Accepted Manuscript

Submission Date: 2023-12-05
Accepted Date: 2024-06-05
Accepted Manuscript online: 2024-06-10

Endoscopy International Open

Colorectal tumor comorbidity is common in patients with duodenal tumors: An exploratory cross-sectional study

Mari Mizutani, Motohiko Kato, Kazuhiro Yamanoi, Akiko Matsubara, Atsushi Nakayama, Kayoko Kimura, Kentaro Iwata, Kurato Miyazaki, Teppei Masunaga, Yoko Kubosawa, Yukie Sunata, Yusaku Takatori, Teppei Akimoto, Noriko Matsuura, Rieko Bessho, Tomohisa Sujino, Kaoru Takabayashi, Hitoshi Ichikawa, Kazuhiro Kashiwagi, Hiromasa Takaishi, Yasunori Sato, Takanori Kanai, Ryoji Kushima, Naohisa Yahagi.

Affiliations below.

DOI: 10.1055/a-2341-9026

Please cite this article as: Mizutani M, Kato M, Yamanoi K et al. Colorectal tumor comorbidity is common in patients with duodenal tumors: An exploratory cross-sectional study. Endoscopy International Open 2024. doi: 10.1055/a-2341-9026

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

Trial registration: UMIN000038749, UMIN Japan (http://www.umin.ac.jp/english/)
, Exploratory cross-sectional study

Abstract:
BACKGROUND AND STUDY AIMS: The duodenum and colorectum are target organs for familial colorectal adenomatous polyposis, however, the association of duodenal epithelial tumors (DETs) and colorectal tumors is still controversial. The aim of our study was to elucidate the association between DET and colorectal tumor.
PATIENTS AND METHODS: This was an exploratory cross-sectional study of patients with DETs treated by endoscopic resection at our hospital, between November 2018 and October 2022. Individuals who underwent colonoscopy as part of the health screening comprised the reference control group for comparison. In both groups, lesions suspected of being tumors were resected. The main outcome was the adenoma detection rate (ADR). Other outcomes were the detection rate of advanced neoplasia (AN) and risk factors for colorectal adenoma and AN, evaluated using univariate and multivariable analyses.
RESULTS: Analyses were based on the data of 163 individuals in the DET group and 177 in the control group. ADR was higher in the DET (63.2%) than in the control (23.6%) group (p<.001). AN and invasive cancer rates were also significantly higher in the DET than in the control group (AN: 20.9% vs 3.4%, respectively, p<.001; invasive cancer: 3.1% vs 0%, respectively, p<.001). On logistic regression analysis, DET was found to be associated with a 5-fold increase in the detection rate of adenoma and 6-fold increase in AN detection.
CONCLUSIONS: The study revealed significant association between DET and high ADR and a higher frequency of AN and invasive cancer. Screening colonoscopy is suggested for patients with DETs.

Corresponding Author:
Dr. Motohiko Kato, Keio University School of Medicine Graduate School of Medicine, Center for Diagnostic and Therapeutic Endoscopy, Tokyo, Japan, motohikokato@keio.jp

Affiliations:
Mari Mizutani, Keio University School of Medicine Graduate School of Medicine, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Tokyo, Japan
Motohiko Kato, Keio University School of Medicine Graduate School of Medicine, Center for Diagnostic and Therapeutic Endoscopy, Tokyo, Japan

Kazuhiro Yamanoi, Keio University School of Medicine Graduate School of Medicine, Department of Pathology, Shinjuku-ku, Japan
[...]
Naohisa Yahagi, Keio University School of Medicine Graduate School of Medicine, Division of Research and Development for Minimally Invasive Treatment, Cancer Center, Shinjuku-ku, Japan

INTRODUCTION

With recent improvements in endoscopy instruments and increased technical endoscopy skill among endoscopists, endoscopic treatment has become more prevalent for the treatment of duodenal epithelial tumors (DET) [1, 2]. Duodenal adenomas are common in patients with familial adenomatous polyposis [3], associated with colorectal tumors. Indeed, adenoma detection rates (ADR) have been reported to be significantly higher in patients with DETs compared to the general population [4-7]. However, as these studies used a retrospective case-control design, effects of bias and inappropriate selection of controls cannot be denied. Moreover, a recent multicenter retrospective study indicated that there was no significant difference in the incidence of colorectal tumors in patients with synchronous and metachronous duodenal lesions compared to those with a single DET [8]. Therefore, it remains controversial whether DETs are, in fact, associated with a higher risk for colorectal tumors. Accordingly, our aim was to conduct a cross-sectional study to evaluate the ADR for patients with DET compared to a general population control group, consisting of individuals who underwent a regular health checkup, to elucidate the association between DET and colorectal tumors.

MATERIALS AND METHODS

Study design and statement of ethics

This was an exploratory, cross-sectional, observational study conducted at our hospital.

The study was conducted in accordance with the 2008 revision of the Declaration of Helsinki and the study protocol was approved by our Institutional Review Board (20190233). The study was registered in the University Hospital Medical Information Network (UMIN 000038749). Patients provided consent for the use of their data for research and publication.

Study sample

The study sample for the DET group consisted of consecutive patients who underwent endoscopic treatment for their DETs which was not ampullary tumors at our hospital between November 2018 and October 2022. The reference control group for comparison consisted of individuals who were scheduled to undergo colonoscopy as part of their health screening but not as part of any treatment paid through health insurance in the same period and had no previous diagnosis of DET. The exclusion criteria for both groups were as follows: colonoscopy performed for any reason within the 3 years prior; previous colorectal resection excluding appendectomy; contraindication to discontinuing antithrombotic medications according to the guidelines of the Japan Gastroenterological Endoscopy Society [9, 10]; diagnosis of familial adenomatous polyposis or hereditary non-polyposis colorectal cancer; and history of inflammatory bowel disease. For patients with metachronous lesions in the DET group, findings of larger lesions are described.

Outcomes

The main outcome of this study was the ADR in both the DET and control group. Other outcomes were the number and maximum diameter of adenomas per patient, as well as the percentage of advanced neoplasia (AN) and invasive cancer detected in both groups. The risk factors between individuals with and without colorectal adenomas and AN were evaluated in both groups.

Colonoscopy procedure

Before the colonoscopy, individuals completed a bowel preparation using an oral polyethylene glycol lavage solution. Colonoscopy was performed under conscious sedation, using benzodiazepines and/or pethidine. Scopolamine butyl bromide or glucagon was used as an antispasmodic agent. Colonoscopies were performed by 16 endoscopists, with experience in performing >300 colonoscopies. A high-definition endoscope with a water-jet function (PCF-Q290ZI, EVIS LUCERA ELITE, EVIS X1 endoscopic system; Olympus Medical Systems, Tokyo, Japan; EC-L600ZP7, ELUXEO 7000 endoscopic system; Fujifilm, Tokyo, Japan) was used in all cases. We measured the time to withdrawal using white light. All lesions suspected of being tumors were resected during the examination, excluding those with endoscopic findings suggestive of hyperplastic polyps of <10 mm in size, located in the left colon segment. A pathological examination was

performed on all resected lesions. Of note, a specific endoscopic resection modality, such as cold forceps polypectomy, cold snare polypectomy, endoscopic mucosal resection (EMR), underwater EMR, or endoscopic submucosal dissection, was not prescribed. Lesions considered to have submucosal invasion, for which endoscopic resection was not indicated, surgical resection was subsequently performed, with pathological examination to confirm diagnosis.

Pathological diagnosis

Histopathological diagnosis of colorectal tumors was performed by a single pathologist (K.Y.), with gastroenterology specialization, using the World Health Organization classification [11]. AN was defined as an adenoma >10 mm in size, high-grade adenoma, villous adenoma, or carcinoma. The histopathological diagnoses of DETs were made by three pathologists (A. M., R. K., and K. Y.), with gastroenterology specialization. The histological grades of DET were classified according to the Vienna classification [12].

Statistical analysis

We consulted a statistician (Y. S.) about the analysis.

Based on previous reports [4, 5, 13, 14], we assumed an ADR of 0.55 for patients with DET and 0.4 for the control group. To identify a between-group difference with a power of 80% and type I error of 0.05, assuming a dropout rate of 5%, 180 individuals were included in each group.

We analyzed all data by full analysis set. For the baseline variables, we constructed summary statistics, with frequencies and proportions for categorical data, and means and standard deviations (SDs) or median and interquartile range (IQR) for continuous variables. We compared patient characteristics using the Fisher's exact test for categorical outcomes and t tests or the Wilcoxon rank sum test for continuous variables, as appropriate. Moreover, propensity-matched cohorts of the DET group and control group were derived and compared using a 1:1 ratio with greedy matching on the propensity score, with a caliper of 0.2 standard deviations of the propensity score logit with no replacement. We examined standardized differences and variance ratios to determine whether the matched cohort had balanced patient characteristics.

To analyze risk factors for adenoma or AN, we divided individuals for two groups, with or without adenoma and with or without AN, and thus, we performed logistic regression analysis. We chose factors which might be related to the adenoma or AN which were significantly more for presence of adenoma or AN in the univariate analysis and whose *p* value were under 0.06.

Statistical analyses were performed using JMP software ver. 16.2.0 and SAS ver.9.4 (SAS Institute, Inc., Cary, NC, USA). All p-values were two sided and a p-value of less than 0.05 was deemed significant.

RESULTS

Selection of the study sample

The selection of individuals for the DET and control groups is shown in Figure 1. Of the 645 patients with DET who underwent duodenal endoscopic resection at our facility during the study period, 465 were excluded based on our *a priori* selection area. Finally, of the 180 meeting our selection criteria, 163 patients attended their scheduled colonoscopy, and their data were used in the analysis. Similarly, for the control group, of the 331 individuals who underwent planned colonoscopy screening, 151 were excluded based on our selection criteria, leaving 180 of which 177 attended their schedule colonoscopy and their data included in the analysis.

Characteristics of the study sample

Demographic, clinical, and lesion characteristics for the DET and comparative control group are reported in Table 1. Demographic (age, sex) and clinical (body mass index (BMI), comorbidities, and family history of colorectal cancer) characteristics were not different between the two groups, with the exception of age (mean, 64 years, DET group, and 57 years, control group, $p<.001$). The most common location for DETs was the descending part and distal papilla of the duodenum, with a median (interquartile range [IQR]) lesion size of 15 [10-25] mm.

Between-group differences in any tumors identified on colonoscopy

The ADR, the main outcome of the study, was 63.2% in the DET group and 23.6% in the control group (Odds ratio (OR), 5.69; 95% confidential interval (CI), 3.55-9.13; *p*<.001; Table 2). The number of adenomas per patient was higher in the DET (median 1; range 0-9) than the control (median 0; range 0-7) group (*p*<.001). As well, the maximum diameter of adenomas per patient was larger in the DET (median 4 mm; range 0-26 mm) than control (median 0; range 0-10 mm) group (*p*<.001). AN and invasive cancer rates were significantly higher in the DET than control group: AN, 20.9*% versus* 3.4%, respectively (OR, 7.51; 95%CI, 3.06-18.42; *p*<.001); and invasive cancer, 3.1% *versus* 0%, respectively (*p*=.024).

Characteristics and main outcome after propensity score matching

The result of propensity score matching test was showed in Table 3. In each of the two groups, 124 individuals were matched. The analysis showed that ADR was higher in the DET group than in the control group (61.3% *versus* 23.4; OR, 5.19; 95%CI, 2.99-9.00; *p*<.001). Moreover, the detection rate of AN and invasive cancer were significantly higher in the DET than control group: AN, 20.2*% versus* 3.2%, respectively (OR, 7.58; 95%CI, 2.55-22.50; *p*<.001); and invasive cancer, 4.0% *versus* 0%, respectively (*p*=.006).

Univariate and multivariable analysis for adenoma and AN detection

We performed logistic regression analysis to confirm whether there is an association of adenoma/AN detection and DETs even after adjustment of confounding factors.

On univariate analysis, older age, male sex, and the presence of DET were associated with adenoma detection. On multivariable analysis, older age, male sex and the presence of DET were retained as independent factors of a higher adenoma detection rate and DET was associated with a 5-fold more (OR, 5.43; 95%CI, 3.29-8.98; p<.001)in the rate of adenoma detection even after adjusting for age, sex, BMI, and family history of colorectal cancer (Table 5).

For AN detection rate, older age and the presence of DET were increased on univariate analysis. On multivariable analysis, older age and the presence of DET were independent factors of higher AN detection rate and 6-fold more (OR, 6.54; 95%CI, 2.62-16.27; p<.001) for AN detection (Table 5),

DISCUSSION

To the best of our knowledge, this is the first cross-sectional study to analyze the association between DET and colorectal tumors. We identified a significantly higher ADR in the DET than control group, with the number of colorectal adenomas per patient and the maximum diameter of colorectal adenomas being higher for the DET than control group. DET was associated with a 5-fold more in the rate of adenoma detection and 6-fold more in AN detection, even after adjusting for age, sex, and BMI.

The association between DET and colorectal tumors has not previously been specifically determined due to methodological issues, including the use of retrospective study designs,

which are susceptible to undetected bias effects [4-7], and the various factors known to influence ADR, including individual background factors, such as age sex, BMI, history of colonoscopy, interval between colonoscopies [15], and the quality of colonoscopy [16], such as the use of image-enhanced endoscopy. To control for bias to the extent possible, we used an exploratory cross-sectional study design, with strict eligibility criteria defined *a priori*, including the exclusion of individuals who had a history of colonoscopy within three years prior to the study period. Therefore, both the DET and control group were comparable with regard to background characteristics. Moreover, the same endoscopy instruments and procedures, including pretreatment medications and polyp excision to confirm the pathological results, were used in both groups. Pathological diagnoses of DETs and colorectal tumors were performed by expert pathologists using evidence-based classifications. In particular, colorectal tumors were diagnosed by a single specialist. Therefore, we are confident in the stability of the diagnostic process, and our study provided an objective analysis of the risk of colorectal tumors associated with DETs.

The positive association between DETs and colorectal tumors might indicate shared risk factors for these two conditions, such as smoking, overweight, and red meat consumption that are known risk factors for colorectal tumors [17, 18]. A systematic review regarding the risk factors for duodenal tumors [19] did not yield specific findings. In our study, we note

that BMI was not different between the DET and control group; however, lifestyle habits were not assessed and, therefore, further investigation of risk factors for DETs is warranted.

With regard to application of findings to practice, the higher frequency of colorectal tumors in patients with DETs underlines the importance of colonoscopy examination for all patients with DET, regardless of age, sex, BMI, or family history of colorectal cancer. In fact, in our study, asymptomatic invasive cancer was found in the DET group but not the control group. This practice would improve early detection of colorectal tumors in this clinical population and, ultimately, improve their prognosis.

The limitations need to be acknowledged. First, the control group consisted of individuals who selected to undergo colonoscopy as part of their health screening. Therefore, it is possible that these individuals were more health-conscious than the general population. As such, the rates of detection might not be representative of the general population. It is important to note, however, that ADR was not higher in the control than DET group. Therefore, the difference between DET and the general population would not be less than that observed in this study. Second, the study included only individuals who had not undergone colonoscopy in 3 years prior to the study period. We based this decision on the Japanese guidelines which recommend colonoscopy screening every 2-3 years after

polypectomy [20]. We note that the American Cancer Society recommends endoscopy every 10 years [21]. Therefore, there are significant differences in surveillance intervals between Japan and the United States and, thus, it is unknown if our selection of a 3-year period is appropriate. Third, we controlled for age, sex, BMI, comorbidities of diabetes, and family history of colorectal cancer in our propensity score matched analyses and multivariable analyses. However, there may be other potential confounding factors, such as aspirin use [22], amount of meat intake [23], and smoking status [24], which were not considered. Moreover, the potential adjustment bias was also remained even with propensity score matching. Forth, this study was not longitudinal and had no follow-up, the association of two groups in this study was at a specific time point. Lastly, the dropout rate was higher than expected. The main reason for this was that the study period was during the coronavirus infectious disease epidemic period and, therefore, many individuals selected to not follow through with the scheduled colonoscopy for fear of infection. We excluded dropouts in our analysis; however, we did not performed colonoscopy for excluded individuals, we cannot perform an intention-to-treat analysis or sensitivity analysis.

In conclusion, our cross-sectional study identified a significantly higher ADR in patients with DETs. In addition, DET was associated with higher frequency of adenomas, AN, and

invasive cancers. On the basis of these results, colonoscopy is suggested for patients with DETs.

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FIGURE LEGEND

Figure 1. Flow chart of the selection of individuals in the DET and control groups.

DET, duodenal epithelial tumor

Table 1. Relevant characteristics of the study sample before matching

		DET Group (n = 163)	Control Group (n = 177)	Odds ratio	95% CI	*p*-value
Age	(years), median [IQR]	64 [55-71]	57 [49-67]			<.001
Sex	Male, n (%)	104 (63.8)	115 (65.0)	0.95	0.68-1.48	.822
BMI	median [IQR]	23.2 [20.9-25.8]	23.3 [20.9-25.8]			.991
Comorbidity	Hypertension, n (%)	48 (29.5)	41 (23.0)	1.38	0.85-2.25	.178
	Hyperlipidemia, n (%)	24 (14.7)	40 (22.5)	0.59	0.34-1.04	.067
	Diabetes, n (%)	16 (9.8)	12 (6.7)	1.50	0.69-3.27	.302
	Ischemic heart disease, n (%)	4 (2.5)	1 (0.6)	4.43	0.49-40.03	.197
	Cerebral infarction, n (%)	4 (2.5)	1 (0.6)	4.43	0.49-40.03	.197
Family history of colorectal cancer	n (%)	20 (13.3)	24 (13.6)	0.98	0.52-1.86	.952
History of colonoscopy	Present, n (%)	46 (28.2)	75 (42.4)	0.53	0.34-0.84	.007
History of polyp	Present, n (%)	23 (14.1)	18 (10.2)	1.45	0.85-2.80	.318
Location of DET	Bulbs, n (%)	27 (16.6)				
	Descending part, proximal papilla, n (%)	31 (19.0)				
	Descending part, distal papilla, n (%)	96 (58.9)				

	Transvers, n (%)	9 (5.5)
Lesion size of DET	(mm), median [IQR]	15 [10-25]
Histopathology of DET	VC 3 (Low-grade adenoma), n (%)	99 (60.7)
	VC 4.1 (High-grade adenoma), n (%)	47 (28.8)
	VC 4.2 (Non-invasive carcinoma), n (%)	12 (7.4)
	VC 5.1 (Intramucosal carcinoma), n (%)	2 (1.2)
	VC 5.2 (Submucosal carcinoma), n (%)	3 (1.8)

BMI, body mass index; *CI*, confidence interval

DET, duodenal epithelial tumor; *IQR*, interquartile range; *VC*, Vienna classification

Table 2. Between-group differences in the detection of any tumors during colonoscopy

		DET Group	Control Group	Odds ratio	95% CI
Adenoma	n, (%)	103 (63.2)	41 (23.0)	5.69	3.55-9.13
Number of adenomas per patient	median [range]	1 [0-9]	0 [0-7]		
Maximum size of adenoma	(mm), median [range]	4 [0-26]	0 [0-10]		
Advanced neoplasia	n, (%)	34 (20.9)	6 (3.4)	7.51	3.06-18.42
Invasive cancer	n, (%)	5 (3.1)	0 (0.0)	12.32	0.68-224.56

DET, duodenal epithelial tumor.

Table 3. Relevant characteristics and detection rate of the study sample after matching

		DET Group (n = 124)	**Control Group (n = 124)**	**Odds ratio**	**95% CI**
Age	(years), median [IQR]	60 [51-70]	59 [51-69]		
Sex	Male, n (%)	77 (62.1)	77 (62.1)	1	0.60-1.6
BMI	median [IQR]	23.1 [21.0-25.8]	22.9 [20.9-25.4]		
Comorbidity	Hypertension, n (%)	30 (24.2)	31 (25.0)	0.96	0.54-1.7
	Hyperlipidemia, n (%)	20 (16.1)	21 (16.9)	0.94	0.48-1.8
	Diabetes, n (%)	10 (8.1)	9 (7.3)	1.12	0.44-2.8
	Ischemic heart disease, n (%)	1 (0.8)	1 (0.8)	1	0.06-16.1
	Cerebral infarction,	2 (1.6)	1 (0.8)	2.01	0.18-22.5

	n (%)				
Family history of colorectal cancer	n (%)	17 (13.7)	20 (16.1)	0.83	0.41-1.6
Adenoma	n, (%)	76 (61.3)	29 (23.4)	5.19	2.99-9.0
Number of adenomas per patient	median [range]	1 [0-8]	0 [0-7]		
Maximum size of adenoma	(mm), median [range]	4 [0-26]	0 [0-10]		
Advanced neoplasia	n, (%)	25 (20.2)	4 (3.2)	7.58	2.55-22.5
Invasive cancer	n, (%)	5 (4.0)	0 (0.0)	11.46	0.63-209.5

BMI, body mass index; *CI*, confidence interval; *DET*, duodenal epithelial tumor; *IQR*, interquartile range

Table 4. Univariate and multivariable analyses of the risk factors for adenoma

Factors		① Univariate analysis			② Multivariable analysis		
		Odds ratio	95% CI	*p*-value	Adjusted odds ratio	95% CI	*p*-value
Age	(each 10-year interval)	1.63	1.28-1.91	<.001	1.34	1.08-1.63	.009
Sex	Male	1.73	1.09-2.75	.018	1.88	1.08-3.26	.025
	Female	1			1		
BMI	(each 5 kg/m^2 interval)	1.11	0.85-1.46	.448	1.01	0.73-1.40	.970
Family history of colorectal cancer	Present	1.11	0.58-2.11	.750	1.07	0.52-2.24	.846
	Absent	1			1		
Duodenal epithelial tumor	Present	5.56	3.47-8.90	<.001	5.43	3.29-8.98	<.001
	Absent	1			1		

BMI, body mass index; *CI*, confidence interval

Table 5. Univariate and multivariab;e analyses of the risk factors for advanced neoplasia

Factors		① Univariate analysis			② Multivariable analysis		
		Odds ratio	95% CI	*p*-value	Adjusted odds ratio	95% CI	*p*-value
Age	(each 10-year interval)	1.82	1.31-2.57	<.001	1.58	1.12-2.26	.007
Sex	Male	2.05	1.08-3.26	.057	2.02	0.89-4.57	.078
	Female	1			1		
BMI	(each 5 kg/m^2 interval)	1.10	0.73-1.66	.649			
Family history of colorectal cancer	Present	1.04	0.38-2.84	.936			
	Absent	1					
Duodenal epithelial tumor	Present	7.56	3.08-18.54	<.001	6.54	2.62-16.27	<.001
	Absent	1			1		

1 *BMI*, body mass index; *CI*, confidence interval

Figure1