

Department of Endoscopy

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General Summary

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

Research Activities

Pharyngeal, esophageal and gastric malignancies

1. Endoscopic diagnosis in esophagogastric neoplasia

The early detection and accurate diagnosis of premalignant and malignant lesions in the pharynx, esophagus, and stomach are essential for selecting the most appropriate treatments 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. Most recently, we have introduced transnasal ultrathin endoscopy, which is expected to improve patient compliance. This is particularly useful for screening patients from the nonreferral 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. Our goal of our current research is to develop algorithms for NBI technology which allow the histological type and the extent of tumors in gastric carcinoma to be predicted without biopsy. We also aim to evaluate this technology for the early detection of precancerous changes in the specialized columnar epithelium of Barrett's esophagus. Preliminary results have been reported at several conferences and published. On the basis of our findings with magnified NBI, we have also developed a novel classification system for gastric cancer and demonstrated its advantages compared with the conventional diagnostic system in a prospective study.

2) AFI

The AFI endoscopic system has recently been developed to visualize the autofluorescence emitted from the gastrointestinal wall. Theoretically, AFI may allow the detection

of premalignancies or early stage malignancies that do not have a distinct endoscopic appearance. 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.

3) Ultrathin endoscopy (transnasal endoscopy)

Ultrathin endoscopes can reduce discomfort during endoscopic examination. However, ultrathin endoscopes have a lower image resolution than do conventional endoscopes and, therefore, are associated with a higher risk of false-negative results. Accordingly, we found that gastric lesions are detected at a lower rate with ultrathin endoscopes than with conventional high-resolution endoscopes.

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 will be described later.

4) 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 on endoscopic examination. These lesions include those 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 any malignant cells. We are now evaluating the technical safety and usefulness of this technique.

2. Endoscopic treatment of esophageal and gastric malignancies

With recent advances in endoscopic diagnostic techniques and instrumentation, the indications for endoscopic therapy have increased in the treatment of early gastric and esophageal carcinomas. Research on the following endoscopic therapeutic modalities is now under way to standardize the use of these techniques in the treatment of 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 the use of endoscopic submucosal dissection (ESD) in the treatment of early gastric cancer, based on the histopathological findings of the cancer. We are also evaluating the possible use of EMR in the treatment of gastric cancers, including small, poorly differentiated adenocarcinomas lacking ulceration, well-differentiated adenocarcinomas 30 mm or less in diameter or confined to the mucosa, and carcinomas lacking submucosal microinvasion. Current indications for the use of 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 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 by means of ESD is considered necessary to further develop the use of endoscopic treatment. Development of a series of endoscopic knives and long-lasting submucosal fluid has 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 following endoscopic treatment, by monitoring intragastric pH after endoscopy. A study to evaluate the risk of sepsis and endotoxemia following ESD, using blood culture, is underway.

2) Therapeutic interventions employing innovative endoscopy systems

The multibending scope (M-scope) is a new type of endoscope that provides greater access to poorly accessible sites. 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 regions not accessible with a conventional endoscope. 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 has a special mechanism allowing the forceps to move laterally and vertically, in addition to the multibending function, are being performed to raise the potential of endoscopic therapy. We have also performed several studies using natural orifice transluminal endoscopic surgery, 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 *Helicobacter pylori* infection and the development of gastric cancer. However, many unknown factors still affect this association. Because this department routinely performs endoscopic treatment for gastric cancer, clarifying these factors is important. Experiments on this topic, particularly on DNA methylation due to *H. pylori* infection, have been performed in collaboration 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 demonstrated that the eradication of *H. pylori* plays an important role in 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 have been published in Japan and 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 has improved prognoses. However, this technique is difficult to perform in such locations as the oropharynx and hypopharynx. Metachronous or synchronous cancer in the oropharynx or hypopharynx has become the main factor adversely affecting the prognosis or quality of life of patients with esophageal cancer. Because of the importance of detecting cancer at an early stage, we have found that using magnifying endoscopy in combination with the NBI system has allowed hard-to-find cancers to be detected at an early stage without Lugol chromoendoscopy. A multicenter randomized controlled study of the clinical value of this new combination endoscopy has been performed.

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. It is important to establish methods to evaluate hypersensitivity and dysmotility of the gastrointestinal tract to understand disease pathophysiology and choose effective treatments. Hence, we have developed a new method for 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 using color Doppler endoscopic ultrasonography to study the hemodynamics of the portal venous system in patients with esophagogastric varices. These studies have clarified some of the factors associated with an increased likelihood of esophagogastric varices to recur after endoscopic treatment. When all such factors are identified, we expect to be able to predict and prevent early recurrence 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 in the detection of gastrenal shunts, which can complicate the treatment of esophagogastric varices, and can delineate the shunt in detail. Therefore, this diagnostic system could be extremely useful for selecting patients with esophagogastric varices who are suitable candidates for treatment by interventional radiology and for predicting its efficacy.

Enteroscopy and Colonoscopy

1. Diagnostic techniques

Capsule endoscopy is a breakthrough modality that can be used to detect lesions located in parts of the small intestine unreachable with an ordinary endoscope system. Internationally, capsule endoscopy has been performed for more than 1 million patients before May 2009. It is recommended as a first-line examination to detect diseases of the small intestine. However, because capsule endoscopy is purely diagnostic, we have introduced single-balloon enteroscopy, which allows biopsies to be performed and hemostatic techniques to be applied to hemorrhaging lesions of the small intestine.

The incidence of colon cancer has markedly increased in Japan. In Europe and the United States, studies describing the use of capsule endoscopy for examining the large intestine have been published. The Jikei University is 1 of 6 Japanese hospitals collaborating on studies of capsule endoscopy for screening patients for diseases of the large intestine.

Accurate preoperative evaluation of the degree of tumor invasion is essential for appropriate decision-making and for determining the optimal therapeutic strategy for patients with colonic lesions. Hence, to maximize diagnostic accuracy, we use a magnifying endoscope with NBI or AFI or both along with conventional white-light examination.

2. Research in endoscopic interventions

Surgical resection has been the first choice for treating large, sessile tumors of the colon.

Recently, some colonic lesions have been treated with endoscopic en bloc resection performed with ESD (a standard treatment for gastric 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 current efforts are focused on establishing safe and reliable endoscopic methods for removing large colonic lesions and to start preliminary use of ESD. Additionally, an infrared endoscopy system is used to evaluate the risk of bleeding from vessels on the base of the ulcer produced with ESD.

3. Capsule endoscopy and enteroscopy

Capsule endoscopy is a minimally invasive endoscopic modality that can be used to detect lesions of the small intestine that traditional push enteroscopy cannot reach. In Western countries, capsule endoscopy has recently been recommended as the first-line endoscopic examination for evaluating and managing obscure gastrointestinal bleeding. We have performed capsule endoscopies for 109 patients since Japanese health insurance began covering the modality in April 2007. Our study found that capsule endoscopy should be performed as soon as possible after a patient visits a hospital with a complaint of melena. We are aiming to further improve the diagnostic accuracy of capsule endoscopy in evaluating obscure gastrointestinal bleeding, by re-evaluating the traditional bowel preparation regimen.

Pancreatobiliary endoscopy

1. Diagnosis of biliary and pancreatic diseases

Owing to the recent introduction of the Diagnosis Procedure Combination (a specialized Japanese insurance system), establishing 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-row computed tomography, magnetic resonance cholangiopancreatography, and endoscopic retrograde cholangiopancreatography (ERCP). Additionally we have introduced a second-generation contrast medium for ultrasonic imaging in EUS diagnosis.

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

For diagnosing ampullary tumors of the duodenum, we have characterized in detail the mucosal surface structures in this region using NBI to magnify microstructures and to help determine whether lesions are benign or malignant. Furthermore, convex array EUS is performed to evaluate the depth of tumor invasion. On the basis of these findings, the need for endoscopic papillectomy is determined. Favorable clinical outcomes have been obtained to date.

2. Treatment with 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 practicality of this approach.

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

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 in palliative care, especially in supporting food intake. In our department, percutaneous endoscopic gastrostomy is performed when patients cannot maintain sufficient oral intake. Although percutaneous endoscopic enterostomy is usually 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 its usefulness. Kits for placing percutaneous endoscopic gastrostomy developed by us have reduced the frequency of complications associated with percutaneous endoscopic enterostomy placement. To alleviate stenosis due to tumors of the digestive tract or bile duct, we have performed endoscopic ballooning/bougienage and subsequent metallic stenting and have obtained good 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 help improve the quality of life of patients who are not candidates for radical surgery. The cost-effectiveness of these interventions is another benefit.

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