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BRIEF ARTICLE

Clinicopathological evaluation of duodenal well-differentiated endocrine tumors

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Abstract

AIM: To assess the clinicopathological characteristics of duodenal well-differentiated endocrine tumors.

METHODS: We examined clinicopathological characteristics in 11 consecutive patients with duodenal well-differentiated endocrine tumors treated by endoscopic therapy or surgery in our hospital from 1992 through 2007. Patients with well-differentiated endocrine tumors of the papilla of Vater or with gastrinoma were excluded.

RESULTS: Three patients received endoscopic treatment, and 8 underwent surgery. In patients who received endoscopic treatment, the tumor diameter was less than 1.0 cm, with no histopathological evidence of lymphovascular invasion or invasion of the muscularis. There were no complications such as late bleeding or perforation after treatment. Among 8 patients with tumors less than 1.0 cm in diameter, 3 underwent partial resection, and 2 underwent radical surgery. Three patients had lymphovascular invasion, 1 had invasion of the muscularis, and 1 had proximal lymph node metastasis. Among 3 patients with tumors 1.0 cm or more in diameter, 1 underwent partial resection, and 2 underwent radical surgery. One patient had lymphovascular invasion, with no lymph node metastasis. After treatment, all patients are alive and have remained free of metastasis and recurrence.

CONCLUSION: Duodenal well-differentiated endocrine tumors less than 1.0 cm in diameter have a risk of lymphovascular invasion, invasion of the muscularis, and lymph node metastasis, irrespective of procedural problems.

Key words: Duodenal well-differentiated endocrine tumors; Endoscopic resection; Surgical operation

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INTRODUCTION

Neuroendocrine tumor is defined as a tumor associated

with neuroendocrine differentiation. There has been confusion regarding the concept of neuroendocrine tumor. This has been especially complicated by the long standing concept of "Karzinoide Tumor" proposed by Oberndorfer in 1907[1], which develop more slowly than carcinomas arising at the same site clinically. Neuroendocrine tumor is currently classed into: (1) Well-differentiated endocrine tumor (WDET) (synonymous with carcinoid tumor); (2) Well-differentiated endocrine carcinoma (synonymous with malignant carcinoid tumor); (3) Poorly-differentiated endocrine carcinoma (synonymous with small cell carcinoma); (4) Mixed-endocrine tumor; and (5) Tumor-like lesion associated to its degree of differentiation, cell proliferation or other histological features[2].

About 70% of WDET arise from the gastrointestinal tract. In Japan the most common site is the rectum (41.5%), followed by the stomach (26.3%), duodenum (16.5%), and cecum (7.2%). In Europe and North America, the cecum is the most common site, followed by the ileum and rectum. Duodenal WDET account for only 2.6% of all neuroendocrine tumors[3,4]. Increased use of upper gastrointestinal endoscopy for health checkups has led to increased detection rates of WDET. However, duodenal WDET are a rare disease diagnosed in only a small number of patients. The natural history of duodenal WDET is therefore poorly understood, and standard treatment strategies have yet to be established.

Soga[5] reported that lymph node metastasis was associated with 9.8% of gastrointestinal neuroendocrine tumors with submucosal invasion, even when the tumor diameter was 1.0 cm or less, suggesting that the risk of metastasis does not differ appreciably from that of carcinomas. Burke *et al*[6] studied a series of 99 patients with duodenal WDET and reported that a tumor diameter of 2.0 cm or greater, invasion of the muscularis propria, and mitotic figures are risk factors for lymph node metastasis. On the basis of safety, effectiveness, and patients' quality of life, Dalenbäck *et al*[7] recommended endoscopic therapy for the management of duodenal WDET 1.0 cm or less in diameter with no evidence of distinct invasion of the muscularis on endoscopic ultrasonography.

Many studies have reported the usefulness of endoscopic treatment for WDET of the rectum[8] and stomach[9]. Duodenal WDET have also been treated endoscopically[10]. At present, the decision to perform endoscopic treatment for duodenal WDET is primarily made on the basis of tumor diameter (1.0 cm or less) and the depth of invasion (up to submucosal). However, even small lesions have a risk of lymph node metastasis[4,5,11]. The indications for endoscopic treatment and radical surgery with lymph node dissection remain controversial. We studied the clinicopathological characteristics in 11 patients with duodenal WDET treated in our hospital.

MATERIALS AND METHODS

The study group comprised 11 patients with duodenal WDET who received endoscopic treatment or surgery at the Department of Gastroenterology or the Department of Gastrointestinal Surgery, Kitasato University East Hospital from 1992 through 2007. Before treatment, all patients underwent upper gastrointestinal endoscopy. WDET were diagnosed by biopsy. Patients with WDET of the papilla of Vater and those with gastrinoma were excluded from the study. Abdominal computed tomography (CT) and upper gastrointestinal endoscopic ultrasonography (EUS) were performed to evaluate the depth of tumor invasion and the presence or absence of metastasis. Local resection (endoscopic treatment or partial resection) or radical surgery with extended (D2) lymph node dissection was performed.

From 1992 to 2005, all patients underwent open surgery. Local resection was performed if the tumor diameter was less than 1.0 cm on preoperative evaluation, and more radical resections with lymph node dissection were performed if the tumor diameter was 1.0 cm or greater. (Table 1, No. 1 to 7). However, curative resection was additionally performed in patients who were found to have a tumor diameter of 1.0 cm or greater or invasion of the muscularis, lymphovascular invasion, mitotic figures, or nuclear atypia on postoperative histopathological examinations. From 2005 through 2007, tumors less than 1.0 cm in diameter on preoperative evaluation were treated endoscopically. Curative resection was additionally performed on the basis of the results of histopathological examination (Table 1, No. 8 to 11).

For endoscopic treatment, endoscopic aspiration mucosectomy was performed as described by Tanabe *et al*[12]. The lesion margins were marked by argon plasma coagulation (APC), and a solution of 10% glycerin plus fructose (Glyseol, Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) was locally injected into the submucosa to cause the lesion to bulge. To perform endoscopic treatment safely, the endoscope (GIFXQ-230; Olympus Optical Co., Tokyo, Japan) was inserted through an overtube (Sumitomo Bakelite Co., Ltd., Tokyo, Japan). An aspiration mucosector (Top Co., Ltd., Tokyo, Japan) was attached to the tip of the endoscope. The endoscope was then reinserted, and the lesion was aspirated into a hood. The tumor margin was confirmed, the snare was opened, and the lesion was strangled. Mucosectomy was then performed by applying high-frequency current.

The following clinicopathological findings were recorded: age, sex, the presence or absence of symptoms, the presence or absence of carcinoid syndrome, endoscopic findings (the presence or absence of a central depression, erosions, and ulcers), tumor diameter, depth of invasion, lymphovascular invasion, mitotic figures, grade of nuclear atypia, and the presence or absence of lymph node metastasis. Proliferative activity of tumor cells was assessed by immunostaining with a monoclonal mouse antihuman Ki-67 antibody (MIB-1, N1633, DAKO, ChemMate Envision kit) and a monoclonal mouse antihuman p53 antibody (DO-7, M7001, 1:500, DAKO, ChemMate Envision kit). Tumor diameter was measured postoperatively on histopathological specimens. WDET were diagnosed histopathologically according to the criteria of the World Health Organization International Histological Classification of Tumors[2,13].

Table 1 Clinicopathological features of 11 patients with duodenal neuroendocrine tumors

Patient No.	Location	Age (yr)	Sex	Size (cm)	EUS	Accuracy rate	Depth of invasion	Lymphatic invasion	Venous invasion	LN	Treat	L/D metastasis
1	Bulbs	42	M	0.2	sm		sm	0	0	0	LR	None
2	Bulbs	68	F	0.7	NE		sm	0	0	0	LR	None
3	Bulbs	56	F	1.1	m		sm	0	0	0	LR	None
4	Bulbs	57	F	0.9	sm		mp	0	2	0	SG	None
5	Bulbs	62	M	1.1	sm	7/9 (77%)	sm	0	2	0	SG	None
6	2nd portion	55	M	1.2	sm		sm	0	0	0	PD	None
7	Bulbs	71	M	0.7	sm		sm	0	1	0	LR	None
8	2nd portion	59	M	0.9	sm		sm	0	0	0	EMR	None
9	Bulbs	56	M	0.9	sm		sm	0	1	1 (No. 4 d)	SG	None
10	Bulbs	60	M	0.7	sm		sm	0	0	0	EMR	None
11	Bulbs	54	M	0.7	NE		sm	0	0	0	EMR	None

EUS: Endoscopic ultrasonography; NE: Not evaluated; LN: Lymph node metastasis; No. 4 d LN: Lymph node metastasis along the right gastroepiploic vessels; sm: Submucosa; mp: Muscularis propria; EMR: Endoscopic mucosal resection; LR: Local resection; SG: Subtotal gastrectomy; PD: Pancreaticoduodenectomy; L/D metastasis: Local/distant metastasis.

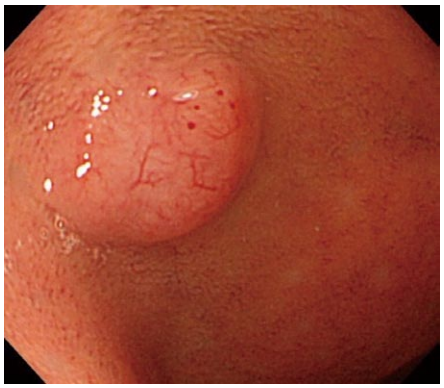

Figure 1 Upper gastrointestinal endoscopy showed a submucosal-tumor-like, protruding lesion 0.7 cm in diameter, arising in the anterior wall of the duodenal bulb. The top of the tumor was yellowish white, with dilated blood vessels.

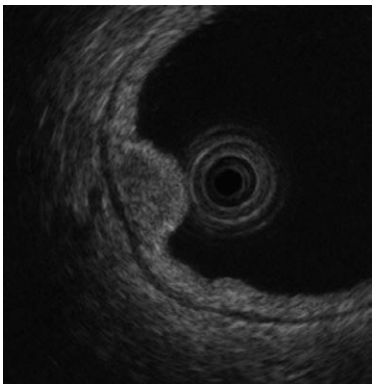

Figure 2 Upper gastrointestinal endoscopy showed a homogenous, oval hypoechoic mass, mainly located in the third layer.

Follow-up

The site that underwent endoscopic treatment was confirmed by the presence of a scar. To check for local recurrence around the scar formed at the site of endoscopic therapy, upper gastrointestinal endoscopy was performed 2, 6 and 12 mo after treatment and at 6 mo intervals thereafter. To confirm the presence or absence of distant metastasis, CT was performed at 6 mo intervals. In patients who underwent surgical resection of their tumors, upper gastrointestinal endoscopy and CT were performed at 6 mo intervals to confirm the presence or absence of recurrence.

RESULTS

Eleven consecutive patients with duodenal WDET (8 men and 3 women) were studied. Their median age was 57 years (range 42 to 71 years). The median follow-up period was 54 mo (range 6 to 201 mo) (Table 1). The tumors were located in the duodenal bulb in 9 patients and in the descending duodenum in 2 (Figure 1). All patients had only 1 lesion. No patient had carcinoid syndrome. No WDET was associated with von Recklinghausen disease, multiple endocrine neoplasm type I or asynchronous or synchronous malignant tumors. As for symptoms, 1 patient had dysphagia, and 1 had melena. All other patients were asymptomatic. Most WDET were diagnosed coincidentally on follow-up evaluation of gastric ulcers, follow-up after endoscopic mucosal resection (EMR) of early gastric cancer, follow-up for duodenal ulcers, or routine health screening. Among 9 tumors in the duodenal bulb and 2 in the descending duodenum, 7 had a central depression, including 1 with a deep depression. No patient had erosions or ulcers.

Upper gastrointestinal EUS was performed in 9 patients. All lesions had round or oval, homogenous, low-level internal echoes (Figure 2). Invasion of the muscularis was misdiagnosed as submucosal invasion in only 1 patient. As compared with the results of histopathological examination of the resected specimens, the depth of invasion was correctly diagnosed on EUS in 7 (77%) of 9 patients, indicating good results. On preoperative abdominal CT, no patient had evidence of lymph node metastasis, liver metastasis, or distant metastasis to other organs. Three patients were treated endoscopically, and 8 underwent surgery. The median tumor diameter was 0.9 cm (range 0.2-1.2 cm). All 3 patients who received endoscopic treatment had tumors less than 1.0 cm in diameter that were confined to the submucosa, with no distinct evidence

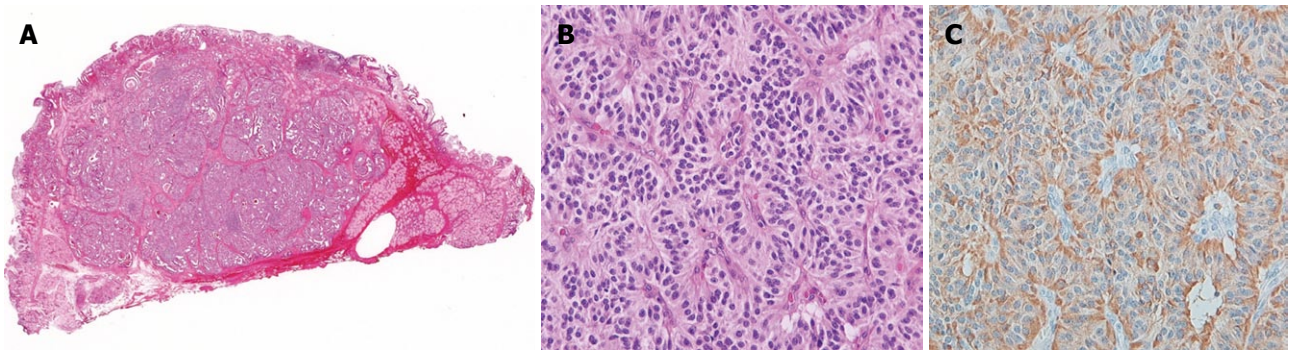

Figure 3 Histopathological examination. A: Macroscopic view of resected specimens obtained by endoscopic mucosal resection (hematoxylin and eosin staining). The longest diameter was 0.7 cm; B: Histopathological examination of specimens (hematoxylin and eosin staining, × 10) showed that cubic, atypical cells forming follicular or glandular patterns, with rounded nuclei and eosinophilic syncytia; C: Histopathological examination of specimens (chromogranin A staining, × 10) showed that tumors stained positively for chromogranin A.

Table 2 Pathological findings of 11 patients with well-differentiated endocrine tumor

Patient No.	Location	Size (cm)	Histological type	Depth of invasion	Lymphatic invasion	Venous invasion	Mitotic count (HPF)	Ki67/MIB1 Index (%)	LN	Direct invasion	Treatment
1	Bulbs	0.2	WD	sm	0	0	< 2	< 1	0	0	LR
2	Bulbs	0.7	WD	sm	0	0	< 2	< 1	0	0	LR
3	Bulbs	1.1	WD	sm	0	0	< 2	< 1	0	0	LR
4	Bulbs	0.9	WD	mp	0	2	< 2	< 1	0	0	SG
5	Bulbs	1.1	WD	sm	0	2	< 2	< 1	0	0	SG
6	2nd portion	1.2	WD	sm	0	0	< 2	< 1	0	0	PD
7	Bulbs	0.7	WD	sm	0	1	< 2	< 1	0	0	LR
8	2nd portion	0.9	WD	sm	0	0	< 2	< 1	0	0	EMR
9	Bulbs	0.9	WD	sm	0	1	< 2	< 1	1 (No. 4 d)	0	SG
10	Bulbs	0.7	WD	sm	0	0	< 2	< 1	0	0	EMR
11	Bulbs	0.7	WD	sm	0	0	< 2	< 1	0	0	EMR

WD: Well-differentiated; LN: Lymph node metastasis; No. 4 d LN: Lymph node metastasis along the right gastroepiploic vessels; sm: Submucosa; mp: Muscularis propria; EMR: Endoscopic mucosal resection; LR: Local resection; SG: Subtotal gastrectomy; PD: Pancreaticoduodenectomy; 10HPF (high power field): At least 10 fields (at 40 × magnification) evaluated in area of highest mitotic density.

of lymphovascular invasion or invasion of the muscularis on histopathological examination (Figure 3). There were no treatment-related complications, such as bleeding or perforation. Among 8 patients with tumors less than 1.0 cm in diameter, 3 received partial resection and 2 curative resection (distal gastrectomy in both). Three patients had lymphovascular invasion, 1 had invasion of the muscularis, and 1 had proximal lymph node metastasis (Table 1, No. 9). Among 3 patients with tumors 1.0 cm or greater in diameter, 1 received partial resection and 2 curative resection (distal gastrectomy in 1 and pancreaticoduodenectomy in 1). One patient had lymphovascular invasion, with no evidence of lymph node metastasis. No tumor showed distinct nuclear atypia or mitotic figures. On immunostaining, all tumors had a Ki-67 labeling index of 1% or less and tested negative for p53. In the patient with proximal lymph node metastasis (Table 1, No. 9), the tumor diameter was 0.9 cm, with no invasion of the muscularis, nuclear atypia, or mitotic figures. The Ki-67 labeling index was less than 1%, but lymphovascular invasion was positive. In 1 patient with a tumor less than 1.0 cm in diameter, lymphovascular invasion was found on local resection (Table 2). Because of advanced age, the patient was followed up without performing additional resection (Table 1, No. 7). At the time of this writing, all patients are alive, with no distinct evidence of metastasis or recurrence.

DISCUSSION

Our retrospective study showed even duodenal WDET 1.0 cm or less in diameter can be associated with invasion of the muscularis or lymphovascular invasion, considered high-risk factors for metastasis. One patient in our series had lymphovascular invasion with proximal lymph node metastasis. Whether endoscopic treatment is indicated for duodenal WDET has not been fully examined because of the rarity of these tumors. As for biologic malignancy, duodenal WDET are characterized by lower grades of atypia and malignancy than carcinomas. Similar to rectal WDET[5,14-16], endoscopic therapy has been used to treat duodenal WDET up to 1.0 cm in diameter that are limited to the submucosa. Such lesions are considered to have a relatively low risk of lymph node metastasis. Duodenal WDET arise from endocrine cells in the gastrointestinal mucosa and penetrate beyond the muscularis mucosae and invade the submucosa at an early stage. Because of these features, duodenal WDET appear to be submucosal tumors, although they arise from the mucosal endothelium[17]. EUS is

Table 3 Risk factor without metastasis of duodenal well-differentiated endocrine tumors

Author	*n*	Risk factor without metastasis of duodenal WDET
Burke *et al*[6], 1990	99	2.0 cm or less in diameter, no mitotic figures, no invasion of the muscularis propria
Zyromski *et al*[21], 2001	27	2.0 cm or less in diameter
Mullen *et al*[11], 2005	24	1.0 cm or less in diameter, submucosal lesions

WDET: Well-differentiated endocrine tumors.

very useful for evaluating the depth of invasion of duodenal WDET. If the tumor is confined to the submucosa, the lesion is mainly present in the third layer, depicted as a well demarcated, hypoechoic mass with homogenous, low-level internal echoes[18,19]. In our series, a correct diagnosis was made on EUS in 7 (77%) of 9 patients. Preoperative EUS is thus considered useful for diagnosis.

In patients with gastrointestinal neuroendocrine tumors, tumor diameter and depth of invasion are related to the risk of metastasis. The depth of invasion is mucosal in 1.7% of tumors, submucosal in 10.5%, the muscularis propria in 29.6%, and subserosal or serosal in 42.8%[20]. The incidence of metastasis in patients with gastrointestinal neuroendocrine tumors invading the submucosa increases in parallel to tumor diameter: 0.5 cm or less, 6.0%; 1.0 cm or less, 13.3%; 2.0 cm or less, 23.9%; and more than 2.0 cm, 38.4%[5]. Soga[5] retrospectively studied 1914 cases of gastrointestinal neuroendocrine tumors limited to the submucosa and found that tumor diameter was 0.5 cm or less in 8.3% of lesions, 1.0 cm or less in 10.5%, 2.0 cm or less in 13.8%, and greater than 2.0 cm in 25.8%. In Western countries, Burke *et al*[6] studied 99 patients with duodenal WDET and found that lesions that were 2.0 cm or less in diameter or had no mitotic figures or invasion of the muscularis propria had a low risk of lymph-node metastasis (Table 3). Zyromski *et al*[21] studied 27 patients with duodenal WDET and reported that tumors 2.0 cm or less in diameter could be safely and effectively treated by local resection alone, without recurrence. On the basis of the safety, effectiveness, and patients' quality of life, Dalenbäck *et al*[7] recommended endoscopic therapy for the management of duodenal WDET 1.0 cm or less in diameter that have no evidence of muscular invasion on EUS. Among 24 patients with duodenal WDET, however, Mullen *et al*[11] found that 2 of 7 patients with lymph node metastasis had submucosal lesions that were 1.0 cm or less in diameter, indicating that lymph node metastasis could not be accurately predicted solely on the basis of tumor diameter or depth of invasion. Biologic markers of cell proliferative activity, such as Ki-67 and p53, have sporadically been reported to be related to metastasis from gastrointestinal neuroendocrine tumors[13,14,22], but these markers were negative in all of our patients.

At present, endoscopic treatment is mainly indicated for duodenal WDET 1.0 cm or less in diameter that are confined to the submucosa, with no distinct invasion of the muscularis. In our series, radical surgery with lymph node dissection was performed in all patients with tumors 1.0 cm or more in diameter or with suspected invasion of the muscularis on preoperative examinations, including EUS. Tumors that were less than 1.0 cm in diameter and confined to the submucosa underwent local resection or endoscopic treatment. However, patients with duodenal WDET should be carefully followed up, including histopathological examination after endoscopic treatment, because postoperative examination of histopathological specimens showed that even duodenal WDET less than 1.0 cm in diameter can be associated with lymphovascular invasion, muscular invasion, or proximal lymph node metastasis. The incidence of metastasis associated with duodenal WDET is estimated to be about 10% even when the tumor diameter is 1.0 cm or less, similar to that of carcinomas[23]. The biologic malignancy of duodenal WDET may thus differ from that of carcinoid tumors arising in the rectum[5,8,14-16] and stomach[9].

As for the endoscopic treatment of duodenal WDET, EMR is more difficult to perform in the duodenum than in the stomach because of its very thin wall and narrow lumen[24]. Moreover, EMR can cause complications such as late bleeding and perforation. In particular, the incidence of late bleeding is very high (25.5% to 33.0%) after EMR for duodenal tumor[25,26], as compared with early gastric cancer (1.4%)[27], early esophageal cancer (3.6%)[28], and early colorectal cancer (0.3% to 2.7%)[29,30]. Lépilliez *et al*[26] reported that therapeutic or prophylactic hemostasis by clipping or APC decreased the rate of late bleeding from 21.7% to 0% in patients who underwent EMR for sporadic duodenal adenomas. In our study, EMR was done in 3 patients with tumors arising in the duodenal bulb or descending duodenum. After the procedure, the exposed vessels at the ulcer floor were treated with a hemostatic forceps. Complications such as late bleeding were prevented by performing second-look endoscopy on the day after treatment. Future studies examining the correlation between tumor diameter in millimeters and the presence or absence of lymph node metastasis in large numbers of patients may help to more clearly define the indication range for endoscopic treatment. The discovery of new biomarkers may also assist physicians in deciding whether additional surgery is needed.

In conclusion, we clinically and histopathologically studied 11 patients with duodenal WDET treated in our hospital. Duodenal WDET less than 1.0 cm in diameter have a risk of lymphovascular invasion, invasion of the muscularis, and lymph node metastasis, irrespective of procedural problems. Fully informed consent should be obtained, and patients should be closely followed up, including histopathological evaluation, after endoscopic therapy.

COMMENTS

Background

The diameter and depth of invasion of well-differentiated endocrine tumors (so-called carcinoid tumors) have been shown to correlate with lymph node metastasis. The treatment strategy of choice remains controversial.

Research frontiers

Many studies described tumor diameter of 1.0 cm or greater, invasion of the

muscularis propria, and mitotic figures as risk factors for lymph node metastasis of well-differentiated endocrine tumors.

Innovations and breakthroughs

Duodenal well-differentiated endocrine tumors less than 1.0 cm in diameter have a risk of lymphovascular invasion, invasion of the muscularis, and lymph-node metastasis.

Applications

Patients with duodenal well-differentiated endocrine tumors should be closely followed up, including histopathological evaluation, if endoscopic treatment has been performed.

Peer review

Ishido *et al* reported their institutional experience on the clinicopathological evaluation of carcinoid tumors of the duodenum.

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