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Abstract

Background

Little is known about submucosal invasive non-ampullary duodenal carcinoma because of its extreme rarity, so we investigated the clinicopathological features, comparing submucosal invasive carcinoma (SM-Ca) with mucosal carcinoma (M-Ca) and advanced carcinoma (Ad-Ca).

Methods

We retrospectively analyzed 165 sporadic non-ampullary duodenal carcinomas (SNADCs) at 4 institutions between January 2003 and December 2018. In addition, we compared the mucin phenotype between SM-Ca and M-Ca.

Results

There were only 11 cases (7%) of SM-Ca, while there were 70 cases of M-Ca (42%) and 84 cases of Ad-Ca (51%). Although the distribution of M-Ca was almost equal between the oral and anal sides of the papilla of Vater, all SM-Ca was located on the oral-Vater ($P = 0.013$) and Ad-Ca tended to be located on the oral-Vater ($P = 0.020$). Mixed macroscopic type was more frequent in SM-Ca than in M-Ca (64% vs. 10%, $P < 0.001$). There was no significant difference in tumor diameter between M-Ca and SM-Ca, but 45% of SM-Ca were ≤ 10 mm. 73% (8/11) of SM-Ca were classified as gastric phenotype and no lesions were intestinal phenotype, whereas most M-Ca were intestinal phenotype (67%, 8/12).

Conclusions

SM-Ca was highly associated with tumor location (oral-Vater) and gastric mucin phenotype, different from M-Ca. The possibility of SM-Ca should be considered when superficial SNADCs are located on oral-Vater and have mixed macroscopic type even if tumor diameters are ≤ 10 mm.

Background

Although superficial non-ampullary duodenal epithelial neoplasms were rare [1, 2], an opportunity of detection is increasing nowadays because of progress of endoscopic diagnosis [3]. However, the incidence of submucosal invasive carcinoma (SM-Ca) remains very rare [3, 4]. This can be judged by the fact that even a multicenter case series study comprised only 10 lesions of SM-Ca out of 396 superficial non-ampullary duodenal epithelial neoplasms [3]. Another reported that SM-Ca was found in only 1.4% of patients with superficial non-ampullary duodenal epithelial neoplasms [5]. Whereas most of duodenal adenocarcinomas were discovered at an advanced stage [6, 7]. Because of the large discrepancy in the

incidence between SM-Ca and mucosal carcinoma (M-Ca) or advanced carcinoma (Ad-Ca), there are few studies focusing on non-ampullary duodenal SM-Ca.

A multicenter retrospective study revealed that sporadic non-ampullary duodenal epithelial neoplasms on the oral side of the papilla of Vater (oral-Vater) were more likely to be invasive carcinomas than those on the anal side of the papilla of Vater (anal-Vater) [8]. Another study reported that Ad-Ca was more frequently seen on oral-Vater than M-Ca [9]. However, the reason for these discrepancies in the incidence between SM-Ca and M-Ca or Ad-Ca and the distribution between invasive carcinoma and M-Ca have not been fully investigated. A better knowledge of the clinicopathological features of SM-Ca in comparison with M-Ca and Ad-Ca may improve our understanding these discrepancies, because SM-Ca plays an initial and an essential part in the tumor progression from M-Ca to Ad-Ca.

Therefore, we conducted a multicenter study to elucidate the clinicopathological features of non-ampullary duodenal SM-Ca. We examined the relationship of SM-Ca with M-Ca and Ad-Ca, focusing on the clinicopathological data, especially tumor location, and also performed an immunohistochemical study to compare the mucin phenotype between SM-Ca and M-Ca.

Methods

Patients

This multicenter, retrospective, observational study included a total of 165 patients at the following 4 hospitals from January 2003 and December 2018: Okayama University Hospital, Tsuyama Chuo Hospital, Hiroshima City Hiroshima Citizens Hospital, and Kurashiki Central Hospital. Patient data were collected after approval by the institutional review boards of each hospital. The ethics committee of each hospital approved this retrospective study and informed consent was acquired by the opt-out method.

Inclusion And Exclusion Criteria

We included patients diagnosed with sporadic non-ampullary duodenal carcinoma (SNADC) based on a histological examination of a resected specimen or endoscopic biopsy. The exclusion criteria were as follows: (1) tumor located on the ampulla of Vater, (2) familial adenomatous polyposis, (3) suspected invasive tumor of the pancreatic or bile duct carcinoma, and (4) duodenal metastasis from the cancer of other organs. Patients' medical records were reviewed, and the following clinicopathological parameters were collected: sex, age, site of primary tumor, diameter of primary tumor, macroscopic type of primary tumor, histological type, mucin phenotype, and Union for International Cancer Control (8th ed.) cancer stage based on the tumor, nodes, metastasis (TNM) classification. The macroscopic types of SNADC were classified using the Paris endoscopic classification [10]. If a patient had multiple SNADCs, we evaluated the lesion that was the largest and most advanced. A lesion located at the same level as the ampulla of Vater ampulla was categorized as anal-Vater.

Histological Examination

Histological features were evaluated according to the revised Vienna classification of gastrointestinal epithelial neoplasia [11]. Category 4.2 (carcinoma in situ), 4.3 (suspicious for invasive carcinoma), 4.4 (intramucosal carcinoma), and 5 (invasive neoplasia) were classified as cancer. In the present study, we classified SNADC into three groups: M-Ca, defined as carcinoma limited to the muscularis mucosae, SM-Ca, as carcinoma invasive to the submucosa, and Ad-Ca as carcinoma invading the muscularis propria (T2) and deeper (T3 and T4). All of the cases were subdivided into differentiated-type or undifferentiated-type depending on histopathological grading. All of the pathological examinations were performed by qualified pathologists in each hospital.

Immunohistochemistry

For all cases of SNADCs with submucosal invasion, immunohistochemical examinations were performed with an autoimmunostaining system (Dako EnVision System; Dako Denmark A/S, Glostrup, Denmark). The same examinations were also performed for the cases of M-Ca in Okayama University hospital as a control group. The mucin phenotype was examined using MUC2 (Ccp58, monoclonal mouse; Leica Biosystems, Newcastle, UK, dilution 1:50), MUC5AC (CLH2, monoclonal mouse; Leica Biosystems; dilution 1:50), MUC6 (CLH5, monoclonal mouse; Leica Biosystems; dilution 1:50), CD10 (56C6, monoclonal mouse; Leica Biosystems; dilution 1:50), and CDX2 (DAK-CDX2, monoclonal mouse; Dako Denmark A/S; dilution 1:50).

Immunohistochemical Evaluation

We performed immunohistochemistry (IHC) for MUC5AC (a marker of gastric foveolar mucin), MUC6 (a marker of gastric pyloric gland mucin), MUC2 (a marker of intestinal mucin), CDX-2 (a marker of intestinal origin), and CD 10 (a marker of the brush border of intestinal epithelial cells). Distinct staining in more than 10% of the tumor cells was recorded as positive immunoreactivity for the relevant marker [12].

SNADCs were classified into four types based on the immunohistochemical results. Gastric-type was regarded as tumor positive for only gastric markers (MUC5AC and MUC6). Similarly, intestinal-type was regarded as tumor positive for only intestinal markers (MUC2, CD10, and CDX2). Tumor positive for both gastric and intestinal markers was regarded as mixed-type, while tumor with neither gastric nor intestinal markers was regarded as null-type.

The two specialist gastrointestinal pathologists were blinded to the patients' clinical information and together they assessed the immunohistochemical results. If there was any inconsistency in the assessment of the IHC, a final diagnosis was decided on by a joint assessment.

Statistical analysis

All continuous variables are reported as the median (range), and all categorical variables are summarized as frequencies (percentages). Wilcoxon's rank-sum test was used to compare the continuous variables. Pearson's chi-square test or Fisher's exact test was used to compare the categorical variables. The Kruskal–Wallis test was used for the comparison among mucosal, submucosal, and advanced carcinoma. All tests were two-sided, and a *P*-value under 0.05 was considered statistically significant. Statistical analyses were performed using the JMP 14 software program (SAS Institute Inc., Cary, NC, USA).

Results

Patient and lesion characteristics among M-Ca, SM-Ca, and Ad-Ca

One-hundred and sixty-five patients from the 4 institutions were included in this study, and their characteristics are summarized in Table 1. Median age of all patients was 68 years (range, 29–91), and 113 of the 165 (68%) patients were men while 52 (32%) were women. Of the 165 patients with SNADC examined, 70 (42%), 11 (7%), and 84 (51%) were diagnosed with M-Ca, SM-Ca, and Ad-Ca, respectively. There were no significant differences in sex or age among the three groups. Large tumor diameter and symptom were significantly correlated with Ad-Ca ($P < 0.001$), while there were no significant differences in tumor diameter or symptom between M-Ca and SM-Ca. With regard to histological type, the proportion of undifferentiated-type carcinomas was significantly higher in SM-Ca and Ad-Ca than in M-Ca ($P < 0.05$ and $P < 0.001$, respectively). Regarding the macroscopic type of Ad-Ca, 4 (5%) lesions were superficial, 7 (8%) were protruded, 66 (79%) were ulcerated, and 7 (8%) were sclerotic type among 84 lesions.

Table 1
Patient and lesion characteristics among M-Ca, SM-Ca, and Ad-Ca

	All SNADC <i>n</i> = 165	M-Ca <i>n</i> = 70	SM-Ca <i>n</i> = 11	Ad-Ca <i>n</i> = 84	<i>P</i> -value*
Sex (male/female) (%)	113/52 (68/32)	47/23 (67/33)	7/4 (64/36)	59/25 (70/30)	0.86
Age, median (range)	68 (29–91)	67.5 (36–86)	68 (60–84)	68 (29–91)	0.49
Lesion diameter, median (range)	21 (4-100)	12 (4–60)	12 (6–40)	36 (8-100)	< 0.001**
Histology (differentiated/undifferentiated) (%)	144/21 (87/13)	70/0 (100/0)	10/1 (91/9)	64/20 (76/24)	< 0.001***
Symptomatic at diagnosis (%)	81 (49)	12 (17)	3 (27)	66 (79)	< 0.001****
TNM stage (0-I/II/III/IV)	85/16/23/41	70/0/0/0	11/0/0/0	4/16/23/41	
* <i>P</i> -value was calculated among M-Ca, SM-Ca, and Ad-Ca.					
** M-Ca, SM-Ca vs. Ad-Ca; <i>p</i> < 0.001, M-Ca vs. SM-Ca: NS					
*** M-Ca vs. SM-Ca: <i>p</i> < 0.05, M-Ca vs. Ad-Ca; <i>p</i> < 0.001, SM-Ca vs. Ad-Ca: NS					
**** M-Ca, SM-Ca vs. Ad-Ca; <i>p</i> < 0.001, M-Ca vs. SM-Ca: NS					

Comparison of the proportion of SNADC between oral-Vater and anal-Vater

A total of 120 (73%) SNADCs were located on oral-Vater, while 45 (27%) were located on anal-Vater. Table 2 shows the proportion of SNADC according to the tumor location. All SM-Ca was located on oral-Vater and Ad-Ca tended to be located on oral-Vater, whereas M-Ca lesions were almost equally located on oral-Vater and anal-Vater. The proportion of SNADC on oral-Vater was significantly higher in SM-Ca and Ad-Ca than in M-Ca (100% vs. 61%, $P=0.013$ and 79% vs. 61%, $P=0.020$, respectively).

Table 2
The proportion of SNADC according to tumor location

	All SNADC <i>n</i> = 165	Oral-Vater <i>n</i> = 120	Anal-Vater <i>n</i> = 45	<i>P</i>-value
M-Ca	70	43 (61)	27 (39)	
SM-Ca	11	11 (100)	0 (0)	0.013*
Ad-Ca	84	66 (79)	18 (21)	0.02**
* <i>P</i> -value was calculated between M-Ca and SM-Ca.				
** <i>P</i> -value was calculated between M-Ca and Ad-Ca.				

Comparison Of Endoscopic Features Between M-ca And Sm-ca

Table 3 shows endoscopic findings of M-Ca and SM-Ca. There were no significant differences in tumor diameter. As shown in Table 2, all SM-Ca lesions were located on oral-Vater. More specifically classified, 64% of SM-Ca were located in the bulb. The proportion of SNADCs in the blub was significantly higher in SM-Ca than in M-Ca (64% vs. 23%, $P=0.005$). With regard to macroscopic type, the proportion of mixed type was significantly higher in SM-Ca than M-Ca (64% vs. 10%, $P<0.001$). Figure 1 shows distribution of M-Ca and SM-Ca according to the tumor diameter. Although no significant differences were seen in tumor diameter between the two groups, notably 45% (5/11) of SM-Ca were ≤ 10 mm in diameter.

Table 3
Endoscopic features of M-Ca and SM-Ca

	M-Ca <i>n</i> = 70	SM-Ca <i>n</i> = 11	<i>P</i>-value
Lesion diameter, median (range)	12 (4–60)	12 (6–40)	0.58
Tumor location (%)	16 (23)	7 (64)	0.005
Blub (1st part)	26 (37)	4 (36)	0.96
Oral side of descending (2nd) part	24 (34)	0 (0)	0.02
Anal-side of descending (2nd) part	4 (6)	0 (0)	0.42
Transverse (3rd) part			
Macroscopic type (%)	31 (44)	2 (18)	0.10
Superficial elevated (IIa)	21 (30)	1 (9)	0.15
Protruded (Is, Isp, Ip)	11 (16)	2 (18)	0.84
Depressed (IIc)	7 (10)	7 (64)	< 0.001
Mixed (IIa + I, IIa + IIc, I + IIc)			

Comparison of Immunohistochemical Features Between Sm-ca And M-ca

The immunohistochemical features of the mucin phenotype were investigated for all SM-Ca. As a control group, we performed the same immunohistochemical staining for all 12 consecutive cases of M-Ca in Okayama University Hospital during the same period. Figure 2 also shows the proportions of mucin phenotype according to the tumor location in SM-Ca and M-Ca. Mucin phenotype differed between the two groups ($P = 0.0014$). SM-Ca lesions were classified as gastric-type ($n = 8$), mixed-type ($n = 2$), and null-type ($n = 1$), and no lesions were intestinal-type, whereas most of M-Ca were intestinal-type ($n = 8$). Although not statistically significant, the proportion of gastric-type was higher in SM-Ca than in M-Ca (73% vs. 33%, $P = 0.059$). The proportion of intestinal-type was significantly lower in SM-Ca than in M-Ca (0% vs. 67%, $P = 0.0008$). Figure 3 shows a representative case of SM-Ca with gastric mucin phenotype.

Table S1 shows the results for clinical features in 11 SM-Ca and 12 M-Ca lesions stained by immunohistochemistry. There were no significant differences in sex, age, tumor diameter, or macroscopic type between the two groups.

Treatments And Outcomes Of Sm-ca

Four of 11 patients with SM-Ca were initially treated by endoscopic resection. 2 patients of them had lympho-vascular invasion and received additional surgery including removal of regional lymph nodes. The others were followed up without surgery. Among the patients who underwent surgical resection, 1 underwent local resection and 8 underwent radical resection such as pancreatoduodenectomy or distal gastrectomy. Lympho-vascular invasion was observed in 4 patients, however no lymph node metastasis was observed of them. During the median follow-up of 38.8 months, no recurrence occurred in all patients with SM-Ca. There was no death due to the SM-Ca.

Discussion

This is, to our knowledge, the first study to focus on the clinicopathological features of duodenal SM-Ca by comparing SM-Ca with M-Ca and Ad-Ca. We also performed an immunohistochemical examination for SM-Ca. We demonstrated that the incidence of SM-Ca was lower than M-Ca and Ad-Ca, and showed that mixed macroscopic type was a characteristic feature of SM-Ca and that not a few lesions measured ≤ 10 mm in diameter. SM-Ca was found to be strongly related to tumor location (anal-Vater) and gastric mucin phenotype, and these findings were significantly differed from those of M-Ca. These marked clinicopathological features suggest that the origin or pathway of carcinogenesis might differ according to the tumor location.

In the current study, tumor location was clearly different between SM-Ca and M-Ca. SM-Ca was all located on oral-Vater, whereas M-Ca was almost equally located on oral-vater and anal-Vater. Previous reports referred to the carcinogenic pathway of adenoma-carcinoma sequence in duodenal carcinoma similar to that in colon cancer [13–15]. However, the clear difference in the distribution between SM-Ca and M-Ca noted in the present study prompted us to hypothesize a different origin or progression pathway, depending on the location. Furthermore, the age at diagnosis and tumor diameter were similar between the SM-Ca and M-Ca groups (SM-Ca vs. M-Ca, 68 vs. 67.5 years of age and 12 vs. 12 mm in diameter, respectively). Given the different distribution and the similar ages and diameters between these two groups, some cases of SNADC on oral-Vater seem to invade the submucosal layer at early phase, while many cases of SNADC on anal-Vater might stay in the mucosa. That suggests that the carcinogenesis pathway of lesions with invasive potential are different from that of the lesions confined to the mucosal layer for a long time according to the tumor location.

We demonstrated that SM-Ca was highly associated with gastric phenotype, different from M-Ca. It is known that the mucosa in the proximal duodenum can potentially undergo gastric metaplasia in the duodenum (GMD) caused by exposure to gastric acid, leading into gastric phenotype [16, 17]. Furthermore, other studies reported that SNADC with gastric phenotype might arise from heterotopic gastric-type epithelium, including GMD and gastric heterotopia (GH), because of their similar genetic alterations [18–20]. These matters implied that GMD and GH often seen on oral-Vater were potential precursors to SNADC with gastric phenotype [20], which is thought to be the reason why almost all gastric-type tumors are located on oral-Vater [5, 17, 21]. In the present study, all SM-Ca and three of four cases of M-Ca with gastric-type were observed on oral-Vater. The close relationship between gastric-type and location of oral-

Vater was consistent with the findings of previous studies [5, 17, 21]. On the other hands, with regard to SM-Ca, almost all lesions were gastric-type and no lesions were intestinal-type, whereas most Ma-Ca were intestinal-type. Gastric carcinoma with gastric phenotype is reported to have a higher potential to invade deep layers in a diffuse infiltration pattern than intestinal phenotype [22]. In a previous study, all 2 cases of SM-Ca in SNADC expressed gastric phenotype [5]. Our finding that most of the SM-Ca were gastric-type suggested that gastric phenotype may have higher potential for submucosal invasion in SNADC than intestinal phenotype as well as gastric carcinoma. These characteristics of gastric phenotype may be one of the reasons for which SM-Ca is likely to be seen on oral-Vater.

We found that about one-half of SM-Ca had small diameter of ≤ 10 mm, which proportion was higher than that in M-Ca ≤ 10 mm (37%). A previous study also reported that 10–33% of SM-Ca were ≤ 10 mm in diameter [3, 4]. These results indicate that there is the possibility of SM-Ca even in the small lesion ≤ 10 mm in diameter. This fact may imply the existence of the *de novo* pathway [17] rather than adenoma-carcinoma sequence in which submucosal invasive rate increases according to the size of colorectal neoplasmas [23].

The comparative analysis of endoscopic findings in the present study revealed that the mixed type appearance represented the characteristic morphological difference between M-Ca and SM-Ca. Similarly, a multicenter case series study of 10 SM-Ca showed 7 SM-Ca (70%) showed mixed macroscopic type [3]. Takinami et al also reported that 58% were mixed macroscopic type among 12 lesions, but not significance between M-Ca and SM-Ca [4]. Regarding the macroscopic type for Ad-Ca, in our study, 5% were superficial, 8% were protruded, 79% were ulcerated, and 8% were sclerotic type among 84 lesions. Another reported that 26% were protruded, 65% were ulcerated and 10% were sclerotic type among 31 lesions [24]. Since the incidence of SM-Ca is very rare, mixed type appearance may be observed in a limited period during the tumor invasion to the submucosa. SM-Ca is expected to undergo mixed macroscopic type and eventually change to ulcerative and sclerotic type with further invasion.

Regarding Ad-Ca, the incidence was higher on oral-Vater than on anal-Vater, which was similar tendency to the location of SM-Ca. Furthermore, the proportion of undifferentiated-type Ad-Ca was significantly higher on oral-Vater than on anal-Vater (28.8% vs. 5.6%, $P = 0.040$, not shown in Table). Previous studies have reported that differentiated gastric carcinomas with gastric phenotype appeared more likely to dedifferentiate and behaved more aggressively than intestinal phenotype [9]. In this study, most of the SM-Ca were characterized by gastric-type and located on oral-Vater. In addition, the proportion of undifferentiated-type carcinomas was significantly higher in SM-Ca and Ad-Ca than in M-Ca. These matters suggest that carcinoma on oral-Vater is more likely to infiltrate into the submucosa and dedifferentiate when progressing to Ad-Ca. As a result, Ad-Ca might tend to be located on oral-Vater as well as SM-Ca. The low incidence of SM-Ca compared with Ad-Ca suggests the possibility that once SNADC invades to the submucosa, the progression speeds up to become an Ad-Ca, therefore it is difficult to detect a SM-Ca.

This study has several limitations. First, this was a retrospective study; however, considering the rarity of SNADC, the retrospective analysis should be acceptable. Second, although we discussed the mucin

phenotype of M-Ca and SM-Ca, we were unable to examine the immunohistochemical staining findings for Ad-Ca in this study. However, our clinical data clarified that superficial SNADC with gastric-type on oral-Vater had more invasive potential into the submucosal layer than that with intestinal-type. Therefore, the present findings might support future research related to the pathogenesis and pathway of SNADC according to the mucin phenotype and tumor location. Third, M-Ca is often difficult to distinguish from high-grade dysplasia based on a histological diagnosis [25]. Thus, there might be some cases of high-grade dysplasia in the M-Ca group. Conversely, M-Ca might be under-represented to high-grade dysplasia, which might be excluded from this study. However, we were able to collect enough cases of M-Ca for the comparison with SM-Ca and showed clearly distinct clinicopathological features between these two groups.

Conclusions

SM-Ca was highly associated with tumor location of oral-Vater and gastric mucin phenotype, and differed from M-Ca. These distinct features suggest that the origin or carcinogenesis pathway differ according to the tumor location. Even for tumors that measure ≤ 10 mm in diameter, the possibility of submucosal invasion should be considered, when superficial SNADCs are located on oral-Vater and have mixed macroscopic type.

Declarations

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the ethics committee of Okayama University Hospital, Tsuyama Chuo Hospital, Hiroshima City Hiroshima Citizens Hospital, and Kurashiki Central Hospital. Informed consent was acquired by the opt-out method, and written informed consent was waived for enrollment because of retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

There are no financial or other relations that could lead to a conflict of interest.

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Authors' contributions:

K.M. and H.K. drafted the article; T.T. and T.T. are responsible for acquisition and interpretation of the experimental data; R.T., M.N. and K.M. are responsible for acquisition and interpretation of the clinical data; M.I., S.K., Y.K., T.Y., T.F. and H.O. revised it critically for important intellectual content.

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Figures

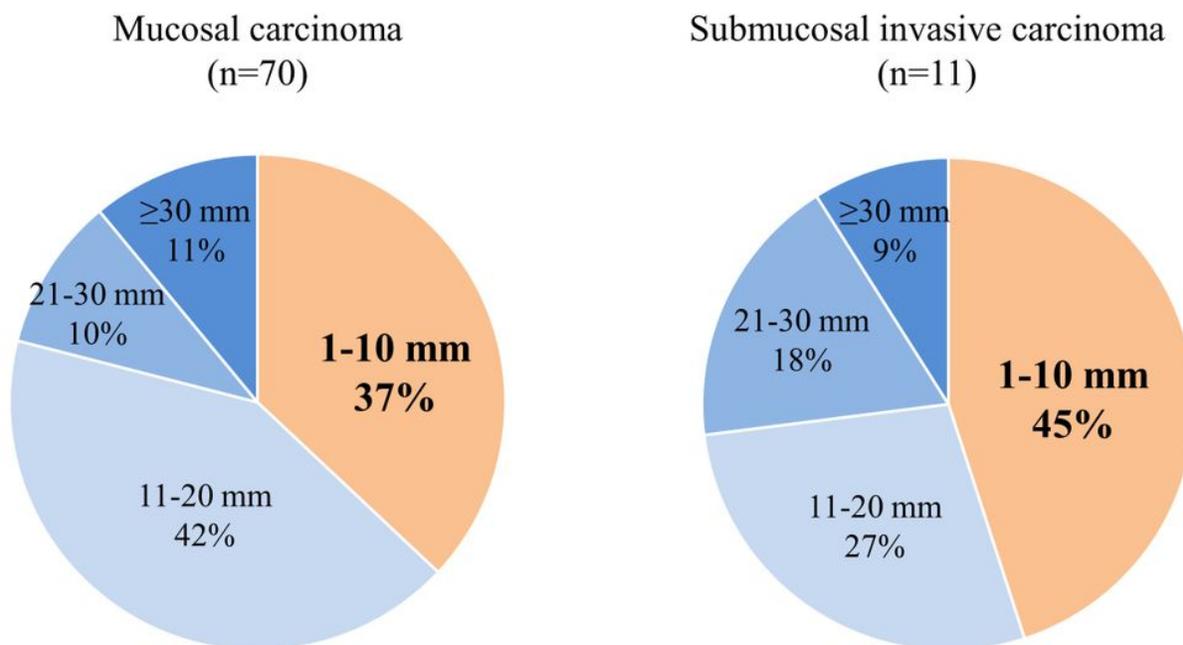
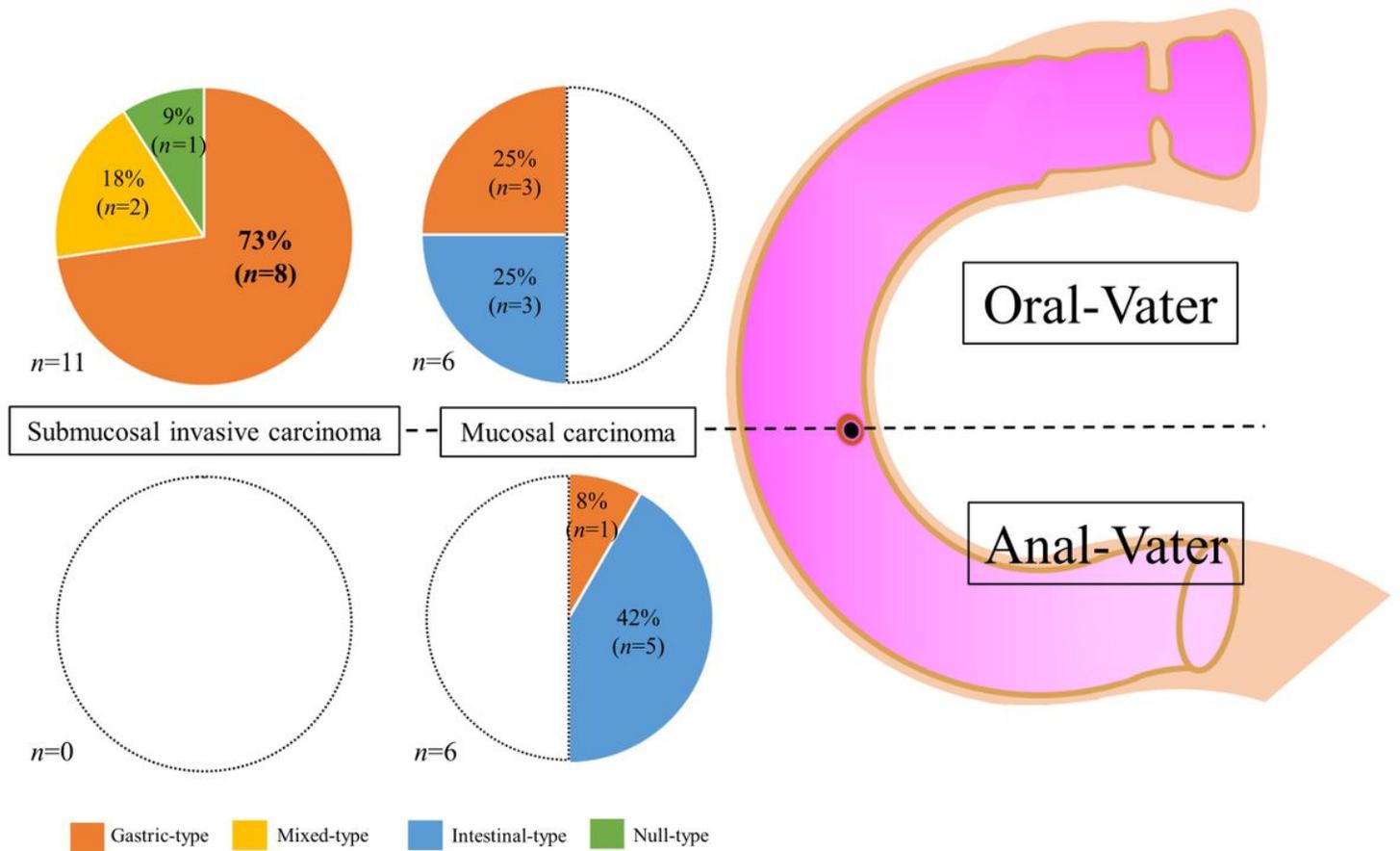


Figure 1

Proportion of mucosal and submucosal invasive duodenal carcinomas according to tumor diameter



	SM-Ca <i>n</i> =11	M-Ca <i>n</i> =12	<i>P</i> -value
Mucin phenotype (gastric/mixed/intestinal/null-type) (%)	8/2/0/1	4/0/8/0	0.0014

Figure 2

The proportions of mucin phenotype depending on tumor location between submucosal invasive and mucosal carcinoma. Submucosal invasive carcinoma, which was all located on oral-Vater, showed a gastric-type in 8 lesions (72.7%), mixed-type in 2 (18.2%) and null-type in 1 (9.1%). No lesions showed an intestinal-type in submucosal invasive carcinoma. In contrast, mucosal carcinoma, which was located equally on oral-Vater and anal-Vater, showed an intestinal-type in 8 lesions (66.7%) and gastric-type in 4 (33.3%).

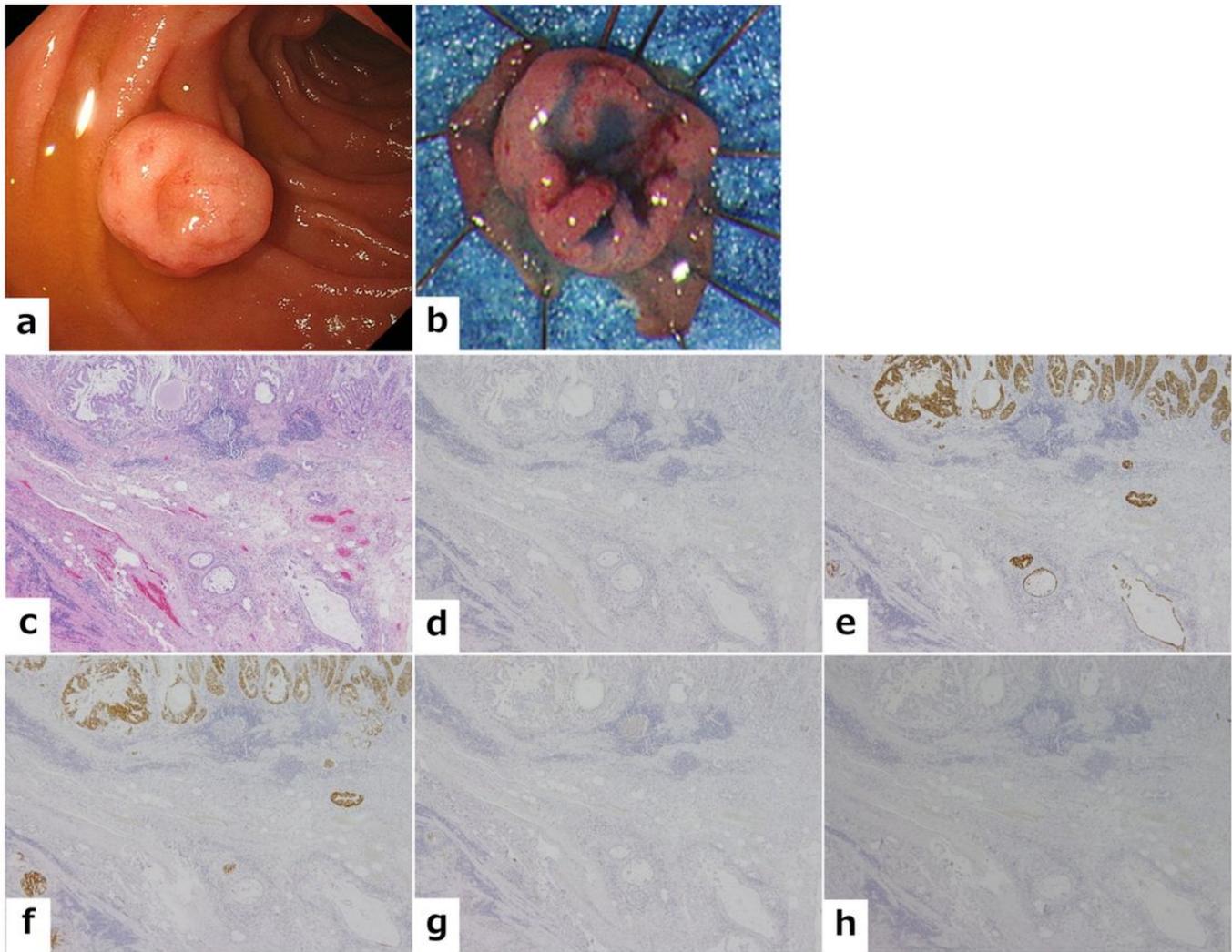


Figure 3

A representative case of a submucosal invasive carcinoma with gastric phenotype (a) A 10-mm semipedunculated lesion with surface depression (Isp+IIc) is observed on the oral side of the papilla of Vater in the second portion of the duodenum. (b) Macroscopic appearance of the resected specimen shows a clear depression on top of the protrusion. (c) Histological finding shows a well-differentiated adenocarcinoma with submucosal invasion (hematoxylin and eosin stain). Immunohistochemical staining reveals that the tumor cells in both the mucosal and submucosal layer are positive for MUC5AC (e) and MUC6 (f) and negative for MUC2 (d), CD10 (g), and CDX2 (h), revealing a gastric mucin phenotype.

Supplementary Files

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- [TableS1.docx](#)