

Department of Endoscopy

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General Summary

Our main area of research is performing clinical studies of endoscopy for the diagnosis and treatment of gastrointestinal, hepatobiliary, and pancreatic diseases. 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. In our research, we use several 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 reduces discomfort during examination, which makes it particularly useful for screening patients who are undergoing routine medical examination.

1) Magnifying endoscopic observation with 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 identifying superficial neoplasms in the pharynx, esophagus, stomach, and duodenum. In one study, we developed algorithms for NBI technology that would allow the histological type and tumor extent of gastric carcinoma to be determined without a biopsy. On the basis of our findings with magnified NBI, we have developed a novel classification system for gastric cancer and demonstrated, in a prospective study, its advantages over the conventional diagnostic system. We also joined a multicenter study of NBI-magnifying endoscopy for detecting superficial carcinomas of the pharynx and esophagus. In addition, we performed a single-center study to compare NBI-magnifying endoscopy with Lugol chromoendoscopy for detecting superficial carcinoma in the esophagus. Our goal is to

evaluate this technology for the early detection of precancerous changes in the specialized columnar epithelium of Barrett's esophagus. The newly developed dual-focus endoscope and the updated NBI system have addressed the shortcomings of the conventional magnification scope and the NBI system. We prospectively compared dual-focus NBI with conventional magnification NBI for detecting superficial squamous neoplasms in the pharynx and esophagus. Results of these studies have been reported at several conferences and have been published in several English-language journals.

2) Endocytoscopy

Endocytoscopy is a novel optical imaging technique that allows the gastrointestinal mucosa to be visualized with a staining solution *in vivo* and in real time at the cellular level. We joined a multicenter study that employed endocytoscopy for the diagnosis of superficial esophageal squamous cell carcinoma. In addition, 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. Furthermore, we are preparing manuscripts that describe the use of endocytoscopy for superficial esophageal neoplasms and superficial nonampullary duodenal epithelial tumors.

3) AFI endoscopic system

The AFI endoscopic system has recently been developed to visualize autofluorescence emitted from the gastrointestinal wall. Theoretically, AFI can be used to detect premalignant lesions or early-stage malignancies that do not have a distinct appearance on conventional white-light endoscopy. Although it remains associated with a high false-positive rate, we have established that AFI, in combination with conventional white-light imaging and NBI, could improve specificity. This result was recently published in an English-language journal.

4) Ultrathin endoscopy (transnasal endoscopy)

Ultrathin endoscopy can reduce discomfort during endoscopic examination. However, ultrathin endoscopes have a poorer image resolution than do conventional endoscopes and, therefore, have a higher risk of false-negative results. Accordingly, we showed that ultrathin endoscopy was less able to detect gastric lesions than was high-resolution endoscopy. We are developing 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 histopathologic analysis of lesions that are typically undetectable with 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 for the precise guidance of the biopsy needle into lesions. Tissues obtained with EUS-FNA are immediately examined by a cytologist or pathologist to detect the presence of malignant cells. We are currently evaluating the technical safety and value of this technique in ongoing studies.

2. Endoscopic treatment of esophageal and gastric malignancies

Recent advances in endoscopic diagnostic techniques and instrumentation have led to the expansion of indications for endoscopic therapy in early gastric and esophageal carcinomas. Research on the following endoscopic therapeutic modalities is now underway to standardize their use for treating tumors of the upper gastrointestinal tract.

1) New indications for endoscopic treatment and endoscopic submucosal dissection

Currently, we perform endoscopic submucosal dissection (ESD) for superficial neoplasms of the esophagus and stomach. En bloc resection with ESD is considered necessary to further develop endoscopic treatment. Successful development of a series of endoscopic knives and long-lasting submucosal fluid will reduce the technical difficulty of ESD and the risk of complications. We have monitored intragastric pH after endoscopy to evaluate the effectiveness of gastric acid-suppressing drugs, which have been used empirically after endoscopic treatment. We have also used blood cultures to study the risk of sepsis and endotoxemia after ESD.

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 typically difficult to reach. We have previously reported on the use of the M-scope in the treatment of tumors that are not accessible with conventional endoscopes: those of the lesser curvature, greater curvature, and posterior wall of the gastric body, and of the cardiac region. Furthermore, clinical studies using a newly developed therapeutic endoscope (the R-scope) are proceeding to advance the potential of endoscopic therapy. The R-scope has a special mechanism allowing the forceps to move laterally and vertically, in addition to its multibending function. Because current endoscopic treatments are directed only at mucosal diseases but not transluminal diseases, we have also performed several studies using natural orifice transluminal endoscopic surgery, including full-thickness resection.

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

The association between infection with *Helicobacter pylori* and the development of gastric cancer is well documented. However, many of the factors that affect this association are unknown. Determining these factors is important to our department because we routinely perform endoscopic treatment for gastric cancer. Experiments that address the association between infection with *H. pylori* and gastric cancer — particularly 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 role of inducible nitric oxide synthase (iNOS) in the pathogenesis of *H. pylori*-associated diseases. We have demonstrated that the eradication of *H. pylori* plays an important role in the process of repairing disease-associated DNA methylation and in altering the methylation patterns of genes in the mucosa in the 5 years after *H. pylori* has been eradicated. Interim results of this study 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 polymorphisms may contribute to the development of gastric cancer.

4. Diagnosis of oropharyngeal and hypopharyngeal malignancies

Endoscopic screening with iodine staining, or Lugol chromoendoscopy, has allowed esophageal cancer to be detected at an early stage and has thus improved prognoses.

However, this technique is difficult to perform in certain locations, such as the oropharynx or hypopharynx. Metachronous or synchronous cancer of the oropharynx or hypopharynx is the main factor impairing the prognosis and quality of life of patients with esophageal cancer. Detecting cancer at an early stage is important. We have found that, in combination with the NBI system, magnifying endoscopy has allowed hard-to-find cancers to be detected during their early stages, without the need for Lugol chromoendoscopy. We performed a multicenter randomized controlled study of the clinical value of this new combination endoscopy. In addition, we performed a single-center study to evaluate the endoscopic characteristics of superficial carcinoma in the pharyngeal region. These results have been 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 determine. Establishing methods to evaluate the hypersensitivity and dysmotility of the gastrointestinal tract are important for understanding disease pathophysiology and for selecting effective treatment. Hence, we have developed a new method of evaluating esophageal functions with a small-caliber endoscope. We have started basic experiments on esophageal motility and sensitivity, with the goal 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 identified several factors that increase the likelihood of esophagogastric varices recurring after endoscopic treatment. When all such factors have been identified, we will be able to predict and prevent early recurrence of varices after treatment. We have also started a study to confirm the 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 will 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 that are inaccessible with an ordinary endoscope system. Capsule endoscopy was performed in more than 1 million cases worldwide 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 number of cases of colonic cancer in Japan has increased markedly. In major Euro-

pean countries, many studies have described the use of capsule endoscopy for examining the colon. In Japan, we are collaborating with another facility to perform studies with capsule endoscopy to screen patients for colonic neoplasms.

Accurate preoperative evaluation of the depth of invasion into the submucosal layer is essential for appropriate decision-making and for determining the optimal therapeutic strategy for patients with colonic lesions. Hence, to maximize our diagnostic accuracy, we use a magnifying endoscope with NBI and crystal-violet staining, 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, the endoscopic resection of large intestinal lesions is technically difficult because of the large intestinal folds and the higher rate of complications, such as perforation and bleeding. We are currently working to establish safe and reliable endoscopic methods for the complete removal of large colonic lesions to start preliminary use of ESD. In addition, we have used an infrared endoscopy system to evaluate the risk of bleeding from vessels located at the base of ESD-induced ulcers.

3. Capsule endoscopy and enteroscopy

Capsule endoscopy is a minimally invasive endoscopic modality that can be used to detect lesions of the small intestine which are inaccessible with traditional push-type enteroscopy. Recently, particularly in 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 850 patients, since the Japanese health insurance system began covering this procedure in April 2007. We determined that capsule endoscopy should be performed immediately after a patient presents at the hospital with a complaint of melena. Our goal is to continue to 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 defined as a nonneoplastic tumor of the colon. Therefore, endoscopic treatment is not indicated on a histologic basis. However, according to recent reports from Western countries, sessile serrated lesions (SSA) can develop into advanced, invasive submucosal cancers that invade deeper layers of the submucosa. We are presently studying the use of the AFI and NBI systems to detect neoplastic lesions, including sessile serrated polyps (SSA/P). We are also examining biological markers of malignancy in SSA/P, by means of immunohistochemical staining, to evaluate whether such lesions have malignant potential.

In contrast, submucosal invasive cancer, which invades into a depth of less than 1,000 μm , is an indication for endoscopic treatment, according to the 2014 Guideline for the Treatment of Colorectal Cancer from the Japanese Society for Cancer of the Colon and Rectum. Therefore, such invasive cancer warrants further investigation with magnifying endoscopy. We are currently studying the characteristic findings of conventional and magnifying endoscopy. In cases in which the submucosal invasion depth is the only compo-

ment that does not satisfy the criteria for a radical-cure evaluation, and no other risk factors for metastasis are observed, the rate of metastasis to lymph nodes has been reported to be extremely low. Our university is included in an ongoing investigation of the stratification of risk factors for the metastasis of deep submucosal invasive cancers (invasion depths >1,000 μm) to other organs.

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. We have also introduced second-generation contrast media for ultrasonic imaging in the EUS diagnosis of pancreaticobiliary diseases. In addition, we are developing new diagnostic markers for pancreatic carcinoma and a system for their measurement. We will be applying these markers to the differential and prognostic diagnosis of pancreatic carcinoma with specimens obtained with EUS-FNA. Moreover, we are developing a novel molecular imaging system using EUS with microbubbles for pancreatic carcinoma.

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 the common complication of post-ERCP pancreatitis.

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 with EUS and microbubbles to locally control pancreatic cancer.

Palliative care

Palliative care has gained increasing interest. 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 of food. Although percutaneous endoscopic enterostomy is not conventionally 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 clinical usefulness of the technique. We have developed kits for percutaneous endoscopic gastrostomy that have reduced the frequency of complications associated with percutaneous endoscopic enterostomy placement. To alleviate stenosis caused by tumors of the digestive tract and bile duct, we have performed endoscopic bal-

looning/bougienage and subsequent metallic stenting and have obtained 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 improve the quality of life of patients who are not candidates for radical surgery. The cost-effectiveness of these interventions is also beneficial.

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