

Department of Endoscopy

Hisao Tajiri, *Professor*
Hiroshi Arakawa, *Assistant Professor*
Hiroo Imazu, *Assistant Professor*
Keiichi Ikeda, *Assistant Professor*
Kazuki Sumiyama, *Assistant Professor*

Tomohiro Kato, *Associate Professor*
Koji Matsuda, *Assistant Professor*
Shoichi Saito, *Assistant Professor*
Kenichi Goda, *Assistant Professor*

General Summary

Our main area of research is performing clinical studies of endoscopy in the diagnosis and treatment of gastrointestinal, hepatobiliary and pancreatic disease. In addition, we perform basic research to develop novel instrumentation, methods of image processing and analysis, and optical apparatuses, such as autofluorescence imaging (AFI), narrow-band imaging (NBI), endocytoscopy, confocal laser endomicroscopy, endocytoscopy, and therapeutic endoscopy with a high degree of procedural freedom. Our published research outcomes and recent reports are summarized below.

Research Activities

Pharyngeal, esophageal and gastric malignancies

1. Endoscopic diagnosis in esophagogastric neoplasia

Early detection and accurate diagnosis of premalignant and malignant lesions in the pharynx, esophagus, and stomach are essential to allow the most appropriate therapeutic strategy to be selected for each patient. Our research utilizes the following novel optical technologies, along with conventional white light endoscopy, in clinical cases. We have designed a series of prospective clinical studies to evaluate and validate these novel imaging technologies and their potential benefits. We introduced transnasal ultrathin endoscopy, which is expected to improve patient compliance. This type of endoscope is particularly useful for screening patients from the non-referral hospital population, as it will reduce discomfort during endoscopic examination.

1) Magnifying endoscopic observation using an NBI system

This new diagnostic system consists of a magnifying ($\times 90$) endoscope and an NBI light source, which provides detailed morphological information about the capillaries on the mucosal surface. We studied the clinical utility of NBI magnifying endoscopy for superficial neoplasms of the pharynx, esophagus, stomach, and duodenum. One of the studies focused on the development of algorithms for NBI technology which would allow the histological type and tumor extent of gastric carcinoma to be determined without biopsy. On the basis of our findings with magnified NBI, we have also developed a novel classification system for gastric cancer and demonstrated, in a prospective study, its advantages over the conventional diagnostic system. We joined a multicenter study of NBI magnifying endoscopy for detecting superficial carcinomas of the pharynx and esophagus. Moreover, we performed a single-center study comparing NBI magnifying endoscopy with Lugol chromoendoscopy for detecting superficial carcinoma in the

esophagus. We also aim to evaluate this technology for the early detection of precancerous changes in the specialized columnar epithelium of Barrett's esophagus. Results of these studies have been reported at several conferences and published. Most recently, a magnifying endoscope and an NBI light source have been developed and become available for clinical use. We performed a study comparing NBI magnifying endoscopy and conventional high-definition magnifying endoscopy for detecting superficial carcinoma of the pharynx and esophagus.

2) Endocytoscopy

Endocytoscopy is a novel optical imaging technique that allows the gastrointestinal mucosa to be visualized *in vivo* and in real time at the cellular level using a staining solution. We joined a multicenter study using endocytoscopy for diagnosing superficial esophageal squamous cell carcinoma. Moreover, we performed a single-center study to determine the optimal staining regimen for *in-vivo* endocytoscopy of normal mucosa and superficial neoplasms of the duodenum. We are now studying the characteristic endocytoscopy findings of superficial duodenal neoplasms, i.e., adenoma and mucosal adenocarcinoma.

3) AFI

Recently, the AFI endoscopic system has been developed to endoscopically visualize autofluorescence emitted from the gastrointestinal wall. Theoretically, AFI can be used to detect premalignancies or early-stage malignancies that do not have a distinct appearance on conventional white-light endoscopy. Although AFI is still associated with a high false-positive rate, we established that AFI, in combination with conventional white-light imaging and NBI, can improve specificity.

4) Ultrathin endoscopy (transnasal endoscopy)

Ultrathin endoscopy can reduce discomfort during endoscopic examination. However, the ultrathin endoscope has a poorer image resolution than do conventional endoscopes, and, therefore, has a higher risk of false-negative results. Accordingly, we found that ultrathin endoscopy was less able to detect gastric lesions than was high-resolution endoscopy. We are now attempting to develop a method of studying esophageal motility disorders, by using an ultrathin endoscope to assess symptoms evident during examination. Details of this motility study are described later.

5) Endoscopic ultrasound-guided fine needle aspiration biopsy

Endoscopic ultrasound-guided fine needle aspiration biopsy (EUS-FNA) allows histopathological analysis of lesions that are usually undetectable with endoscopic examination. These lesions include lesions within the gastrointestinal walls, such as submucosal tumors of the esophagus and stomach, and mediastinal and lymph-node lesions. In EUS-FNA, real-time ultrasonographic images are used to precisely guide the biopsy needle into lesions. The tissues obtained with EUS-FNA are immediately examined by a cytologist or pathologist to detect the presence of malignant cells. We are now evaluating the technical safety and usefulness of this technique in ongoing studies.

2. Endoscopic treatment of esophageal and gastric malignancies

With recent advances in endoscopic diagnostic techniques and instrumentation, indications have expanded for endoscopic therapy in early gastric and esophageal carcinomas. Research on the following endoscopic therapeutic modalities is now under way to

standardize the use of these techniques for treating tumors of the upper gastrointestinal tract.

1) New indications for endoscopic treatment and endoscopic submucosal dissection

Current indications for endoscopic mucosal resection (EMR) are limited by lesion size, depth, and histological type. Our recent efforts have focused on expanding the indications for endoscopic submucosal dissection (ESD) in the treatment of early gastric cancer, on the basis of histopathological findings. We are also evaluating the potential new use of EMR for gastric cancers, including small, poorly differentiated adenocarcinomas lacking ulceration, well-differentiated adenocarcinomas 30 mm or smaller or confined to the mucosa, and carcinomas lacking submucosal microinvasion. Current indications for EMR include esophageal cancer, epithelial cancer (m1), and cancer partially invading the lamina propria mucosae (m2) with a negligible risk of lymph-node metastasis. New indications for EMR now being evaluated include mucosal cancer invading the lamina muscularis mucosae (m3) and lesions with slight submucosal invasion within the inner third of the submucosal layer (sm1). At present, en bloc resection with ESD is considered necessary to further develop the use of endoscopic treatment. A new series of endoscopic knives and long-lasting submucosal fluid have successfully reduced the technical difficulty of ESD and the risk of complications. We have also evaluated the effectiveness of gastric acid-suppressing drugs, which have been used empirically after endoscopic treatment, by monitoring intragastric pH after endoscopy. A study to evaluate the risks of sepsis and endotoxemia after ESD, using blood culture, is currently under way.

2) Therapeutic interventions employing innovative endoscopy systems

The multibending scope (M-scope) is a new type of endoscope that provides greater access to sites that are usually difficult to access. We have previously reported on the use of the M-scope in the treatment of tumors of the lesser curvature, greater curvature, and posterior wall of the gastric body, and the cardiac region, which are not accessible with conventional endoscopes. Studies using an M-scope with magnifying capability are now under way to develop more accurate and safer procedures. Furthermore, clinical studies using a newly developed therapeutic endoscope (R-scope), which a special mechanism allowing the forceps to move laterally and vertically, in addition to the multibending function, are proceeding to advance the potential of endoscopic therapy. We have also performed several studies using natural orifice transluminal endoscopic surgery (NOTES), including full-thickness resection, because current endoscopic treatments are directed only at mucosal diseases.

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

Many studies have demonstrated an association between *H. pylori* infection and the development of gastric cancer. However, there are still many unknown factors affecting this association. Because our department routinely performs endoscopic treatment for gastric cancer, clarification of these factors is important. Experiments concerning this association, particularly on DNA methylation due to *H. pylori* infection, have been carried out in collaboration with the Department of Gastroenterology, Toshiba General Hospital. We have also been exploring the roles of inducible nitric oxide synthase (iNOS) in the pathogenesis of *H. pylori*-associated diseases and have demonstrated that eradication of *H. pylori* plays an important role in the process of repairing disease-associated DNA

methylation and in the alteration of methylation patterns of genes in the mucosa in the 5 years following *H. pylori* eradication. Interim results have been reported at several conferences and been published in Japan as well as internationally. In addition, we have reported that 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, or Lugol chromoendoscopy, has enabled esophageal cancer to be detected at an early stage and, thus, has improved prognoses. However, this technique is difficult to perform in such locations as the oropharynx or hypopharynx. Metachronous or synchronous cancer of the oropharynx or hypopharynx has become the main factor adversely affecting the prognosis and quality of life of patients with esophageal cancer. Because detecting cancer at an early stage is important, we have found that magnifying endoscopy in combination with the NBI system has allowed hard-to-find cancers to be detected during the early stages without the need for Lugol chromoendoscopy. A multicenter randomized controlled study on the clinical value of this new combination endoscopy was performed. In addition, we performed a single-center study to evaluate endoscopic characteristics of superficial carcinoma in the pharyngeal region. These results have reported at medical congresses and in English-language medical journals.

Functional disorders of the upper gastrointestinal tract

The causes of gastroesophageal reflux diseases, including nonerosive reflux disease and gastrointestinal motility disorders, are difficult to identify. Establishing methods to evaluate hypersensitivity and dysmotility of the gastrointestinal tract are important for understanding disease pathophysiology and choosing effective treatments. Hence, we have developed a new method of evaluating esophageal functions using a small-caliber endoscope. We have started basic experiments on esophageal motility and sensitivity, with the aim of transforming this technique from a research tool into a clinical tool.

Diagnosis and treatment of esophagogastric varices

We have recently been involved in color-Doppler endoscopic ultrasonographic studies of the hemodynamics of the portal venous system in patients with esophagogastric varices. These studies have clarified several of the factors that increase the likelihood that esophagogastric varices will recur after endoscopic treatment. When all such factors are identified, we will be able to predict and prevent early recurrence of varices after treatment. We have also started a study to confirm factors that exacerbate hemorrhagic gastritis and cardiac varices. Color-Doppler endoscopic ultrasonography is also highly accurate for detecting gastrosplenic shunts, which can complicate the treatment of esophagogastric varices, and can delineate shunts in detail. Therefore, this diagnostic system could be useful for selecting patients with esophagogastric varices who are candidates for treatment with interventional radiology, and for predicting the efficacy of treatment.

Enteroscopy and colonoscopy

1. Diagnostic techniques

Capsule endoscopy is a breakthrough modality that can be used to detect lesions in parts of the small intestine unreachable with an ordinary endoscope system. Internationally, capsule endoscopy has been performed in more than 1 million cases before May 2011 and is highly recommended as a first-line examination to detect disease of the small intestine. However, because capsule endoscopy is purely diagnostic, we have introduced single-balloon enteroscopy, which allows biopsy and hemostasis to be performed for hemorrhagic lesions of the small intestine.

The numbers of cases of colonic cancer have increased markedly in Japan. In Europe and the United States, several studies have described the use of capsule endoscopy for examining the large intestine. In Japan, we are collaborating with 6 other hospitals to perform studies with capsule endoscopy to screen patients for colonic neoplasms.

Accurate preoperative evaluation of the degree of tumor invasion into deep layers is essential for appropriate decision-making and determining the optimal therapeutic strategy for patients with colonic lesions. Hence, to maximize our diagnostic accuracy, we utilize a magnifying endoscope with NBI and crystal violet staining or AFI technology or both along with conventional white-light observation.

2. Research in endoscopic interventions

Surgical resection has been the treatment of first choice for large, flat, elevated tumors of the colon. Recently, endoscopic en bloc resection performed with ESD (a standard treatment for gastric lesions) has been used for such colonic lesions. However, endoscopic resection of large intestinal lesions is technically difficult because of the wide lumen and the higher rate of complications, such as perforation and bleeding. Our present efforts are focused on establishing safe and reliable methods to remove large colonic lesions endoscopically and to start preliminary use of ESD. Additionally, an infrared endoscopy system has been used to evaluate the risk of bleeding from vessels located at the base of the ulcer created with ESD.

3. Capsule endoscopy and enteroscopy

Capsule endoscopy is a minimally invasive endoscopic modality that can be used to detect lesions in the small intestine which have been unreachable with traditional push-type enteroscopy. Recently, particularly in the Western countries, capsule endoscopy has been recommended as the first-line endoscopic examination for evaluating and managing obscure gastrointestinal bleeding. We have performed capsule endoscopy for 289 patients since the Japanese health insurance system began covering this procedure in April 2007. Our study found that capsule endoscopy should be performed as soon as possible following a patient visiting hospital with a complaint of melena. We are aiming to further improve the diagnostic accuracy of capsule endoscopy for evaluating obscure gastrointestinal bleeding by re-evaluating the traditional bowel preparation regimen.

4. Basic research

Hyperplastic polyp is a nonneoplastic tumor of the colon. Therefore, endoscopic treatment is not indicated on a histologic basis. However, according to recent reports in Western countries, sessile serrated lesions can develop into advanced, invasive submucosal cancers that invade deeper layers. We are now examining biological markers of

malignancy in sessile serrated lesions by means of immunohistochemical staining to evaluate whether such these lesions have malignant potential.

Pancreatobiliary endoscopy

1. Diagnosis of biliary and pancreatic diseases

Because of the recent introduction of the Diagnosis Procedure Combination (a specialized Japanese insurance system), establishment of a standardized, systematic diagnostic algorithm for biliary and pancreatic diseases has become more important than ever. We are comparing the diagnostic accuracy of EUS-FNA, multidetector-row computed tomography, magnetic resonance cholangiopancreatography, and endoscopic retrograde cholangiopancreatography (ERCP) in hepatopancreatic diseases. Additionally we introduced second-generation contrast media for ultrasonic imaging in the EUS diagnosis of pancreaticobiliary diseases.

The technique of ERCP is well established, but it is associated with a risk of severe complications. To help address this problem we designed a new catheter and multibending duodenoscope to reduce unplanned pancreatic injection of contrast medium, which is considered a major cause of post-ERCP pancreatitis, a common complication.

2. Treatment using endoscopic techniques in pancreatobiliary diseases

The technique of EUS-guided celiac plexus block has been performed to control persistent pain due to chronic pancreatitis, even in benign disease. We have performed EUS-guided celiac plexus neurolysis using a small amount of injected ethanol and are now evaluating the feasibility of this approach.

We have also started animal experiments to develop new interventional technologies to locally control pancreatic cancer and to diagnose gallbladder neoplasms.

Palliative care

More and more interest is being shown in palliative care. Various techniques have been developed to provide the best quality of life for critically ill or terminally ill patients. Endoscopic procedures may play an important role in palliative care, especially in supporting food intake. In our department, percutaneous endoscopic gastrostomy is performed for patients who are unable to maintain sufficient oral intake. Although percutaneous endoscopic enterostomy is conventionally not indicated for patients who have undergone gastric surgery, since 1994 we have extended the use of this procedure to include such patients and have investigated the technique's clinical usefulness in this situation. Kits for percutaneous endoscopic gastrostomy developed by us have reduced the frequency of complications associated with percutaneous endoscopic enterostomy placement. To alleviate stenosis attributable to digestive tract and bile duct tumors, we have performed endoscopic ballooning/bougienage and subsequent metallic stenting, with good therapeutic results. To reduce the pain associated with chronic pancreatitis and inoperable pancreatic cancer, we have performed transgastric celiac plexus blocks using EUS. These endoscopic procedures may greatly contribute to improving the quality of life of patients who are not candidates for radical surgery. The cost-effectiveness of these interventions is another benefit.

Publications

Kakutani H, Sasaki S, Ueda K, Takakura K, Sumiyama K, Imazu H, Hino S, Kawamura M, Tajiri H. Is it safe to perform endoscopic band ligation for the duodenum? A pilot study in ex vivo porcine models. *Minim Invasive Ther Allied Technol.* 2013; **22**: 80-3. Epub 2012 Jul 16.

Imazu H, Kanazawa K, Mori N, Ikeda K, Kakutani H, Sumiyama K, Hino S, Ang TL, Omar S, Tajiri H. Novel quantitative perfusion analysis with contrast-enhanced harmonic EUS for differentiation of autoimmune pancreatitis from pancreatic carcinoma. *Scand J Gastroenterol.* 2012; **47**: 853-60.

Sumiyama K, Kiesslich R, Ohya TR, Goetz M, Tajiri H. In vivo imaging of enteric neuronal networks in humans using confocal laser endomicroscopy. *Gastroenterology.* 2012; **143**: 1152-3.

Kanazawa K, Imazu H, Mori N, Ikeda K, Kakutani H, Sumiyama K, Hino S, Ang TL, Omar S, Tajiri H. A comparison of electronic radial and curvilinear endoscopic ultrasonography in the detection of pancreatic malignant tumor. *Scand J Gastroenterol.* 2012; **47**: 1313-20.

Tamai N, Saito Y, Sakamoto T, Nakajima T, Matsuda T, Tajiri H. Safety and efficacy of colorectal endoscopic submucosal dissection in elders: clinical and follow-up outcomes. *Int J Colorectal Dis.* 2012; **27**: 1493-9.

Aihara H, Saito S, Ohya T, Tamai N, Kato T, Tajiri H. A pilot study using reduced-volume oral

sulfate solution as a preparation for colonoscopy among a Japanese population. *Int J Colorectal Dis.* 2013; **28**: 83-7.

Aihara H, Saito S, Tajiri H. Rationale for and clinical benefits of colonoscopy with narrow band imaging: pathological prediction and colorectal screening. *Int J Colorectal Dis.* 2013; **28**: 1-7.

Yoshida Y, Matsuda K, Tamai N, Yoshizawa K, Nikami T, Ishiguro H, Tajiri H. A pilot study using an infrared imaging system in prevention of post-endoscopic submucosal dissection ulcer bleeding. *Gastric Cancer.* 2013 Feb 8. Epub ahead of print.

Horiuchi H, Kaise M, Inomata H, Yoshida Y, Kato M, Toyozumi H, Goda K, Arakawa H, Ikegami M, Kushima R, Tajiri H. Magnifying endoscopy combined with narrow band imaging may help to predict neoplasia coexisting with gastric hyperplastic polyps. *Scand J Gastroenterol.* 2013; **48**: 626-32. Epub 2013 Mar 4.

Reviews and Books

Kakutani H, Hino S, Koyama S, Uchiyama Y, Sumiyama K, Imazu H, Kawamura M, Tajiri H. How do we select an endoscopic treatment for esophageal varices on the basis of hemodynamic analysis using color Doppler endoscopic ultrasonography. *Surg Laparosc Endosc Percutan Tech.* 2012; **22**: 410-4.