

## Department of Endoscopy

---

Hisao Tajiri, *Professor*  
Hiroshi Kakutani, *Associate Professor*  
Takeshi Suzuki, *Assistant Professor*  
Hiroo Imazu, *Assistant Professor*

Mitsuru Kaise, *Associate Professor*  
Tomohiro Kato, *Assistant Professor*  
Matsuda Koji, *Assistant Professor*  
Muneo Kawamura, *Assistant Professor*

### General Summary

Our main fields of research are clinical studies of endoscopic diagnosis and the treatment of gastrointestinal (GI) and hepatobiliary-pancreatic diseases. In addition, we performed basic research for the development of novel instrumentation, image processing and analysis, and optical apparatuses, such as autofluorescence imaging (AFI), narrow-band imaging (NBI), supermagnified images, confocal endoscopy, and high degree of freedom therapeutic endoscopes. Published achievements and recent reports are summarized below.

### Research Activities

#### *Pharyngeal, esophageal and gastric malignancies*

##### 1. Endoscopic diagnosis of esophagogastric neoplastic lesions

Early detection and accurate diagnosis of esophagogastric premalignant and malignant lesions are essential for selecting the most appropriate therapeutic strategy for each patient. At our institution, the following novel optical technologies are used in addition to conventional white-light endoscopy. We have designed a series of prospective clinical research studies to evaluate and validate the benefits of the following novel imaging technologies. Most recently, we have introduced transnasal ultrathin endoscopy, which is expected to improve patient compliance, especially for screening in nonreferral hospitals, by reducing discomfort during the examination.

1) Magnifying endoscopic observation using an NBI system: This new diagnostic system consists of a magnifying ( $\times 80$ ) endoscope and an NBI light source that provides detailed morphological information of capillaries on the mucosal surface. Our current study focus is to develop algorithms for the NBI technology, which may allow accurate analysis of the histological type of gastric carcinoma and the tumor extent without biopsy and allow early detection of precancerous changes in the specialized columnar epithelium of Barrett's esophagus. The preliminary achievements have already been reported at several conferences and have been published. We have also introduced our own classification of Barrett's cancer based on magnified NBI findings and demonstrated its advantages over conventional diagnosis in a prospective study.

2) AFI: The AFI endoscopy system has recently been developed to visualize autofluorescence emitted from the wall of the GI tract. In theory, AFI will allow detection of premalignant lesions or early malignant lesions that lack a distinct endoscopic appearance. Although AFI is still associated with a high false-positive rate, we found that AFI in combination with conventional white-light imaging and NBI can improve

specificity.

3) Ultrathin endoscope (transnasal endoscope): The ultrathin endoscope can reduce discomfort during examinations. However, the image resolution of the ultrathin endoscope is lower than that of conventional endoscopes and, therefore, is associated with a higher false-negative rate. We found a higher false-negative rate for gastric lesions with the ultrathin endoscope than with a high-resolution endoscope. We are attempting to develop a method to study motility disorders with the ultrathin endoscope by assessing symptoms during the examination. Details of this motility study will be described in detail later.

4) Endoscopic ultrasound-guided fine needle aspiration biopsy: Endoscopic ultrasound-guided fine needle aspiration biopsy (EUS-FNA) allows histopathological analysis of endoscopically undetectable lesions within and outside the walls of the GI tract such as esophagogastric submucosal tumors and the mediastinal and abdominal lymph nodes. In EUS-FNA, the biopsy needle can be precisely guided into the lesions with real-time ultrasonographic images. The tissues obtained with EUS-FNA are immediately evaluated by a cytologist or a pathologist for the presence of malignant cells. The technical safety and usefulness of this technique are being evaluated.

## 2. Endoscopic treatment of esophageal and gastric malignancies

With recent advances in endoscopic diagnostic techniques and instruments, the indications for endoscopic therapy for early gastric and esophageal carcinomas have been increasing. Research on the following endoscopic therapeutic modalities is now under way to standardize these endoscopic techniques as treatments for upper gastrointestinal tumors.

1) New indications for endoscopic treatment and endoscopic submucosal dissection: Current indications for endoscopic mucosal resection (EMR) are limited by the size, depth, and histological type of the lesions. Our recent efforts have been focused on expanding indications for endoscopic submucosal dissection (ESD) for early gastric cancer based on histopathological analysis. For gastric cancer, new indications for EMR being evaluated are small poorly differentiated adenocarcinoma without ulceration, well-differentiated adenocarcinoma with a diameter of 30 mm or more confined to the mucosa, and carcinomas with microinvasion into the submucosal layer. For esophageal cancer, current indications for EMR are epithelial cancer (m1) and cancer partially invading the lamina propria mucosae (m2) with negligible risk of lymph node metastasis. New indications being evaluated are mucosal cancer invading the lamina muscularis mucosae (m3) and lesions with slight submucosal invasion within the first third of the submucosal layer (sm1). En bloc resection with ESD is considered necessary to expand the indications for endoscopic treatment. Development of a series of knives and long-lasting submucosal fluid successfully reduced both the technical difficulty of ESD and the risk of complications. We also evaluated the effectiveness of acid-suppressive drugs, which has been empirically used after endoscopic treatment, by monitoring intragastric pH after treatment. A study to evaluate the risks of sepsis and endotoxemia after ESD with blood culture is under way.

2) Therapeutic interventions employing innovative endoscopy systems: The multibending scope (M-scope) is a new type of endoscope with a higher degree of freedom. We

have reported previously that the M-scope is useful for the treatment of tumors in the lesser curvature, greater curvature, and posterior wall of the gastric body, and the cardiac region, which are not accessible with a conventional endoscope. Studies using an M-scope with magnifying capability are now underway for more accurate and safer procedures. In addition, clinical studies using a newly developed therapeutic endoscope (R-scope), which has a special mechanism allowing the forceps to move laterally and vertically, in addition to the multibending function, are now under way with the aim advancing endoscopic therapy. We have also performed several research studies related to natural orifice transluminal endoscopic surgery, including full-thickness resection, to develop technologies beyond current endoscopic treatments for mucosal diseases.

### 3. The role of *Helicobacter pylori* infection in the development of gastric cancer

Many studies have shown an association between *Helicobacter pylori* infection and the development of gastric cancer. However, many aspects of this association remain unclear. This department, where endoscopic treatment of the gastric cancer is performed on a routine basis, is an ideal place to investigate this association. Studies of this association, especially of DNA methylation due to *H. pylori* infection, have been performed in cooperation with the Department of Gastroenterology, Toshiba General Hospital. We also have been exploring the roles of inducible nitric oxide synthase (iNOS) in the pathogenesis of *H. pylori* — associated diseases and have found that *H. pylori* eradication plays an important role in the repair process of methylated DNA and in the alteration of mucosal methylation in the 5 years after *H. pylori* eradication. The interim results have already been reported at several conferences and been published in Japan as well as internationally. In addition, we reported that the diverse topographical patterns of *H. pylori* — induced iNOS expression and iNOS gene polymorphism may contribute to the development of gastric cancer caused by *H. pylori* infection.

### 4. Diagnosis of oropharyngeal and hypopharyngeal malignancies

Endoscopic screening with iodine staining has allowed esophageal cancer to be detected at an early stage and has improved prognoses. However, metachronous or synchronous cancer in the oropharynx or hypopharynx has become the main factor affecting prognosis and the quality of life of patients with esophageal cancer. Although detecting such cancers at an early stage is important, performing chromoendoscopy for these cancers can be difficult owing to their location. Magnifying endoscopy performed in combination with the NBI system has enabled us to detect these hard-to-find cancers at an early stage without performing chromoendoscopy. A multicenter randomized controlled study of the clinical value of this new combination endoscopy has been performed.

### *Functional disorders of the upper GI tract*

The etiology of GI reflux diseases, including nonerosive reflux disease and GI motility disorders, is difficult to determine. To understand the pathophysiology of these diseases and to develop treatments for them, methods to evaluate the hypersensitivity and dysmotility of the GI tract should be established.

We developed a new method to evaluate esophageal function using a small-caliber endoscope. We started basic experiments to analyze the motility and sensitivity of the

esophagus with the aim of applying this technique to clinical practice.

#### *Diagnosis and treatment of esophagogastric varices*

We have recently been performing studies of the hemodynamics of the portal venous system in patients with esophagogastric varices by means of color-Doppler endoscopic ultrasonography (CD-EUS); these studies have clarified some of the factors associated with an increased likelihood of recurrence after endoscopic treatment of esophagogastric varices. When all the factors have been identified, we can expect to be able to predict and prevent early recurrence after the treatment of varices. We have also started a study to confirm the factors that aggravate hemorrhagic gastritis and cardiac varices. Studies of CD-EUS are multidirectional. CD-EUS is a highly accurate technique for detecting gastroduodenal shunts and can delineate in detail the shunt status after the treatment of esophagogastric varices. Therefore, this diagnostic system could be useful for selecting patients with esophagogastric varices who are candidates for interventional radiology and for predicting its therapeutic effects.

#### *Enteroscopy and colonoscopy*

##### 1. Diagnostic techniques

Capsule endoscopy is a breakthrough modality that allows of the detection of diseases of the small intestine that cannot be reached with an ordinary endoscope system. In Western countries, capsule endoscopy has been performed for 300,000 patients and is recommended as a first-line examination for detecting diseases of the small intestine. Our department has been involved in a multicenter study of 12 major endoscopy centers to evaluate the usefulness of capsule endoscopy. We have also introduced a novel single-balloon enteroscope that allows interventions, such as biopsy and hemostasis, for lesions of the small intestine.

The prevalence of colon cancer has recently been increasing. Accurate preoperative evaluation of tumor invasion is essential for selecting the most appropriate therapeutic strategy for colonic lesions. To improve diagnostic accuracy, we utilize a magnifying endoscope with NBI/AFI technology.

##### 2. Research on endoscopic intervention

Surgical resection has been the first choice of treatment for large sessile tumors of the colon. Recently, endoscopic *en bloc* resection with ESD, which is the standardized treatment for gastric lesions, has become an option for colonic lesions. However, endoscopic resection of large lesions in the narrow colonic lumen is technically challenging and has a higher risk of severe complications, such as perforation and bleeding. Our current efforts are focused on establishing a safe and reliable method for endoscopic removal of large colonic lesions and on applying ESD techniques to colonic lesions. Additionally, an infrared endoscopy system has been used to evaluate vessels on the ulcer base after ESD to prevent postoperative bleeding.

### *Pancreatobiliary endoscopy*

#### 1. Diagnosis of biliary and pancreatic diseases

Due to recent introduction of the diagnosis procedure combination, establishment of a standardized, systematic diagnostic algorithm for biliary and pancreatic diseases has become more important than ever. We are comparing the diagnostic accuracy for hepatopancreatic diseases of EUS-FNA, multidetector computed tomography, magnetic resonance cholangiopancreatography, and endoscopic retrograde cholangiopancreatography (ERCP). Additionally, we introduced a second-generation contrast medium for ultrasonic imaging for EUS diagnosis.

ERCP is a well-established procedure but is associated with risks of complications, some of which can be severe. We designed a new catheter to reduce trauma to the papilla, which is considered a major cause of pancreatitis after ERCP.

In the diagnosis of ampullary tumors of the duodenum, we perform detailed characterization of the mucosal surface structures using NBI with magnifying microstructures to determine if the lesion is benign or malignant. We also perform convex array EUS to evaluate the depth of tumor invasion. On the basis of these findings, we determine whether endoscopic papillectomy is indicated. Favorable clinical outcomes have been obtained so far.

#### 2. Treatment using endoscopic techniques of pancreatobiliary diseases

A randomized, controlled study was performed to compare the usefulness of endoscopic sphincterotomy (EST) and endoscopic papillary balloon dilation (EPBD) for the removal of stones of the common bile duct. Data obtained from the comparative study are used for selecting the most appropriate treatment for individual patients with stones of the common bile duct. The appropriateness of the procedure selection has also been reviewed and discussed for further improvement of therapeutic results. Studies of long-term results, such as rates of recurrence and long-term complications, are under way. External biliary drainage (endoscopic nasobiliary drainage) and internal biliary drainage using a plastic stent (endoscopic biliary drainage) have been widely adopted for the treatment of obstructive jaundice. No criteria, however, have been established for selecting which of the two drainage methods should be used for individual patients. We are now performing a randomized, controlled study to compare the 2 different endoscopic therapeutic modalities. For cases of inoperable cancers of the bile duct or pancreatic head, we employ a metallic stent made of shape-memory alloy and performed a historical comparison with standard stents. Although EUS-guided celiac plexus block has been performed to control benign but persistent pain due to chronic pancreatitis, durability of the pain relief was short. Therefore, we performed EUS-guided celiac plexus neurolysis with injection of a small amount of ethanol and are evaluating its feasibility.

We also started animal experiments to develop new interventional technologies to achieve local control of pancreatic cancer.

### *Palliative care*

More and more interest is being shown for palliative care. Various techniques have been developed to provide the best quality of life for critically or terminally ill patients.

Endoscopic procedures may play an important role, especially in supporting food intake. In our department, percutaneous endoscopic gastrostomy (PEG) is performed for patients who are unable to maintain sufficient oral intake. Although percutaneous endoscopic enterostomy (PEE) is conventionally not indicated for patients who have undergone gastric surgery, since 1994 we have extended the use of this procedure for such patients and have investigated its clinical usefulness. Kits for PEG that we developed have reduced the frequency of complications associated with PEE placement. To alleviate stenosis attributable to tumors of the GI tract and the bile ducts, we perform endoscopic ballooning/bougienage and subsequent metallic stenting. The therapeutic results have been good. To reduce the pain associated with chronic pancreatitis and inoperable pancreatic cancer, we perform transgastric celiac plexus block with EUS. These endoscopic procedures may greatly contribute to the improvement of the quality of life of patients who are not candidates for radical surgery. The cost-effectiveness of these interventions is another benefit.

## Publications

- Sumiyama K, Gostout CJ<sup>1</sup>, Rajan E<sup>1</sup>, Bakken TA<sup>1</sup>, Knipschild MA<sup>1</sup> (<sup>1</sup>Mayo Clin Coll Med).** Transesophageal mediastinoscopy by submucosal endoscopy with mucosal flap safety valve technique. *Gastrointest Endosc* 2007; **65**: 679-83.
- Sumiyama K, Gostout CJ<sup>1</sup>, Rajan E<sup>1</sup>, Bakken TA<sup>1</sup>, Knipschild MA<sup>1</sup>, Marler RJ<sup>1</sup> (<sup>1</sup>Mayo Clin Coll Med).** Submucosal endoscopy with mucosal flap safety valve. *Gastrointest Endosc* 2007; **65**: 688-94.
- Odagi I, Kato T, Imazu H, Kaise M, Omar S (Univ Malaya), Tajiri H.** Examination of normal intestine using confocal endomicroscopy. *J Gastroen Hepatol* 2007; **22**: 658-62.
- Sumiyama K, Gostout CJ<sup>1</sup>, Rajan E<sup>1</sup>, Bakken TA<sup>1</sup>, Knipschild MA<sup>1</sup>, Chung S<sup>1</sup>, Cotton PB<sup>1</sup>, Hawes RH<sup>1</sup>, Kalloo AN<sup>1</sup>, Kantsevoy SV<sup>1</sup>, Pasricha PJ<sup>1</sup> (<sup>1</sup>Mayo Clin Coll Med).** Transgastric cholecystectomy: transgastric accessibility to the gallbladder improved with the SEMF method and a novel multibending therapeutic endoscope. *Gastrointest Endosc* 2007; **65**: 1028-34.
- Sumiyama K, Gostout CJ<sup>1</sup>. (<sup>1</sup>Mayo Clin Coll Med).** Novel techniques and instrumentation for EMR, ESD, and full-thickness endoscopic luminal resection. *Gastrointest Endosc Clin N Am* 2007; **17**: 471-85.
- Fujishiro M (Univ Tokyo), Takubo K (Tokyo Metrop Geriatr Hosp), Sato Y (Showa Univ Northrn Yokohama Hosp), Kaise M, Niwa Y (Nogoya Univ Sch Med), Kato M (Hokkaido Univ Graduate Sch Med), Muto M (Natl Cancer Cen Hosp1 East).** Potential and present limitation of endocytoscopy in the diagnosis of esophageal squamous-cell carcinoma: a multicenter ex vivo pilot study. *Gastrointest Endosc* 2007; **66**: 551-5.
- Kato M, Kaise M, Yonezawa J, Yoshida Y, Tajiri H.** Autofluorescence endoscopy versus conventional white light endoscopy for the detection of superficial gastric neoplasia: a prospective comparative study. *Endoscopy* 2007; **39**: 937-41.
- Kaise M, Yamasaki T, Yonezawa J, Miwa J, Ohta Y, Tajiri H.** CpG island hypermethylation of tumor-suppressor genes in *H. pylori*-infected non-neoplastic gastric mucosa is linked with gastric cancer risk. *Helicobacter* 2008; **13**: 35-41.
- Rajan E<sup>1</sup>, Gostout CJ<sup>1</sup>, Lurken MS<sup>1</sup>, Talley NJ<sup>1</sup>, Locke GR<sup>1</sup>, Szarka LA<sup>1</sup>, Levy MJ<sup>1</sup>, Sumiyama K, de la Mora-Levy JG<sup>1</sup>, Bakken TA<sup>1</sup>, Stoltz GJ<sup>1</sup>, Knipschild MA<sup>1</sup>, Farrugia G<sup>1</sup> (<sup>1</sup>Mayo Clin Coll Med).** Evaluation of endoscopic approaches for deep gastric-muscle-wall biopsies: what works? *Gastrointest Endosc* 2008; **67**: 297-303.
- Rajan E<sup>1</sup>, Gostout CJ<sup>1</sup>, Lurken MS<sup>1</sup>, Talley NJ<sup>1</sup>, Locke GR<sup>1</sup>, Szarka LA<sup>1</sup>, Sumiyama K, Bakken TA<sup>1</sup>, Stoltz GJ<sup>1</sup>, Knipschild MA<sup>1</sup>, Farrugia G<sup>1</sup> (<sup>1</sup>Mayo Clin Coll Med).** Endoscopic "no hole" full-thickness biopsy of the stomach to detect myenteric ganglia. *Gastrointest Endosc* 2008; **68**: 301-7.
- Sumiyama K, Gostout CJ<sup>1</sup>, Rajan E<sup>1</sup>, Bakken TA<sup>1</sup>, Knipschild MA<sup>1</sup>, Chung S<sup>1</sup>, Cotton PB<sup>1</sup>, Hawes RH<sup>1</sup>, Kalloo AN<sup>1</sup>, Kantsevoy SV<sup>1</sup>, Pasricha PJ<sup>1</sup> (<sup>1</sup>Mayo Clin Coll Med).** Pilot study of transesophageal endoscopic epicardial coagulation by submucosal endoscopy with the mucosal flap safety valve technique (with videos). *Gastrointest Endosc* 2008; **67**: 497-501.
- Sumiyama K, Gostout CJ<sup>1</sup>, Rajan E<sup>1</sup>, Bakken TA<sup>1</sup>, Knipschild MA<sup>1</sup> (<sup>1</sup>Mayo Clin Coll Med).** Chemically assisted endoscopic mechanical submucosal dissection by using mesna. *Gastrointest Endosc* 2008; **67**: 534-8.

## Reviews

**Kaise M, Nakayoshi T, Tajiri H.** Magnifying endoscopy with NBI in the diagnosis of superficial gastric neoplasia and its application for ESD.

Cohen J, editor. Advanced digestive endoscopy: comprehensive atlas of high resolution endoscopy and narrowband imaging. Malden: Blackwell; 2007. p. 104-20.