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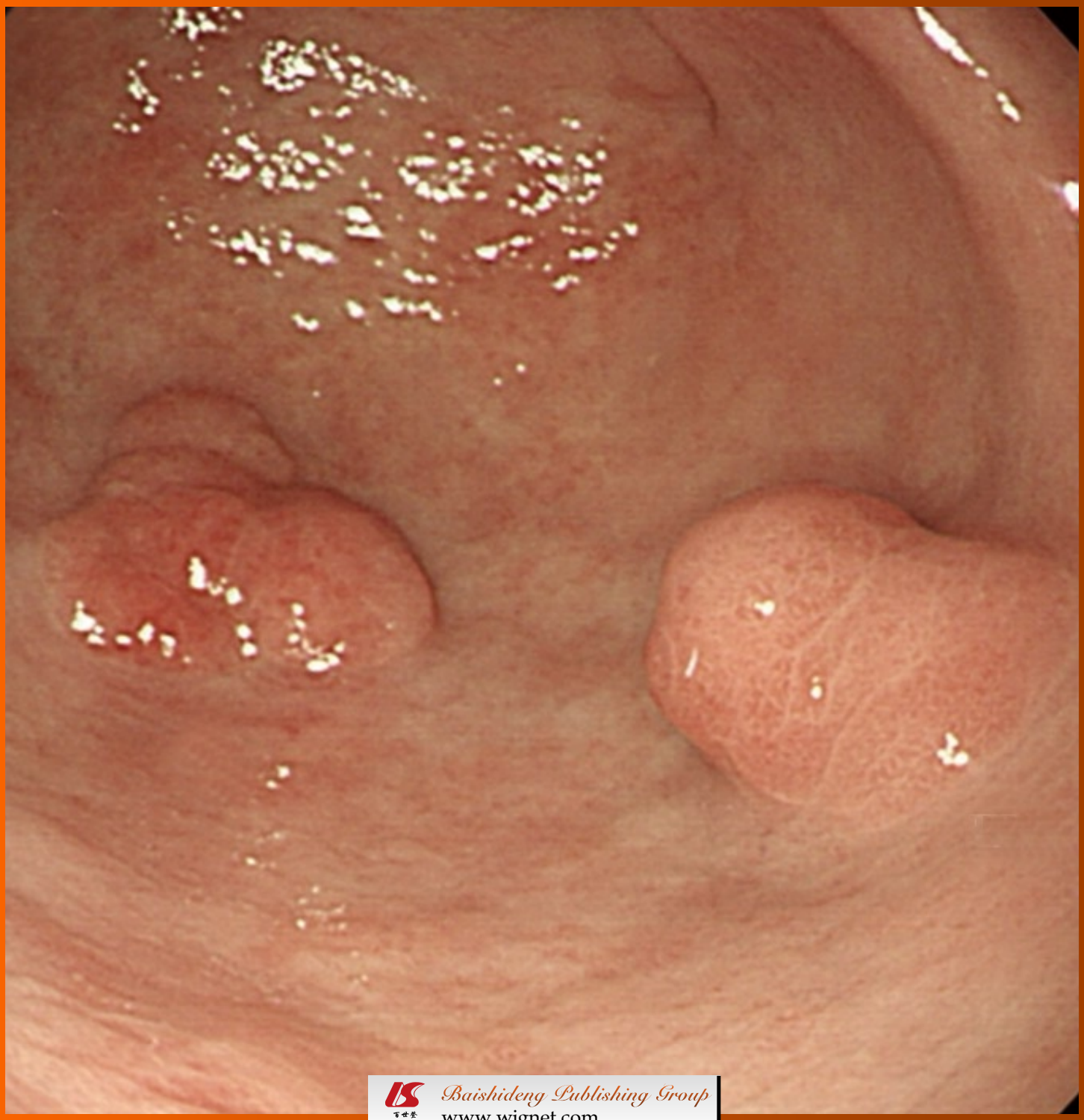

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EDITORIAL

Management of early gastrointestinal neuroendocrine neoplasms

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Abstract

Neuroendocrine neoplasms (NENs) of the stomach, duodenum, appendix or rectum that are small (≤ 1 cm) and well differentiated can be considered "early" tumors, since they generally have a (very) good prognosis. In the new WHO classification of 2010, these neoplasms are called neuroendocrine tumors/ carcinoids (NETs), grade (G) 1 or 2, and distinguished from poorly differentiated neuroendocrine carcinomas (NECs), G3. NETs are increasing, with a rise in the age-adjusted incidence in the U.S.A. by about 700 % in the last 35 years. Improved early detection seems to be the main reason for these epidemiological changes. Both the better general availability of endoscopy, and imaging techniques, have led to a shift in the discovery of smaller-sized (≤ 10-20 mm) intestinal NETs/carcinoids and earlier tumor stages at diagnosis. Endoscopic screening is therefore effective in the early diagnosis, not only of colorectal adenocarcinomas, but also of NETs/carcinoids. Endoscopic removal, followed up with endoscopic surveillance is the treatment of choice in NETs/carcinoids of the stomach, duodenum and rectum that are ≤ 10 mm in size, have a low proliferative activity (G1), do not infiltrate the muscular layer and show no angioinvasion. In all the other intestinal NENs, optimal treatment generally needs surgery and/or medical therapy depending on type, biology and stage of the tumor, as well as the individual situation of the patient.

Key words: Neuroendocrine tumor; Carcinoid; Stomach; Duodenum; Gut; Appendix; Rectum; Small size; Prognosis; Treatment

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INTRODUCTION

Gastrointestinal neuroendocrine neoplasms (NENs) have received much attention in recent years with regard to their diagnosis, classification, incidence, prognosis and treatment[1-3]. The most recent achievement is the new WHO classification, which appeared in the second half of 2010.

Table 1 Comparison of the WHO classification 2010 for gastroenteropancreatic neuroendocrine neoplasms with previous WHO classifications

WHO 1980	WHO 2000	WHO 2010
I Carcinoid	WDET[a]	NET G1 (carcinoid) G2[a]
	WDEC[a]	
	PDEC	NEC G3 Large cell or small cell type
	MEEC	MANEC
II Pseudotumour lesions	TLL	Hyperplastic and preneoplastic lesions

G: Grade (for definition, see text and table 2); [a]In case that the Ki67 proliferation rate exceeds 20%, this NET may be graded G3. WHO: World Health Organization; WDET: Well-differentiated endocrine tumor; WDEC: Well-differentiated endocrine carcinoma; MEEC: Mixed exocrineendocrine carcinoma; TLL: Tumour-like lesions; NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma; MANEC: Mixed adenoneuroendocrine carcinoma.

In essence, this classification stratifies the pure gastroenteropancreatic (GEP)-NENs into three groups (Table 1): neuroendocrine tumors (NETs, equivalent to carcinoids) that are well differentiated and graded according to their proliferative activity into G1 or G2 (Table 2), and neuroendocrine carcinomas (NECs) that are poorly differentiated and graded as G3. The poorly differentiated NECs are divided into small cell and large cell neoplasms. Staging of tumor extension according to the available TNM classifications of ENETS[4,5] and AJCC/UICC[6] leads to a further stratification of NETs and NECs. The neoplasms that show non-endocrine components (usually adenocarcinoma structures) in addition to a considerable number of neuroendocrine cells (exceeding at least 30% of all tumor cells), are distinguished from the pure neuroendocrine neoplasms, and called mixed adeno-neuroendocrine carcinomas (MANEC).

Gastrointestinal NETs/carcinoids are on the rise[3]. In the U.S.A., the prevalence and the incidence of gastrointestinal NETs/carcinoids has recently been calculated to be 35/100 000 and 5/100 000, respectively[7], revealing a 7-fold increase in the last 35 years. Similar observations have been reported from England[8] and Norway[9]. The most obvious reason for this phenomenon is a better awareness of, and improved diagnostic strategies, for NENs, and an increased and more widespread use of gastrointestinal endoscopy[8-15].

The overall 5-year-survival rate for patients with gastrointestinal NETs/carcinoids has improved by almost 20% in the last 35 years[16-18]. This achievement is largely due to early detection, as gastrointestinal NETs/carcinoids are nowadays more frequently diagnosed at an early asymptomatic stage[7], notably tumors with a size below 10 mm and a G1 differentiation. Due to a lack of controlled prospective studies the management of these "early" gastrointestinal NETs/carcinoids has been a matter of debate. Here we review the retrospective data from large national registries and large hospital series, mainly from Japan, the U.S.A. and Korea.

Table 2 Grading of gastrointestinal neuroendocrine neoplasms according to proliferative activity[a]

Grade	Ki-67 index (%)[b]
G1	≤ 2
G2	3-20
G3	> 20

[a]Modified according to reference[4,5,19]; [b]MIB1 antibody, % of 100 tumor cells in areas of highest nuclear labeling.

RISK STRATIFICATION AND PROGNOSIS OF GASTROINTESTINAL NEN DISEASE

The risk of metastatic disease of gastrointestinal NENs correlates with histological differentiation (well or poorly differentiated), proliferative activity (G1-3, Table 2), tumor size, depth of tumor infiltration and angioinvasion. The recently introduced and generally accepted histological grading of gastrointestinal NENs (G1-G3) by the WHO is of major prognostic and therapeutic relevance (Table 2).

Prognosis of gastric NETs/carcinoids

At present, the most common of the gastric NENs, the type 1 (Table 3), is mostly diagnosed at an early stage, with 80%-90% of them being ≤ 1 cm in diameter[13]. These small tumors only rarely cause specific symptoms; in most instances they are found incidentally during a gastroscopy being performed for another reason, such as anemia, reflux symptoms or other non-specific abdominal symptoms. Type 2 gastric NENs, similar to type 1 (Table 3) are usually detected at an early stage, and thus have an excellent long term prognosis. For all gastric carcinoids the prognosis has much improved[3,16,20-22], with the proportion with advanced tumor stages at diagnosis decreasing from 23.8% in the 1950s and 1960s to 6.5%-7.9% in the 1990s, suggesting that early diagnosis is contributing to patients' improved survival. In Japan, the rate of advanced stages at diagnosis today is as low as 5.1%[20]. The 5-year-survival rate of patients with gastric NENs has improved from 51% in the 1970s and 1980s to 63% in the 1990s[3,20-22]. According to a recent analysis of the SEER data by Landry *et al*[21], the 5-year-survival is now up to 71%.

Small (≤ 1cm), well-differentiated (G1) carcinoids/NETs of the stomach that do not infiltrate the muscularis propria and do not show angioinvasion have been shown to have a very low risk of distant metastatic spread or carcinoid-related death; they are considered early NETs/ carcinoids of the stomach.

Prognosis of NETs/carcinoids of the small bowel

In the small bowel, ileal NETs/carcinoids are most frequently found (> 70%), but recent data show that the NE-

Table 3 Clinicopathological characteristics of gastric neuroendocrine neoplasms[4,23-26]

	Gastric NETs/carcinoids			Gastric NECs (poorly differentiated NENs)
	Type 1	Type 2	Type 3	Type 4
Relative frequency	70%-80%	5%-6%	14%-25%	6%-8%
Features	Mostly small (< 1-2 cm) and multiple	Mostly small (< 1-2 cm) and multiple	Solitary often > 2 cm	Solitary mostly exulcerated, > 2 cm
Associated conditions	CAG	MEN1/ZES	No	No
Histology	Well differentiated G1	Well differentiated G1	Well/moderate differentiated* G2[a]	Poorly differentiated G3
Serum gastrin	(Very) high	(Very) high	Normal	(Mostly) normal
Gastric pH	Anacidic	Hyperacidic	Normal	(Mostly) normal
Metastases	< 10%	10%-30%	50%-100%	80%-100%
Tumor-related deaths	no	< 10%	25%-30%	⩾ 50%

NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma; CAG: Chronic atrophic gastritis, due to pernicious anemia or Helicobacter pylori infection; MEN1: Multiple endocrine neoplasia type1; ZES: Zollinger-Ellison syndrome; MEN1/ZES: ZES associated with MEN1; G1-3 histological differentiation: see Table 2; ENETS and NANETS nomenclature are identical for G1 and G3 grading: G1: Well differentiated; G3: Poorly differentiated. For G2 grading ENETS and NANETS nomenclature differ: *ENETS-nomenclature: G2: Well-differentiated; [a]NANETS-nomenclature: G2: Moderate differentiated (modified from Scherübl *et al*[13])

Ts of the duodenum are nowadays more common (22%) than previously noted[27]. Regarding prognosis, the 5-year survival rate has risen from 51.9% in the 1970s and 1980s to 60.5% in the 1990s[16]. In an analysis of the years 1999-2004, Strosberg *et al* reported a 5-year survival rate of about 75% in patients with metastatic NET/carcinoid disease of the small intestine, receiving multimodal therapy[17]. An earlier detection of all NETs of the small bowel may have led to improved prognosis[15,18], since the proportion of advanced disease of small intestine NETs (at the time of diagnosis) has decreased from 31.3% in the 1970s and 1980s, to 22.4% in the 1990s and finally to < 18.9% in the years between 2002-2004[7,16,20,27]. With duodenal NETs/carcinoids, distant metastases are nowadays observed in less than 6%-10% of the cases[19,20,28,29,30]. If duodenal NETs/carcinoids are ⩽ 10 mm in size, are G1, show neither angioinvasion nor infiltration of the muscular layer, and have no associated hormonal syndrome, they have a very low metastatic potential and can be considered "early" duodenal NETs/carcinoids. In contrast, duodenal gastrinomas (i.e. duodenal NETs/carcinoids associated with a Zollinger-Ellison syndrome (ZES), with or without multiple endocrine neoplasia 1) as well as jejunal/ileal NETs/carcinoids of only a few millimeters in size, may already have spread to locoregional lymph nodes and/or distant organs such as the liver. Thus, neither for jejunal/ileal NETs/carcinoids nor for duodenal ZES/gastrinomas, is the term "early" appropriate, and should not be used.

Prognosis of rectal NETs/carcinoids

Because of the introduction of colorectal cancer screening, the vast majority (85%-100%) of rectal NETs/carcinoids are nowadays detected at an early stage (Table 4). This has improved patients' 5-year-survival rate by more than 20%[14].

The 5-year-survival rate of rectal NETs/carcinoid patients with distant metastases ranges between 15%-30%[29,31,32]. For nodal-positive rectal carcinoid disease (without distant metastases detected at the time of diagnosis) the 5-year-survival rate is 54%-73%[31,32-34]. In contrast, histologically nodal-negative rectal NETs/carcinoids that are ⩽ 1 cm in size and do not show angioinvasion or infiltration of the muscular layer have an excellent 5-year-survival rate of 98.9%-100%[3,29,31,32]. These rectal NETs/ carcinoids may be regarded as "early" tumors.

Table 4 Impact of endoscopic screening on the size of detected rectal NENs/carcinoids[14]

Size of the primary	Without screening (%)	Endoscopic screening (%)
< 10 mm	65-80	93.3-100
11-20 mm	10-22	0-6.7
> 20 mm	10-15	0

The risk of lymph node metastases of rectal NETs/carcinoids is not lower than the metastatic risk of rectal adenocarcinoma of the same size[29,32,33]. Interestingly, neither is the prognosis of patients with metastatic rectal NET/carcinoid disease better than that of patients suffering from metastastic rectal adenocarcinoma of the same size[31-34].

The clinical significance of histological lymph node involvement in G1-G2 differentiated rectal NETs/carcinoids of 1-2 cm in size is not well studied and therefore not known, at least not in Western countries. Current guidelines published by NANETS do not recommend follow-up of patients with well-differentiated rectal carcinoids/NETs of 1-2 cm in size that have been completely resected and that had not invaded the muscular layer[35]. Yet ENETS recommends further surveillance of these patients when angioinvasion or invasion of the muscular layer or G2 grading have been reported[36].

DIAGNOSIS OF EARLY NETS/ CARCINOIDS OF THE STOMACH, DUODENUM OR RECTUM

Endoscopic screening and the increasingly widespread

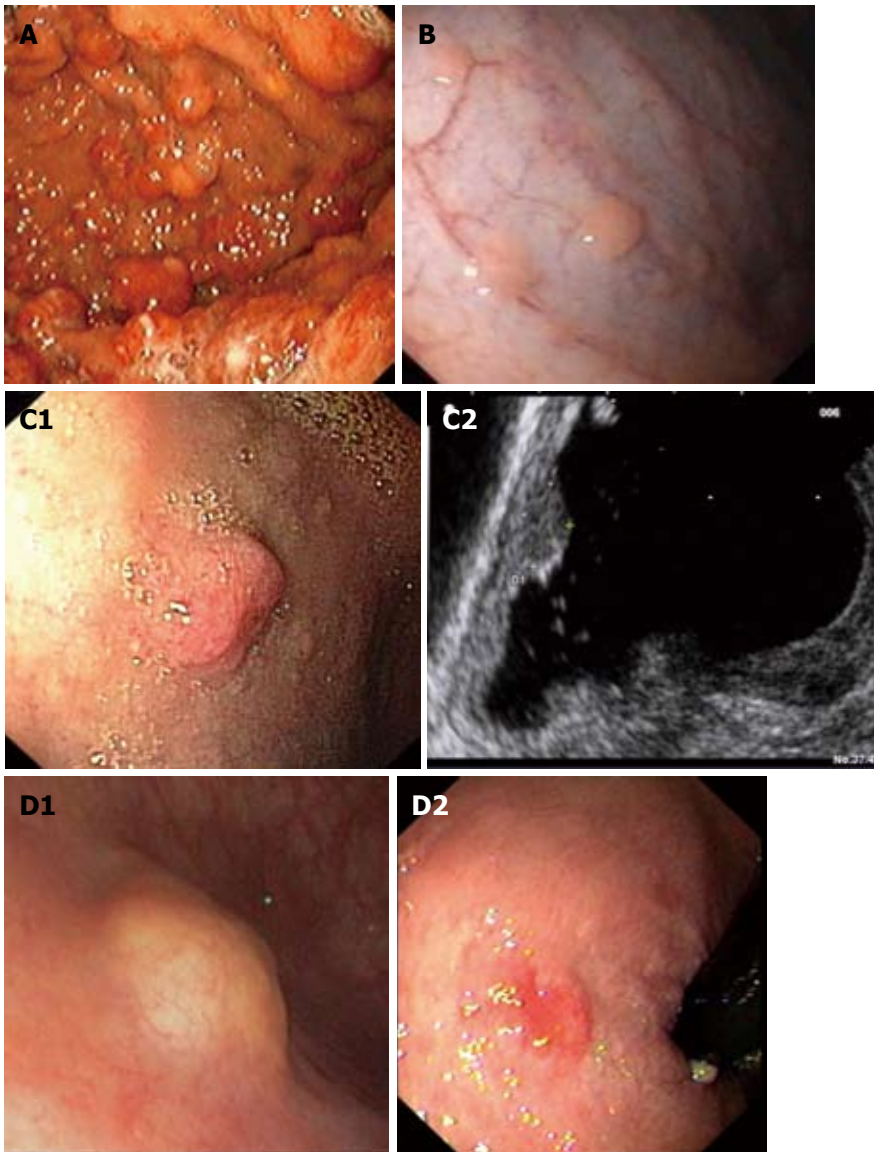

Figure 1 Endoscopic images of early gastrointestinal NETs/carcinoids. A: Multiple small (< 1 cm), well differentiated (G1) type 2 gastric NETs/carcinoids associated with Zollinger-Ellison-syndrome (ZES) and multiple endocrine neoplasia type 1 (MEN1); B: Multiple small (< 1 cm), well differentiated (G1) type 1 gastric NETs/carcinoids associated with autoimmune chronic atrophic gastritis and pernicious anemia; C: 8 mm measuring NET/carcinoid in the duodenal bulb (C1). Endoscopic ultrasound shows the infiltration of mucosa and submucosa (C2). The duodenal NET/carcinoid exhibits a low echogenic pattern on EUS; D: 10 mm measuring NET/carcinoid of the rectum (D1). 7 mm measuring NET/carcinoid of the rectum (D2). Modified from reference[13-15]. NETs: neuroendocrine tumors; EUS: Endoscopic ultrasound.

availability of gastrointestinal endoscopy have led to a shift in the discovery of smaller-sized (≤ 10-20 mm) gastrointestinal carcinoids/NETs at the time of diagnosis. Most of these tumors are asymptomatic, but occasionally they may present with abdominal discomfort, gastrointestinal bleeding, altered bowel habits or in the case of an ampullary NET with jaundice. If they present with hormonal hypersecretion syndromes, as for instance as duodenal gastrinomas associated with ZES (see above), they have often already spread to the regional lymph nodes, despite their small size. These functional intestinal NETs that almost never represent "early" tumors, will not be discussed here in detail (see recent reviews).

Endoscopy is the only method of choice to detect (asymptomatic) gastric, duodenal or rectal NETs/carcinoids at an early stage. So far there are no data available concerning the sensitivity and specificity of radiological and scintigraphic imaging techniques to visualize early gastric, duodenal or rectal NETs/carcinoids (Figure 1).

THERAPY OF EARLY GASTROINTESTINAL NETS/CARCINOIDS

For early NETs/carcinoids of the stomach, duodenum or rectum, the treatment of choice is endoscopic resection. For the treatment and management of more advanced NETs/carcinoids, all the prognostically relevant parameters (see below) have to be taken into account. Best palliative therapy is required for far advanced tumor disease.

Stomach, duodenum and rectum

Small (≤ 1 cm), well-differentiated (G1) NETs/carcinoids of the stomach, duodenum or rectum that do not infiltrate the muscularis propria and do not show angio-invasion have a very low risk of metastatic spread, i.e. they are considered early NETs/carcinoids of the stomach, duodenum or rectum. Endoscopic ultrasound is excellent for determining exact tumor size and to exclude infiltration of the NETs/carcinoids into the muscular wall (muscularis

Table 5 Therapy of gastric NENs

	No risk factors (for metastatic disease)		risk factors[a]
Size	⩽ 1 cm	1-2 cm	
Type 1	Surveillance[b] optionally EMR	EMR followed by surveillance	Surgery[c]
Type 2	Surveillance[b]	EMR followed by surveillance	Surgery[c]
Type 3	EMR	Surgery[c]	Surgery[c]
Type 4	-	-	Surgery[d]

[a]risk factors for metastatic disease are angioinvasion or G2-G3 histological grading or infiltration of the muscularis propria or tumor size > 2cm; [b]somatostatin analogs are being tested in ongoing clinical trials, they should not be used except in clinical trials; [c]followed by endoscopic surveillance of the gastric remnant. Adjuvant (medical) therapy is not established in NET/carcinoid disease; [d]surgery in localized type 4 gastric/d NEC disease (or systemic cytoreductive chemotherapy in advanced type 4 gastric NEC disease). Type 4 gastric NECs are never benign, they are neuroendocrine carcinomas. EMR: Endoscopic mucosal resection; NENs: Neuroendocrine neoplasms.

Table 6 Therapy of duodenal NENs

Type	⩽ 1 cm[a]	1-2 cm[a]	Any size but risk factors[b]
Sporadic NET (no gastrinoma, no MEN1)	EMR	Surgery (in case of surgical risk: EMR followed by surveillance)	Surgery
Sporadic gastrinoma	Surgery[c]	Surgery[c]	Surgery[c]
Gastrinoma and MEN1	PPI therapy and surveillance (or surgery)	Surgery (particularly if the gastrinoma is growing) or PPI therapy combined with surveillance	Surgery (or PPI therapy combined with surveillance in G1 gastrinomas and/or surgical risk)
NEC (G3)	-	-	Surgery or cytoreductive chemotherapy

[a]without risk factors (for metastatic disease) such as G2-G3, angioinvasion, infiltration of the muscularis propria or tumor size > 2 cm; [b]in the presence of risk factors for metastatic disease, surgery is generally indicated, regardless of tumor size; [c]Surgery is the therapy of choice for sporadic gastrinoma (without distant metastases). In (very) elderly patients conservative management may, however, be preferred to surgery. Adjuvant (medical) therapy is not established in NET/carcinoid disease. NET: Well differentiated neuroendocrine tumor; EMR: Endoscopic mucosal resection; PPI: Proton pump inhibitor; MEN1: Multiple endocrine neoplasia type 1.

propria). Endoscopic ultrasound is not mandatory for NETs/carcinoids measuring less than 1 cm, because those do generally not infiltrate the muscular layer. Early, G1-differentiated NETs/carcinoids of the stomach, duodenum or rectum should be removed by endoscopic polypectomy or by endoscopic mucosal resection (EMR). In early rectal NETs/carcinoids endoscopic submucosal dissection (ESD) may be considered, too. The resected specimen has to

Table 7 Therapy of rectal NENs

	No risk factors (for metastatic disease)		Risk factors[a]
Grade/Size	⩽ 1.0 cm	1.1 - 2 cm	Any size
G1	EMR or polypectomy or ESD	Surgery[b] (EMR or ESD in case of surgical risk or for carcinoids of 11-14 mm in diameter)	Surgery[b]
G2	EMR, ESD, surgery[b]	Surgery[b]	Surgery[b]
G3	-	-	Surgery[b]

[a]risk factors for metastatic disease are angioinvasion or infiltration of the muscularis propria, or tumor size of > 2cm; [b]surgery only in localized NET/NEC disease and systemic medical therapy in advanced tumor/cancer disease. Adjuvant medical therapy is not established for curatively resected, well-differentiated NETs/carcinoids of the rectum. G3 neuroendocrine neoplasms of the rectum are always neuroendocrine carcinomas. EMR: Endoscopic mucosal resection; ESD: endoscopic submucosal dissection; NENs: Neuroendocrine neoplasms.

be carefully evaluated for grade, angioinvasion, and infiltration of the deep resection margin. In case of angioinvasion, histological infiltration of the muscular wall or grade G2/G3, surgery is the first line therapy. The management of G1 NETs/carcinoids of 1-2 cm in size is a matter of debate[16-18]. Unfortunately, there are no controlled prospective studies available that have compared the endoscopic to the surgical approach for these 1-2 cm sized carcinoids/NETs. Due to the particular tumor biology of G1 NETs/carcinoids (of 1-2 cm in size) the endoscopic approach should be preferred to surgery in patients with significant comorbidities and, in elderly patients, a (high) surgical risk. No adjuvant therapy has been established for curatively resected, G1-G2 gastrointestinal NETs/carcinoids. Analogous to the situation of small cell or large cell neuroendocrine cancer disease of the lungs, cytoreductive chemotherapy is generally recommended for gastrointestinal NECs (G3 neuroendocrine carcinomas). G3 NENs are never "early" and almost always metastatic at diagnosis. The specific therapeutic strategies for early NETs/carcinoids of the rectum, duodenum and stomach are outlined in Table 5-7.

APPENDIX

Appendiceal NENs are usually NETs/carcinoids that are found incidentally in (young) patients undergoing appendectomy for suspected acute appendicitis. The term "early appendiceal NET/carcinoid" may be considered for the tumors that are G1, measure ⩽ 10 mm, show no angioinvasion, are confined both to the tip of the appendix and to the wall (without invasion of the mesoappendix) and have been completely (R0) removed. Such early appendiceal carcinoids have a very low risk of distant metastatic spread. Neither ENETS nor NANETS recommend further surveillance of patients with these early appendiceal tumors[38,39]. The management of other appendiceal carci-

noids/NETs is not discussed here; we refer to recent review and guideline papers[38,39].

CONCLUSION

New diagnostic techniques have led to increasingly early recognition of early gastrointestinal NETs/carcinoids. The general widespread use and availability of gastrointestinal endoscopy has led to a shift in the discovery of smaller-sized (≤ 10-20 mm) gastrointestinal NETs/carcinoids at the time of diagnosis. In the last 35 years, the overall 5-year-survival rate of patients with gastrointestinal carcinoid/NEN disease has increased by almost 20%. Most patients with early, well differentiated (G1) NETs/carcinoids of the stomach, duodenum and rectum can be treated conservatively, and be followed-up by endoscopic surveillance. It should be noted that patients with (previous) NET/carcinoid disease have a 15%-25% risk for second malignancies including breast, prostate, colorectal or gastric cancer.

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REVIEW

Radiation dose to patients during endoscopic retrograde cholangiopancreatography

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) is an important tool for the diagnosis and treatment of the hepatobiliary system. The use of fluoroscopy to aid ERCP places both the patient and the endoscopy staff at risk of radiation-induced injury. Radiation dose to patients during ERCP depends on many factors, and the endoscopist cannot control some variables, such as patient size, procedure type, or fluoroscopic equipment used. Previous reports have demonstrated a linear relationship between radiation dose and fluoroscopy duration. When fluoroscopy is used to assist ERCP, the shortest fluoroscopy time possible is recommended. Pulsed fluoroscopy and monitoring the length of fluoroscopy have been suggested for an overall reduction in both radiation exposure and fluoroscopy times. Fluoroscopy time is shorter when ERCP is performed by an endoscopist who has many years experience of performing ERCP and carried out a large number of ERCPs in the preceding year. In general, radiation exposure is greater during therapeutic ERCP than during diagnostic ERCP. Factors associated with prolonged fluoroscopy have been delineated recently, but these have not been validated.

Key words: Endoscopic retrograde cholangiopancreatography; Radiation dose; Fluoroscopy; Radiation exposure; X-ray

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is an important tool for the diagnosis and treatment of the hepatobiliary system. Recent data indicate that ERCP is becoming a major therapeutic strategy for biliary disease in developed and developing countries. In the diagnosis process, MRCP is generally preferred to ERCP. During the performance of ERCP, a large number of X-ray fluoroscopy and digital radiographs are performed, making it an interventional radiological (IR) procedure. ERCP is highly technical and depends on endoscopist's experience. High quality ERCP outcomes and limitation of ERCP-related complications depend on good training. The use of fluoroscopy to aid ERCP, places both the patient and the endoscopy staff at risk of radiation-induced injury[1,2]. It is essential to establish the appropriate conditions for radiography in all circumstances, in order to avoid unnecessary exposure of patients and staff to potentially harmful radiation. This means that precautions should be taken to keep the radiation dose to both the personnel participating in ERCP pro-

cedures and to patients as low as reasonably achievable (ALARA principle).

The identification of predictive factors of fluoroscopy time and radiation exposure to patients undergoing ERCP are beyond the scope of this guideline.

DEFINING RADIATION QUANTITIES

X-rays consist of ionizing radiation, such as gamma rays, emitted by radioactive substances. They cause ionization in the medium through which they pass. The ionization produced can lead to DNA damage or cell death. Radiation effects are broadly divided into two categories: *deterministic effects (*e.g. cataract formation, infertility, skin injury, and hair loss); and *stochastic effects* (cancer and genetic effects). The harm depends on the amount of radiation absorbed by the body, known as the radiation dose or, simply -dose.

There are two types of expression for quantities of radiation, those that express the concentration of radiation at some point, or to a specific tissue or organ, and those that express the total radiation delivered to a body.

Exposure indicators usually measured in ERCP are absorbed dose, as a measure of radiation concentration, two measures of total radiation (effective dose and dose-area product) and fluoroscopy time.

Absorbed dose is the measure used to quantify the concentration of radiation energy actually absorbed in a specific tissue. This is the measure that is most directly related to biological effects. Dose values can be in the traditional unit of the rad or the SI unit of the gray (Gy).

Effective dose is a very useful radiation quantity for expressing relative risk to humans, both patients and other personnel. It is actually a simple and very logical concept, and is expressed as joules per kilogram (J kg-1), expressed in the SI unit of the sievert (Sv). For the purpose of determining effective dose, the different areas and organs have been assigned tissue weighting factor (w_T**)** values. It is generally assumed that the exposure to natural background radiation is somewhat uniformly distributed over the body. Since the tissue W_T for the total body has the value of one (1), the effective dose is equal to the absorbed dose.

Effective dose (Sv)= Absorbed dose (Gy) × W_T (1)

Dose-area product (DAP) provides a good estimation of the total radiation energy delivered to a patient during a procedure and is strongly correlated to the fluoroscopy time. It is the most practical measure for monitoring the radiation delivered to patients. DAP is just the product of the air kerma ,in Gy or mGy, and the exposed area in cm^2 (Gy-cm^2)(Figure 1).

RADIATION DOSE MONITORING IN ERCP

Radiation dose monitoring in patients undergoing diagnostic or IR procedures has been widely adopted in clinical practice, but data on patient doses during ERCP are very scarce[3-7].

Gastroenterologists who are involved in ERCP procedures may work at specialized centres and may perform multiple procedures daily. In all circumstances in which fluoroscopic and/or x-ray equipment is used, gastroenterologists should minimize the risks to patients, themselves, and other members of the staff[3,4,7]. The amount of radiation currently being used by endoscopist is relatively small, effective doses of 0-3 mSv/year, in comparison with interventional radiologists and interventional cardiologists[8]. When physician doses were serially measured, endoscopists was found to be exposed to larger amounts of radiation than their assistants because the endoscopist was typically closer to the x-ray sources[7]. The dose limit that is recommended by the International Commission on Radiological Protection (ICRP) and adopted by most countries is 20 mSv/year[9]. For situations where the annual dose limit exceeds 20 mSv, it is recommended that the dose should not exceed 50 mSv in any particular year or 100 mSv over 5 years. This dose limit is based on the calculation of radiation risk over a full working life from the age of 18 years to 65 years (47 years) at the rate of 20 mSv per year, amounting to 20 × 47 = 940 mSv (approximately 1 Sv). Epidemiologic research has estimated a 10% increase in cancer risk with a lifetime occupational exposure of 1 Sv[10]. An occupational exposure of 1 Sv of radiation is probably significantly greater than the true effective dose that would be accumulated by an endoscopist with radiation exposure solely from ERCP. Despite the relatively low risk of radiation-induced injury, endoscopists should be aware that all exposure carries a cumulative risk[11]. Additionally, tracking the radiation dose can be difficult because almost 50% of endoscopist performing ERCPs never wear a dosimeter[12]. For the patient, the source of exposure is the direct beam from the x-ray tube. It is estimated that patients receive about 2-16 min of fluoroscopy during ERCP, with therapeutic procedures taking significantly longer[13]. Studies have found that DAP values of approximately 13-66 Gy/cm^2 are used during ERCP, with effective doses ranging from 2 to 6 mSv per procedure[11].

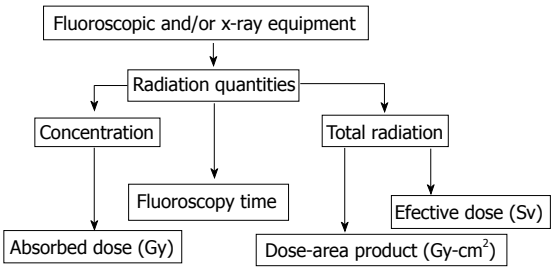

Figure 1 Radiation quantities used in endoscopic retrograde cholangiopancreatography

FACTORS ASSOCIATED WITH RADIATION

Radiation dose to patients during ERCP depends on many factors[14], and the endoscopist cannot control some variables, such as patient size, procedure type, or fluoroscopic

equipment used.

During ERCP, the positioning of catheters and guide wires is verified fluoroscopically. Once contrast injections have been given, fluoroscopy is used to evaluate the anatomy of the ductal systems of both the biliary tree and pancreas and to help assess whether disease is present. Photographic documentation is usually obtained to record the findings by capturing the last fluoroscopic image, spot image, or image sequence, depending on the available features of the equipment used. Finally, fluoroscopy is also needed to assist with therapy in, for example, sphincterotomy, stone extraction, biopsy or cytology, and stent placement. Additional devices that allow direct visualization of the ductal anatomy may ultimately reduce the need for fluoroscopy.

Previous reports have demonstrated a linear relationship between radiation dose and fluoroscopy duration[2,3,13]. When fluoroscopy is used to assist ERCP, the shortest fluoroscopy time possible is recommended[11].

Monitoring the length of fluoroscopy has been recommended as part of an overall reduction in both radiation exposure and fluoroscopy times[15]. Factors associated with prolonged fluoroscopy duration have been delineated recently[11], but have not been validated.

In order to determine what factors influence fluoroscopy time, several aspects should be considered.

Pulsed fluoroscopy

Some factors, such as the type of equipment (fixed units *vs* portable C-arm units) have been shown to reduce radiation dose but are unfortunately not easily implemented[16]. The radiation beam can be adjusted to use the lowest effective voltage required to a produce clinically useful image, and shielding of patients and staff with either permanent (walls or barriers) or portable (drapes, aprons) mechanisms has also been shown to reduce exposure effectively[7].

A specific intervention directed at decreasing radiation exposure involves the use of intermittent or pulsed fluoroscopy that substantially reduces the radiation dose without sacrificing image quality[17]. Time-limited fluoroscopy, in which x-ray exposure was limited to a set period each time that the foot- operated switch is depressed, led to decreased fluoroscopy duration in a prospective study[18]. In addition, alarms that indicate prolonged fluoroscopy time could potentially reduce radiation by increased awareness during the procedure.

More modern equipment incorporates features such as pulsed fluoroscopy, whereby the x-ray beam is turned on and off at a fixed rate (eg, at 4, 8, or 15 pulses per second), significantly reducing exposure compared with an x-ray beam used continuously[4,18].

Patient positions: supine and prone

ERCP is traditionally performed with the patient in the prone position as this is considered optimal for cannulation of the papilla, for obtaining high-quality radiographic images and for the prevention of pulmonary aspiration. Patients who cannot tolerate the prone position for ERCP are often placed in the left lateral decubitus or supine positions. However, the supine position allows improved fluoroscopic visualization, especially when rotatable fluoroscopic equipment (eg, C-Arm) is not available[19]. In addition, the supine position sometimes allows superior visualization of hilar anatomy[20]. Nonetheless, little data exist regarding performance of ERCP with the patient in the supine position. In one randomized trial of patients undergoing ERCP in the prone and supine positions, there were significantly more failures and a significantly higher number of adverse cardio-respiratory events in the supine group when they were not endotracheally intubated[21]. In another retrospective study of 649 patients undergoing ERCP by a single endoscopist, success and complication rates were similar for supine and prone patients (90.2% and 11.2% for supine and 92.5% and 9.1%for prone, respectively), although the degree of procedural difficulty was significantly higher in the supine group[20].

Endoscopist experience

Both cumulative years of performing ERCP and ERCP volume in the preceding year have been independently associated with shorter fluoroscopy exposure.Currently, there are insufficient data to support the use of fluoroscopy time as a surrogate end point for competency, even though this is an easily measureable and comparable variable. Fluoroscopy time is shorter when ERCP is performed by endoscopist with many years of performing ERCP and a large number of ERCPs in the preceding year[14]. In interventional radiology, increased levels of physician training have been found to correlate with decreases in patient radiation exposure during fluoroscopic procedures[22]. Uradomo *et al*[23] showed that radiation exposure during ERCP was directly related to the experience of trainees. Furthermore, as GI fellows accumulate ERCP experience, the amount of time that patients are exposed to fluoroscopy, and thus radiation exposure, is decreased. Jowell *et al*[24] assessed the ability of GI fellows to competently complete specific technical component of ERCP. They found that between 180 and 200 ERCPs were required for the trainees to consistently complete these procedures. The median fluoroscopy duration decreased by almost 3 min during cases performed by GI fellows with experience of more than 50 previous ERCPs[11]. The lack of correlation of fluoroscopy time and endoscopist experience, reported in another study, may actually reflect case complexity because the more difficult and refractory cases were clearly referred to the more senior endoscopist[11].

Technical considerations

In general, radiation exposure is greater during therapeutic ERCP than during diagnostic ERCP[4,7,23,25]. In a recent prospective study[11], the procedure variables that significantly increased fluoroscopy duration were stent insertion, lithotripsy, use of a needle-knife, biopsies, the use of a guide wire or additional wires other than the standard, and use of a balloon catheter.

The factors found to extend the length of the procedure and increase fluoroscopy duration probably relate to differences in case complexity. Stent insertion may prolong fluoroscopy duration because this procedure requires

fluoroscopy to confirm proper placement[25]. The use of a lithotripter is associated with a significant increase in fluoroscopy duration because this device is often used for difficult stone extractions. A needle-knife is usually used for second-line access techniques when conventional methods have failed and is often associated with long procedures. Guide wires used during ERCP are associated with longer fluoroscopy. The use of an "other wire" is associated with one of the greatest increases in fluoroscopy duration and is probably associated with difficult access/cannulation during procedures where there have been multiple previous attempts using more conventional guide wires. Finally, the use of the balloon catheter is often followed by a balloon cholangiogram, requiring more fluoroscopy time.

PERSONAL PROTECTION AND RADIATION SAFETY

A person's biological risk is measured by using the conventional unit rem (radiation equivalents in man) or the SI unit equivalent called the sievert, where 1 Sv = 100 rem. Estimates of radiation exposure to endoscopy staff vary, but it should be noted that radiation exposure is cumulative over time. In a recent study, the estimated annual whole-body effective dose equivalent received by the endoscopist ranged between 3.35 and 5.87 mSv[26]. The ICRP has classified radiation exposure as low ($\leqslant$ 3 mSv per year), moderate (3-20 mSv per year), or high (> 20-50 mSv per year).

The primary source of radiation to endoscopy personnel is radiation scattered from the patient, not the primary x-ray beam. Positioning staff as far away from the patient as possible is essential in limiting exposure. If an endoscopy staff member is standing 1 m from the patient, the radiation exposure for that individual is 1/1000 the patient's exposure.

Shielding is required for all staff in the fluoroscopy unit. Aprons containing lead shielding 0.5 mm thick are standard in most fluoroscopy units and block more than 90% of scattered radiation[9]. Average effective doses of about 0.07 mSv per procedure have been observed for endoscopists wearing a lead apron. Although the endoscopist's body is well protected by a lead apron, there can also be substantial doses to unshielded parts. Average doses to the eyes in the range of 0.1-1.7 mGy per procedure and doses of about 0.5 mGy to the hands have been reported[9]. Optically clear lead glasses can reduce the operator's eye exposure by 85% to 90%. There are no mandatory requirements for either thyroid shields or leaded glasses, although many have recommend that thyroid shields should be used routinely and leaded glasses should be used by individuals with high case loads[1].

SPECIAL CIRCUMSTANCIES: PREGNANCY

During pregnancy, the most common indication for ERCP is treatment of choledocholitiasis. The incidence of gallstone disease during pregnancy has been estimated to be between 4.5% and 12%[27]. Patients usually require immediate intervention because of potentially life-threatening cholangitis or gallstone pancreatitis.

When a pregnant patient requires ERCP for therapy, the procedure should be optimized by strict adherence to good technique. In addition, if there is a possibility that the primary x-ray beam may intercept the fetus, placing a lead apron between the x-ray source and the fetus is effective. However, a lead apron placed externally is ineffective for protection of the fetus from exposure to radiation that is scattered inside the patient's body. The patient's position (supine, prone, or lateral) should be adjusted to minimize fetal exposure. A poster anterior projection of the x-ray beam is recommended, as this results in a fetal dose that is 20%-30% lower than in the anteroposterior projection due to increased shielding from the mother's tissues[28]. The lateral projection also provides increased fetal shielding, but the patient's entrance dose rate may be three to seven times higher in comparison with a frontal projection. As a result, the lateral projection results in a higher fetal dose[28].

Intraductal ultrasound can be used instead of fluoroscopy to check for bile duct stones and to place guide a wire for a biliary stent. An alternative technique, avoiding radiation exposure completely, involves conducting ERCP without fluoroscopy, using wire-guided cannulation. Choledochoscopy can be used to confirm stone clearance. However, this approach is technically challenging and has only been used by very experienced biliary endoscopists. Further studies are required to prove that the clinical efficiency of radiation-free ERCP remains at the same level as that of conventional fluoroscopically guided ERCP[29].

CONCLUSION

The use of fluoroscopy to aid ERCP, places both the patient and the endoscopy staff at risk of radiation-induced injury. ERCP is highly technical and depends on the endoscopist's experience. Radiation dose to patients during ERCP depends on many factors, and the endoscopist cannot control some variables, such as patient size, procedure type, or fluoroscopic equipment used. Previous reports have demonstrated a linear relationship between radiation dose and fluoroscopy duration. When fluoroscopy is used to assist ERCP, the shortest fluoroscopy time possible is recommended. Factors associated with prolonged fluoroscopy duration have been delineated recently, but these have not been validated.

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BRIEF ARTICLE

Development of a novel endoscopic manipulation system: The Endoscopic operation robot

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Author contributions: Kume K, Kuroki T, Sugihara T and Shingai M developed a novel endoscopic manipulation; Kume K wrote the paper.
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Abstract

AIM: To develop and evaluate the endoscopic operation robot (EOR). The EOR is a robot system designed specifically for remote manipulation of the scope during gastrointestinal endoscopy by a seated endoscopist.

METHODS: Total colonoscopy examinations using a colonoscopy training model were performed compared conventional insertion by manual manipulation and remote-controlled insertion, using the EOR. The author investigated the time taken for each of the 50 examinations.

RESULTS: The median insertion time (in minutes) for each 10 examinations (EOR *vs* manual manipulation) was 73.70 ± 25.37 *vs* 3.77 ± 1.34 in the first group, 38.40 ± 6.24 *vs* 3.40 ± 0.97 in the second group, 27.6 ± 4.01 *vs* 2.70 ± 0.95 in the third group, 23.8 ± 3.65 *vs* 3.10 ± 0.88 in the fourth group, and 22.9 ± 5.02 *vs* 2.60 ± 1.08 in the fifth group.

CONCLUSION: The study suggested the possibility of the clinical application of the EOR.

Key words: Endoscopic operation robot; Robotics; Endoscopy; Minimally invasive therapy

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INTRODUCTION

With an ever-expanding range of indications requiring minimally invasive therapy in the form of therapeutic gastrointestinal endoscopy, endoscopic targets and procedures are becoming more complex and broad ranging. Consequently, the required level of endoscopic precision is rising, and the duration of endoscopy procedures is lengthening. Endoscopic submucosal dissection (ESD)[1,2], natural orifice transluminal endoscopic surgery (NOTES)[3], and other gastrointestinal endoscopic techniques for minimally invasive therapy, lighten the burden on the patient, but increase the burden on the endoscopist in terms of expertise, dexterity, and proficiency. Many ways to reduce the burden on the endoscopic surgeon through the use of telesurgical units, such as da Vinci, developed by Intuitive Surgical, and Zeus, developed by Computer Motion, and other well-known endoscopic robots[4,5], have been developed. These robots, however, are specifically designed for surgeons using rigid endoscopes. In contrast, there have been no reports on the

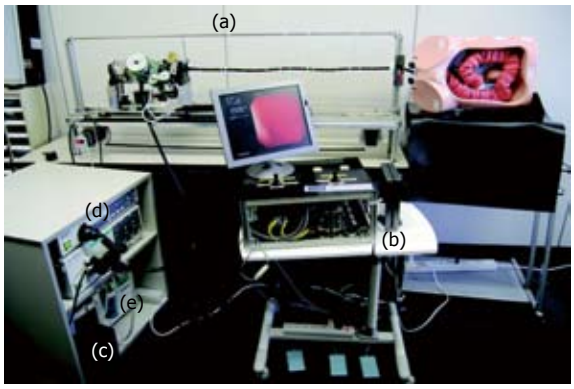

Figure 1 The system of the endoscopic operation robot and colonoscope training model (f). It consists of the main unit (a), the manipulation unit (b), the aspiration control unit (c), the light source unit (d) and the aspiration unit (e)

development of true robots which have been specifically designed for the flexible endoscopes which are required for oral or anal approaches in gastrointestinal endoscopy, other than a robot specifically designed for NOTES, primarily for forceps manipulation[6-8]. Research and development related to gastrointestinal endoscopic therapy has generally focused on tools attached to the endoscope, and surgical tools inserted in the channels[9]. The author has developed and reported several such tools, including an irrigation hood[10-12], an endoscopic aspiration mucosectomy (EAM) hood[13-18], and various ESD devices[19-26].

Further to this, the author has developed a new endoscopic operation robot (EOR) for full robotic manipulation of every procedural element of gastrointestinal endoscopy, including all the basic elements as well, thus eliminating the need for direct physical contact with the endoscope (Figure 1).

In manual endoscopy, the grip of the endoscope is held in the left hand and the vertical angulation (up-down) knob and the horizontal (right-left) angulation knob are manipulated with the fingers of the left hand, thus curving the endoscope tip vertically and horizontally. The tip is rotated by oscillation of the left wrist, and tip extension and retraction are performed by horizontal manipulation in the long-axis direction using the right arm while gripping the insertion unit. It is thus a "four-axis" manipulation, performed by the endoscopist while standing. The technique used for this manipulation input varies with the endoscopist, in terms of individual postures, habits, and customary practices, but these differences cancel out in the gastrointestinal tract, where they are output as mechanical movement. In short, manipulation input tends to vary with the individual endoscopist, but the variations mutually cancel in the output, to obtain relatively simple endoscope movements in the four axial directions. However, these individual differences tend to complicate the necessary acquisition of multifaceted skills by the endoscopist.

The EOR was developed to further the mechanization of this manipulation, with the aim of simplifying the operation by the endoscopist, reducing or even eliminating individual differences, and to facilitate the standardization of endoscope manipulation. This report describes the EOR concept and configuration, as well as its evaluation in complete colonoscopy examinations using a colonoscopy training model.

MATERIALS AND METHODS

System configuration

The EOR consists of the main unit (Figure 2A and 2B), the manipulation unit (Figure 2C), and the aspiration control unit (Figure 2D), all three of which are newly developed, together with (Figure 2D) the light source unit and (Figure 2D) the aspiration unit, both of which are pre-existing devices. The manipulation unit includes a monitor, two joysticks, and three foot switches. The right joystick controls the up-down and right-left angulation knobs, and the left joystick controls tip rotation, extension, and retraction. The three foot switches control the air supply, air suction, and water supply. If the endoscopist's hands are removed from the joysticks, the endoscope simply remains in position, without automatically returning to a neutral position.

The four-axis movement of the endoscope is driven by the four motors of the main unit, each *via* a separate timing belt and pulley transmission, thus serving the up-down and right-left angulation knobs, the rotational oscillation component, and the extension-retraction component. The endoscope is an Olympus GIF-Q230 (Tokyo, Japan), mounted on the rotational-oscillation component of the main unit. In accordance with the properties of the GIF-Q230, tip curvature control by vertical and horizontal movement of the right-hand joystick enables an up-down angulation knob range of 210° up and 90° down and a left-right angulation knob range of 100°. Rotational oscillation control by vertical and horizontal movement of the lefthand joystick enables 150° rotation of the endoscope with an effective length of 1030 mm. The power for these four-axis manipulations is provided by the four motors actuated by a specifically designed computer program.

The air supply and air suction button on the endoscope is set to ON, and the two interim valves of the aspiration control unit are connected to the suction unit and the water supply tank for the light source unit, to enable input of the air supply, air suction, and water supply *via* the three foot switches.

With the EOR, the endoscopist controls the operation with the two joysticks and the three foot switches in a seated position while watching the monitor on the manipulation unit, without touching the endoscope at all once the procedure begins.

Procedures: Insertion in colonoscope training model

The colonoscope training model produced by KYOTO KAGAKU Co., LTD. (Kyoto, Japan) was used (Figure 2E). This model has six training patterns (beginner's grade 1-3, intermediate grade 1-2, and higher grade). For this study, beginner's grade 1 was used. The aims with beginner's

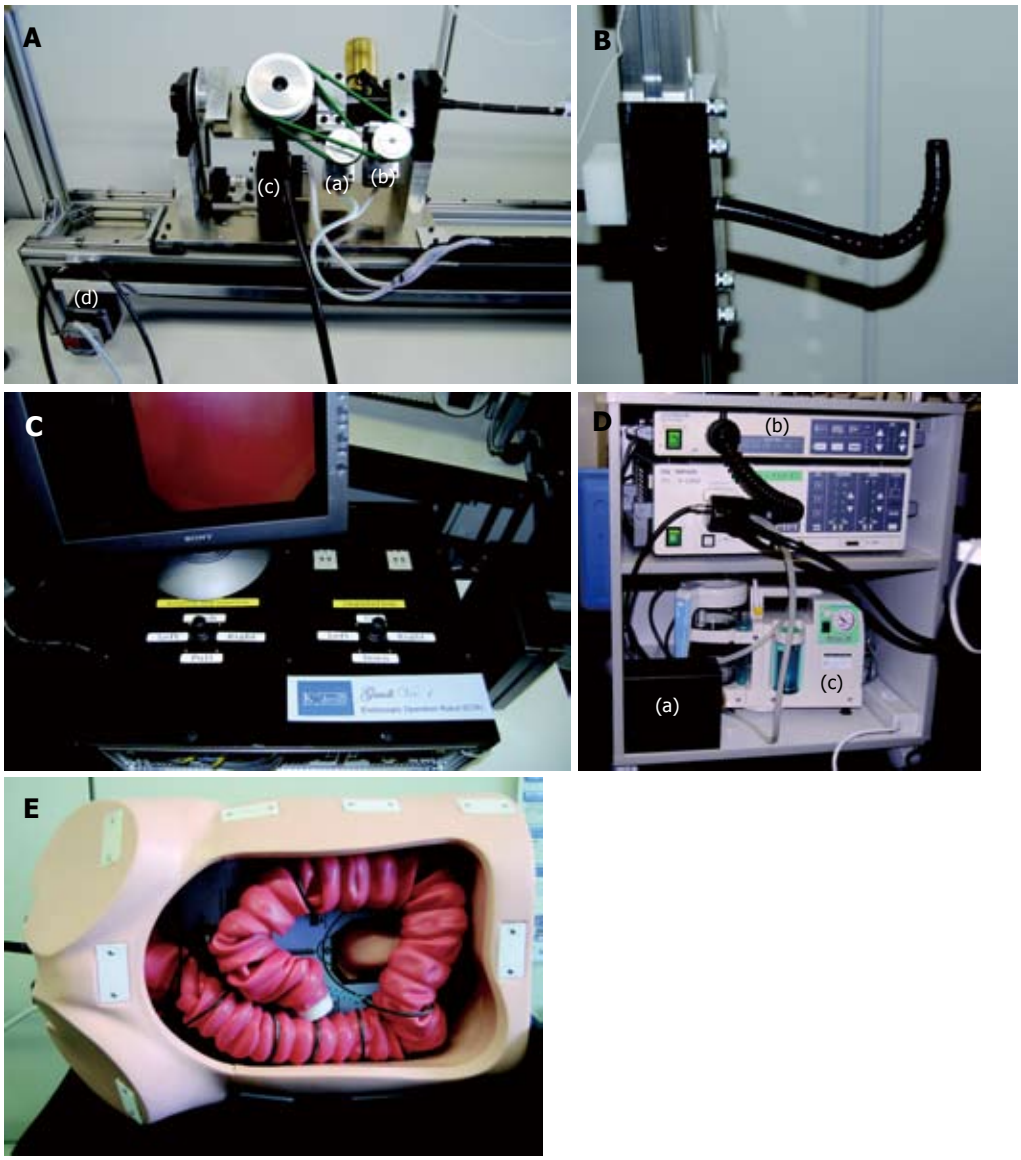

Figure 2 The system of the endoscopic operation robot. A: The left part of the main unit of the endoscopic operation robot (EOR) has four motors; the first motor controls up-down angulation (a), the second motor controls right-left angulation (b), the third motor controls rotation (c) and the fourth motor controls extension and retraction (d); B: The right part of the main unit of the EOR is the insertion part of the endoscope; C: The manipulation unit of the EOR. It includes a monitor, two joysticks, and three foot switches (no photos). The joystick on the right controls the up-down and right-left angulation knobs, and the joystick on the left controls tip rotation, extension, and retraction; D: The aspiration control unit (a), the light source unit (b) and the aspiration unit (d); E: Colonoscope training model produced by KYOTO KAGAKU Co., LTD. (Kyoto, Japan). EOR: Endoscopic operation robot.

grade 1 are as follows: 1) learn how to insert the colonoscope deeply into the transverse colon and the ascending colon, without forming a loop at the sigmoid colon; 2) acquire basic insertion skills required to pass through each part of the colon; 3) learn the "hooking the fold" method to pass through the sigmoid colon; and 4) learn "withdrawal" manipulation to go through the hepatic flexure.

All cases of total colonoscopic examination were performed by the author, who has completed 5000 total colonoscopic examinations.

The author investigated the records of 100 total colonoscopic examinations and compared 50 conventional insertions by manual manipulation and 50 remote-controlled insertions using the EOR. The learning curves of endoscopists using the EOR were also investigated. Learning curves were assessed as the insertion time for each 10 examinations. Insertion time was measured from the model anal region to the cecum.

The tip of the EOR endoscope was manually inserted 3 cm into the model anal region, and the endoscope was thereafter remotely controlled by the operator using the manipulator unit.

The EOR was designed by the author, and was produced by Takeshi KUROKI and Takahiro SUGIHARA at Kyushu Polytechnic Collage.

Statistical analysis

The results, insertion time for each 10 examinations, were presented as mean ± SD. An analysis of variance (ANOVA) was used to compare insertion time for each 10 exa-

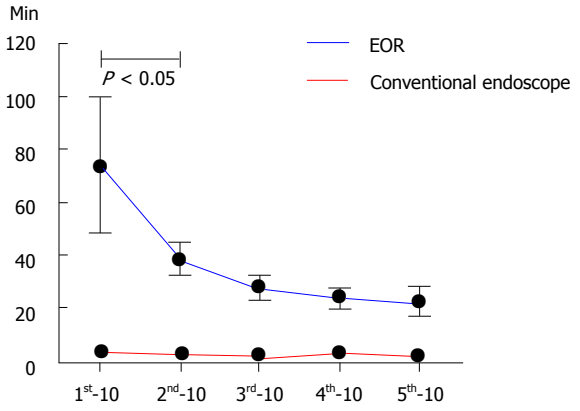

Figure 3 Learning curve assessed based on insertion time. EOR: Endoscopic operation robot.

minations. Qualitative data were analyzed by the Mann-Whitney U test with Bonferroni correction. A *P* value of less than 0.05 was considered significant.

RESULTS

The overall complete insertion rate was 100% (100/100; 50/50 conventional insertions by manual manipulation and 50/50 remote-controlled insertions using the EOR). The median insertion time was 3.6 ± 1.96 min by manual manipulation and 37.28 ± 22.47 min by remote-controlled insertion using the EOR. The median insertion time by EOR insertion for each 10 examinations was 73.70 ± 25.37 in the first group, 38.40 ± 6.24 in the second group, 27.6 ± 4.01 in the third group, 23.8 ± 3.65 in the fourth group and 22.9 ± 5.02 in the fifth group. The median insertion time by manual manipulation 3.70 ± 1.34 in the first group, 3.40 ± 0.97 in the second group, 2.70 ± 0.95 in the third group, 3.10 ± 0.88 in the fourth group and 2.60 ± 1.08 in the fifth group.

Concerning the EOR learning curve, median insertion time was significantly shorter with each succeeding group until the third group of 10 cases, and was less than 30 min after the third group of 10 cases (Figure 3).

DISCUSSION

In planning, designing, and commissioning the construction of the EOR, two questions that were considered and must ultimately be resolved are endoscopist familiarization and endoscopy standardization. Remote manipulation by joysticks while seated is conceptually quite different from the conventional direct manual manipulation of the endoscope while standing, and it is unlikely that an endoscopist well practiced in the manual procedure would find it easy to adapt to the EOR concept. However, many endoscopists are undoubtedly familiar with the control panels and joystick operations of video games and other such devices, and this may ameliorate some initial awkwardness, speed of learning, and heighten proficiency. In regard to the standardization of endoscopic therapy techniques, further investigation on the potential of the EOR for contribution to this goal will be necessary, but the expectation is that a robotic manipulation system, such as the EOR, will greatly facilitate general standardization of endoscopic techniques by reducing the complexities associated with direct manual manipulation of the endoscope arising from the differences among endoscopists in manipulation customs, practices, and levels of dexterity. Moreover, such a system will substantially broaden the range of applications for endoscopic therapies.

The EOR has been developed primarily for utilization in ESD, NOTES, and other orifice-insertion procedures in minimally invasive therapy. In the present study, however, colonoscopy was considered the most appropriate therapy for the initial evaluation of the EOR manipulation capabilities, due to the requirement for maximum precision in 4-axis manipulation.

The learning curve for EOR manipulation in the colonoscopy model was determined from the insertion times in the series of EOR trials performed by the author, who had had no previous experience with EOR manipulation, but who, in clinical practice, has had extensive experience in conventional manual insertion. Insertion time was used as an indication of proficiency in EOR insertion. A learning curve for manual insertion was not determined, due to the author's extensive experience. The learning curve for EOR increased over the first 30 insertions but remained flat thereafter, giving no indication of the prospect for a further shortening in insertion time.

The primary reason for the apparently lower limit in the reduction in EOR insertion time found in these trials may be attributable to the lack of function for presentation of force and tactile sensation by the EOR in its present version. In the intestinal tract shortening maneuver, which is performed to increase insertion efficiency, reliance is placed in part on the tactile sensation of catching the intestinal tract on the curved scope tip. With the present EOR, however, this maneuver is impracticable, due to the absence of tactile sensation. In the absence of feedback-induced control in a clinical setting, an unintended application of force could increase the risk of pain and possibly perforation. It will therefore be necessary to consider the incorporation of kinesthetic and haptic feedback presentation functions into the EOR, together with control systems providing a slight degree of play in the joystick and a target tracking or other function providing automated supplemental control of endoscope tip movement.

The EOR nevertheless has the potential for achieving modes of manipulation that cannot be achieved by manual manipulation of conventional scopes, along with other functional advantages. With the continuing advances in endoscopic therapy, the length, complexity, and proficiency of the related procedures are testing the limits of endoscopists with regard to maintaining their field of vision, and the skill required to coordinate the manipulation of single general-purpose endoscopes. Through the integration of all scope and device manipulations in a single control console, along with breaking down the coordinated manipula-

tions, and allowing seated operation, the EOR holds the promise of substantially reducing the burden on the endoscopist. The breakdown of coordinated manipulations refers to capabilities such as being able to fix the field of vision by the operator, having removedhis or her hand from the joystick, and, as circumstances require, the capability to limit manipulation specifically to the treatment tools.

The advantage of the EOR relating to maintenance of the insertion axis was clearly demonstrated. In conventional manual insertion, maintaining the insertion axis requires manipulation of the handle by finger action and rotation by wrist action in a physiologically constrained environment, and, in some cases, the physiological limits may prevent successful insertion into deep regions. In this case, it is difficult to continue conventional insertion whilst seated. With the EOR, in contrast, the endoscope position does not change when the hand is removed from the joystick. The axis is thus maintained, and insertion to deeper regions can be readily resumed from that angle, without concern for a departure from the axis. The freedom from both the physiological constraints on the range of motion in the joints of the endoscopist and the consequent need to maintain difficult bodily postures is in fact an important advantage, particularly in therapeutic endoscopy, with the related need for manipulation of surgical tools.

Adoption of EOR-based systems for colonoscopic examination could open the way to many new modes of application. It would facilitate the development of advanced systems for EOR training on colonoscopy models, by incorporating systems for time measurement in conjunction with optical sensors appropriately positioned in the intestinal tract model for calculation of intestinal internal observation ratios in the circuit, for counting and recording incidents of simulated pain due to excessive intrusion into the model mesentery, together with a scoring system for each element of the procedure. In clinical implementations, the incorporation of insertion time measurement and input systems responsive to vital changes and the experience of pain signaled by the patient using appropriate buttons could facilitate objective evaluation of insertions and hospital performance. Ultimately, and with the provision that every aspect of safety be considered and assured, it may be possible to achieve completely automated colonoscope insertion for difficult cases, as well as for more routine cases, through the incorporation of balloon, image recognition, and other necessary sensors on the scope tip and effective computerized system control.

Other envisioned developments ultimately include the automation of ESD, NOTES, and other endoscopic therapies. However, many challenges would have to be met for these purposes. The requirements for fully automated ESD, for example, would include lesion recognition, determination of resection and peripheral incision extent, always-on recognition of appropriate resection surfaces, dissection of deep submucosal layers at specific depths, and an effective response to bleeding, breathing changes, peristalsis, and other events.

With these numerous and complex requirements, fully automated procedures remain a long-range goal. However, advances and improvements in individual component systems and devices may hasten progress. The wiper-knife was developed by the author, primarily to simplify endoscope manipulation, but it now appears highly appropriate for the EOR. The multiDOF forceps being developed for NOTES will probably facilitate many aspects of remote manipulation. With effective cooperation between medicine and engineering, it will be possible to incorporate functions such as kinesthetic and haptic feedback, presentation, target tracking, and 3D spatial presentation. With appropriate methods for adopting advances in engineering, higher levels of precision control and automation may be possible. Robotization of endoscopic manipulation such as that of EOR thus facilitates the conceptualization of endoscopic automation. At present, however, the task at hand is the continuation of research and development directed toward the identification of those component processes appropriate for automation by computerized control, and those that are appropriate for remote manipulation by the endoscopist, and their realization for the simplification of endoscopic techniques and the enhancement of their safety.

In conclusion, the EOR is a robot system specifically designed for remote manipulation in oral digestive tract endoscopy by a seated endoscopist, without directly touching the scope. Its operation, which is reminiscent of operating video-game controllers and other such devices, eliminates the physiological constraints that apply in the conventional standing-position necessary for manual endoscopic manipulation, due to the naturally limited range of motion of body joints, and it reduces the tendency for differences to arise among operators in their customary techniques and practices of endoscope manipulation. The EOR is a next-generation endoscope that is expected to bring fundamental changes to endoscopic manipulation techniques, and may ultimately lead to their automation.

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CASE REPORT

Mallory-Weiss tear during gastric endoscopic submucosal dissection

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Abstract

A 78-year-old woman was referred to our department for treatment of an early gastric cancer. Esophagogastroduodenoscopy (EGD) demonstrated a flat elevated lesion and a polypoid lesion on the greater curvature of the antrum. Histological analysis of, endoscopic biopsy samples taken from these lesions revealed an adenocarcinoma and a hyperplastic polyp, respectively. ESD was conducted for removal of the lesions. Carbon dioxide (CO_2) instead of room air was used for insufflation, and the patient was adequately sedated without struggling or vomiting during the treatment. No significant bleeding from the lesion was observed during ESD, but fresh blood was identified endoscopically. Surprisingly, a Mallory-Weiss tear with active bleeding was detected on the lesser curvature of the gastric corpus. A total of eight hemoclips were applied for hemostasis. Both lesions were completely removed *en bloc*, and no bleeding or perforation developed after ESD. Histologically, the first lesion was a papillary carcinoma limited to the mucosal layer and without lymphovascular invasion or involvement of the surgical margins, while the second lesion was a benign hyperplastic polyp.

Key words: Mallory-Weiss tear; Endoscopic submucosal dissection; Early gastric cancer; Hemostasis; Hemoclip

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INTRODUCTION

Endoscopic submucosal dissection (ESD) has gained acceptance for the treatment of early gastric cancers without lymph node metastasis, as this technique enables *en bloc* resection of lesions regardless of their size[1]. Complications associated with ESD include bleeding, perforation and stenosis. Perhaps the most frequently encountered complication is immediate bleeding from vessels in the submucosal layer of the lesions during ESD. This can be managed with coagulation using an electrocautery knife and/or elec-

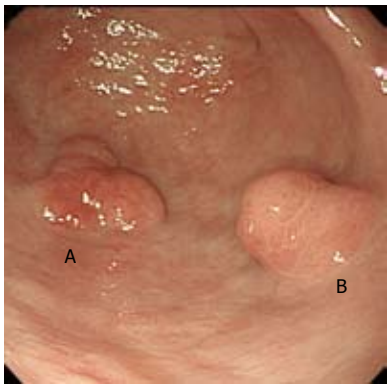

Figure 1 Esophagogastroduodenoscopy findings. Esophagogastroduod noscopy showed a flat elevated lesion, about 20 mm in size (A), and a polypoid lesion, about 15 mm in size (B), which were detected on the greater curvature of the antrum.

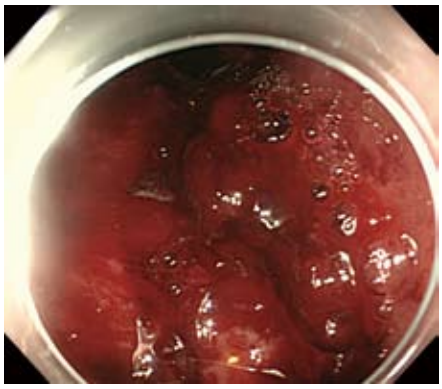

Figure 2 Longitudinal mucosal tears (Mallory-Weiss tear) with active bleeding were detected on the lesser curvature of the gastric corpus.

trocautery forceps[2]. We herein report on a patient who developed Mallory-Weiss tears (MWT), an extremely rare source of active bleeding associated with gastric ESD.

CASE REPORT

A 78-year-old woman was referred to our department for treatment of an early gastric cancer. She was asymptomatic and received the esophagogastroduodenoscopy at a local hospital during a medical checkup. Her medical history included hypertension and hyperlipidemia, for which she was receiving medication. No anticoagulant which might contribute to a bleeding tendency was prescribed for this patient. On July 22, 2010, esophagogastroduodenoscopy (EGD) demonstrated mild hiatal hernia and gastric atrophy. Furthermore, a flat elevated lesion about 20 mm in size, and a polypoid lesion about 15 mm in size were detected on the greater curvature of the antrum (Figure 1). Histological analysis of endoscopic biopsy samples taken from these lesions revealed adenocarcinoma and hyperplastic polyp, respectively. No lymph node swelling was detected by abdominal computed tomography conducted before endoscopic treatment. On August 11, 2010, ESD

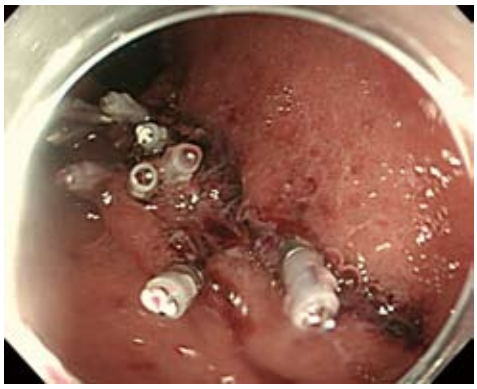

Figure 3 A total of eight hemoclips were applied for hemostasis.

was carried out for removal of the lesions. Carbon dioxide (CO_2) instead of room air was used for insufflation, and the patient was adequately sedated with intravenous administration of midazolam (5 mg) and pentazocine (15 mg) without struggling or vomiting during the treatment. CO_2 insufflation was set at a constant rate of 1.2 L/min, which is a moderate level in the CO_2 regulator (UCR, Olympus Tokyo). Although significant bleeding from the lesion was not observed during ESD, fresh blood was identified at endoscopy. After retroflexion of the scope tip, longitudinal mucosal tears (MWT) (maximal length; about 50 mm in length) with active bleeding were detected on the lesser curvature of the gastric corpus (Figure 2). A total of eight hemoclips were applied for hemostasis (Figure 3). Both of the lesions were completely removed *en bloc* within an hour, and no bleeding or perforation developed after ESD. The patient was discharged uneventfully after staying in the hospital for one week. Histologically, the first lesion was a papillary carcinoma limited to the mucosal layer and without lymphovascular invasion or involvement of the surgical margins, while the second lesion was a benign hyperplastic polyp (Figure 4).

DISCUSSION

MWT which is characterized by longitudinal mucosal lacerations in the distal esophagus and proximal stomach, was first described in 1929 as a syndrome of upper gastrointestinal bleeding (UGIB) caused by nausea and vomiting[3]. The reported incidence of MWT is 5%-15% of all cases of UGIB, although MWT may also occur iatrogenically during endoscopic examination, and its incidence has been estimated to be 0.007%-0.49% of all such procedures[4,5]. MWT usually occurs secondarily to a sudden increase in intra-abdominal pressure, and several predisposing factors including hiatal hernia, alcoholism, gastric atrophy and ageing have been suggested[6]. We used CO_2 for insufflation during ESD, as it is absorbed faster in the body than air and then rapidly expelled through respiration[7]. On the basis of a retrospective review of the video of the procedure in this case, we suspected that

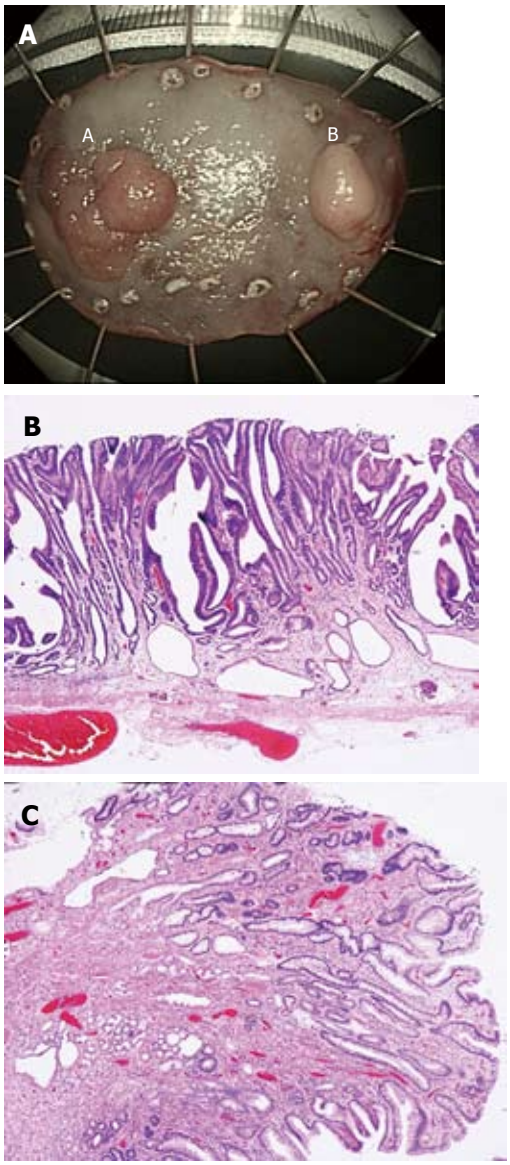

Figure 4 Macroscopic and microscopic findings of resected specimens. Both lesions were completely removed en bloc (A). Histologically, the first was a papillary carcinoma limited to the mucosal layer and without lymphovascular invasion or involvement of the surgical margins (H&E, × 60) (B), whereas the second lesion was a benign hyperplastic polyp (H&E, × 60) (C).

the upper esophageal sphincter did not relax during ESD under sedation. This resulted in a high intra-gastric pressure which caused laceration of the vulnerable atrophic gastric mucosa in this elderly woman, even though CO_2 was used instead of room air for insufflation. Adjustment of the intra-gastric pressure with suction and insufflation during ESD may have made it possible to avoid MWT in this case.

Most patients with iatrogenic MWT can be treated conservatively, with or without endoscopic hemostasis, using techniques including injection, electrocautery and mechanical therapies. Although serious complications such as massive bleeding and perforation are rarely encountered, they are possible[8]. In order to avoid deeper tissue damage which could result in perforation, possibly after a delay, we applied hemoclips instead of thermal or injection therapies to arrest any active bleeding[5].

In conclusion, we have reported the first case of MWT which is a rarely encountered but possible complication of gastric ESD. Iatrogenic MWT should be kept in mind as another possible source of bleeding during gastric ESD, even if CO_2 instead of room air is used for insufflation. Adjustment of the intra-gastric pressure during ESD may be necessary to avoid this kind of complication.

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CASE REPORT

Endoscopic hemostasis for hemorrhage from an ileal diverticulum

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Abstract

Hemorrhage from a non-Meckelian jejunoileal diverticulum is rare, and it is generally difficult to diagnose the source of the bleeding. Here, we report the case of a 59-year-old male with hemorrhage from an ileal diverticulum. Contrast computed tomography scans demonstrated the ileal diverticulum and extravasation of the contrast medium around it. The diagnosis was then made by computed tomography scans, and endoscopic mechanical hemostasis was performed under colonoscopy with three metal clips. The management of hemorrhage from jejunoileal diverticula is discussed.

Key words: Diverticulum; Gastrointestinal hemorrhage; Endoscopic hemostasis

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INTRODUCTION

Colonic diverticula are a common cause of gastrointestinal bleeding. Compared to colonic diverticula, however, the prevalence of jejunoileal diverticula is quite low, and it is usually difficult to identify the source of the bleeding if the hemorrhage stems from a jejunoileal diverticulum[1]. Here, we report the case of a small bowel hemorrhage from an ileal diverticulum diagnosed by computed tomography (CT) scans. Endoscopic hemostasis was successfully carried out by colonoscopy with metal clips. The management of hemorrhaging from small intestinal diverticula is discussed.

CASE REPORT

A 59-year-old Japanese male presented to Hiroshima City Hospital with hematochezia that had begun 3 h previously. The patient had been taking medication for hyperuricemia and hypertension, but had never taken anticoagulants. He had a prior history of obscure gastrointestinal bleeding, which had occurred five years earlier. At the time, he had undergone esophagogastroduodenoscopic and colonosco-

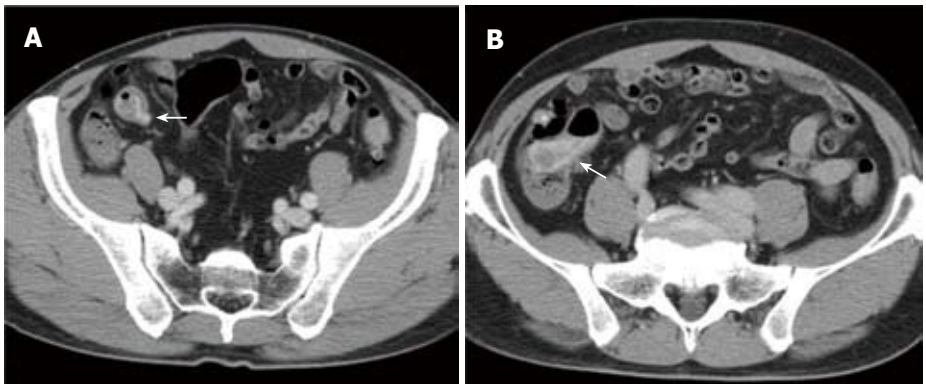

Figure 1 Contrast-enhanced computed tomography scans on admission. A: In the arterial phase, a diverticulum of the terminal ileum was seen and leakage of the contrast medium into the ileal lumen around the diverticulum was also visualized (arrow); B: In the venous phase, the contrast medium spread to the ileocecal valve (arrow).

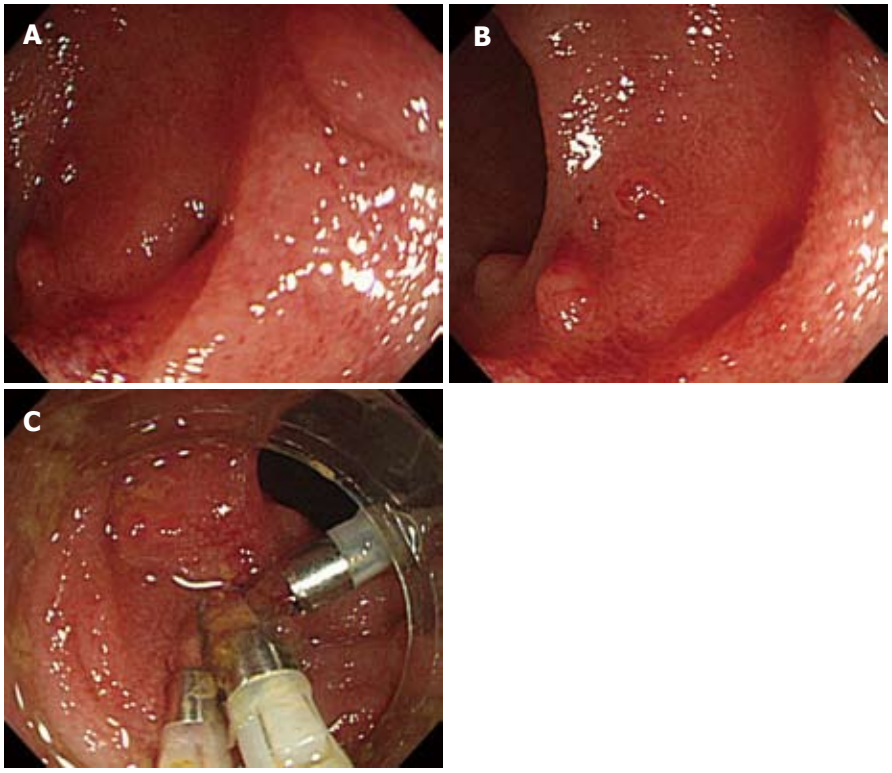

Figure 2 Colonoscopic findings. In the terminal ileum, a diverticulum was seen (A) and active hemorrhage from the diverticulum was demonstrated (B). Closure of the diverticulum was carried out endoscopically with three metal clips (C).

pic examinations at another hospital, but the hemorrhagic source was not determined, and the bleeding stopped spontaneously. On admission to our hospital, a physical examination revealed no abnormalities. The patient's blood pressure was 132/81 mmHg, and his pulse was 64/min. Laboratory examinations revealed slight anemia (red blood cell count, 434 × 10^4/mm^3; hemoglobin, 13.1 mg/dl), though he had no symptoms related to anemia. Abdominal CT scans demonstrated colonic diverticula and an ileal diverticulum, and leakage of the contrast medium into the ileal lumen around the diverticulum of the terminal ileum (Figure 1). The diagnosis of a hemorrhage from an ileal diverticulum was made. Colonoscopic examination, instead of double-balloon endoscopy, was then carried out, because the bleeding point was close to the ileocecal valve. On colonoscopy, active bleeding from the diverticulum in the terminal ileum was demonstrated (Figure 2). Closure of the diverticulum was successfully performed with three metal clips, resulting in hemostasis. The patient remained well and no recurrence of gastrointestinal hemorrhaging was reported for the following nine months.

DISCUSSION

Small intestinal non-Meckelian diverticuloses are identified in 2% to 2.3% of fluoroscopic X-ray studies of the small

intestine[2,3]. Among small intestinal non-Meckelian diverticuloses, those located in the jejunum are considerably more frequently present than those in the ileum. Their prevalence increases with age, peaking in the sixth and seventh decades[4]. The pathogenesis of non-Meckelian jejunoileal diverticula is not yet fully known. It is commonly believed that an acquired defect of the intestinal smooth muscle or myenteric plexus causes jejunoileal diverticula[4]. In most cases, jejunoileal diverticula are asymptomatic and are discovered incidentally during autopsy, laparotomy or fluoroscopic X-ray studies. However, they can sometimes cause severe complications such as hemorraging, inflammation, perforation or intestinal obstruction, as do colonic diverticula[5-8].

CT scans, angiography, capsule endoscopy, and double-balloon endoscopy are available to identify the source of the bleeding, such as a hemorrhage from a jejunoileal diverticulum. In contrast to colonic diverticula, non-Meckelian jejunoileal diverticula are a rare cause of gastrointestinal bleeding[9]. Due to the low incidence of the condition and the difficulty of evaluating the small bowel, a pre-operative diagnosis of bleeding from non-Meckelian jejunoileal diverticula is hard to achieve. Thus, this condition often requires laparotomy[10]; few case reports describe a successful preoperative diagnosis. Zuber-Jerger *et al* report a patient with hemorrhaging from jejunal diverticula that was diagnosed by capsule endoscopy and double-balloon endoscopy[10]. Jejunoileal diverticula sometimes arise in the terminal ileum, such as in our case, and in such patients, the diverticula may sometimes be found by colonoscopic examination[11,12]. Angiography[13] and CT scans[14] are also useful to specify the bleeding focus from a jejunoileal diverticulum. To the best of our knowledge, the present case is only the second report describing a hemorrhage from a jejunoileal diverticulum which was diagnosed by means of CT scans[14].

In our patient, the bleeding spot was detected in the distal ileum, approximately 5 cm from the ileocecal valve. We therefore diagnosed it as a non-Meckelian ileal diverticula rather than Meckel's diverticulum, which is usually located within 60-100 cm of the ileocecal valve. Endoscopic hemostasis was successfully performed using metal clips, as in other reported cases[11-14]. Generally, for hemorrhaging from colonic diverticula, an injection of epinephrine, thermocoagulation or mechanical devices such as metal clips and band ligation[11] enables hemostasis[15,16]. Angiography and the following embolization are used if colonoscopic hemostasis fails, or cannot be performed[15]. This strategy could be applicable to hemorrhaging from non-Meckelian jejunoileal diverticula, even though double-balloon endoscopy must be performed for all jejunoileal diverticula except those in the terminal ileum.

In conclusion, in the present case of a hemorrhage from an ileal diverticulum, contrast CT scans visualized the diverticulum and extravasation of the contrast media, allowing accurate diagnosis. A treatment of endoscopic hemostasis with metal clips was successful.

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Events Calendar 2011

January 14-15, 2011
AGA Clinical Congress of Gastroenterology and Hepatology: Best Practices in 2011
Miami, FL 33101, United States

January 20-22, 2011
Gastrointestinal Cancers Symposium 2011
San Francisco, CA 94143, United States

January 28-29, 2011
9. Gastro Forum München
Munich, Germany

February 04-05, 2011
13th Duesseldorf International Endoscopy Symposium
Duesseldorf, Germany

February 13-27, 2011
Gastroenterology: New Zealand CME Cruise Conference
Sydney, NSW, Australia

February 24-26, 2011
Inflammatory Bowel Diseases 2011-6th Congress of the European Crohn's and Colitis Organisation
Dublin, Ireland

February 24-26, 2011
2nd International Congress on Abdominal Obesity
Buenos Aires, Brazil

February 26-March 1, 2011
Canadian Digestive Diseases Week
Westin Bayshore, Vancouver
British Columbia, Canada

March 03-05, 2011
42nd Annual Topics in Internal Medicine
Gainesville, FL 32614, United States

March 14-17, 2011
British Society of Gastroenterology Annual Meeting 2011
Birmingham, England, United Kingdom

March 17-19, 2011
41. Kongress der Deutschen Gesellschaft für Endoskopie und Bildgebende Verfahren e.V.
Munich, Germany

March 17-20, 2011
Mayo Clinic Gastroenterology & Hepatology 2011
Jacksonville, FL 34234, United States

March 25-27, 2011
MedicReS IC 2011 Good Medical Research
Istanbul, Turkey

April 07-09, 2011
International and Interdisciplinary Conference Excellence in Female Surgery
Florence, Italy

April 15-16, 2011
Falk Symposium 177, Endoscopy Live Berlin 2011 Intestinal Disease Meeting, Stauffenbergstr. 26
Berlin 10785, Germany

April 18-22, 2011
Pediatric Emergency Medicine: Detection, Diagnosis and Developing Treatment Plans
Sarasota, FL 34234, United States

April 20-23, 2011
9th International Gastric Cancer Congress, COEX, World Trade Center, Samseong-dong
Seoul 135-731, South Korea

April 25-27, 2011
The Second International Conference of the Saudi Society of Pediatric Gastroenterology, Hepatology & Nutrition
Riyadh, Saudi Arabia

April 28-30, 2011
4th Central European Congress of Surgery
Budapest, Hungary

May 07-10, 2011
Digestive Disease Week
Chicago, IL 60446, United States

May 12-13, 2011
2nd National Conference Clinical Advances in Cystic Fibrosis
London, England, United Kingdom

May 21-24, 2011
22nd European Society of Gastrointestinal and Abdominal Radiology Annual Meeting and Postgraduate Course
Venise, Italy

May 25-28, 2011
4th Congress of the Gastroenterology Association of Bosnia and Herzegovina with international participation, Hotel Holiday Inn
Sarajevo, Bosnia and Herzegovina

June 11-12, 2011
The International Digestive Disease Forum 2011
Hong Kong, China

June 13-16, 2011
Surgery and Disillusion XXIV Spigc
II ESYS, Napoli, Italy

June 22-25, 2011
ESMO Conference: 13th World Congress on Gastrointestinal Cancer
Barcelona, Spain

September 10-11, 2011
New Advances in Inflammatory Bowel Disease
La Jolla, CA 92093, United States

September 10-14, 2011
ICE 2011-International Congress of Endoscopy, Los Angeles Convention Center, 1201 South Figueroa Street
Los Angeles, CA 90015, United States

September 30-October 1, 2011
Falk Symposium 179, Revisiting IBD Management: Dogmas to be Challenged, Sheraton Brussels Hotel
Brussels 1210, Belgium

October 19-29, 2011
Cardiology & Gastroenterology Tahiti 10 night CME Cruise
Papeete, French Polynesia

October 22-26, 2011
19th United European Gastroenterology Week
Stockholm, Sweden

October 28-November 02, 2011
ACG Annual Scientific Meeting & Postgraduate Course
Washington, DC 20001, United States

November 11-12, 2011
Falk Symposium 180, IBD 2011: Progress and Future for Lifelong Management, ANA Interconti Hotel, 1-12-33 Akasaka, Minato-ku
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GENERAL INFORMATION

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The columns in the issues of *WJGE* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Article: To report innovative and original findings in gastrointestinal endoscopy; (9) Brief Article: To briefly report the novel and innovative findings in gastrointestinal endoscopy; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJGE*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of gastrointestinal endoscopy; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on basic research and clinical practice in gastrointestinal endoscopy.

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2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

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4 **Diabetes Prevention Program Research Group**. Hyperten sion, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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