Department of Endoscopy

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General Summary

The main theme of our research is clinical studies using endoscopy in the diagnosis and treatment of gastrointestinal (GI), 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 for selecting the most appropriate therapeutic strategy for each patient. Our research utilizes 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 important 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 (×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 in the pharynx, esophagus, stomach, and duodenum. Our current studies focus on the development of algorithms for NBI technology which will allow histological type and tumor extent in gastric carcinoma to be predicted without biopsy. On the basis of our findings with magnified NBI, we have also developed a novel classification system for gastric cancer and demonstrated its advantages over conventional diagnostic systems in a prospective study. We joined a multicenter study using NBI magnifying endoscopy to detect superficial carcinoma in the pharynx and esophagus. Moreover, we performed a single-center study to compare 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 that occurs in Barrrett's esophagus. Results of these studies have been reported at several conferences and have been published. Most recently, a magnifying endoscope and light source system equipped with NBI have been developed, and instruments now available for clinical use. We performed a comparative study of this novel NBI magnifying endoscopy and conventional high-definition magnifying endoscopy for detecting superficial carcinomas in the pharynx and esophagus.

2) AFI

Recently, an AFI endoscopic system has been developed to visualize autofluorescence emitted from the GI wall. In theory, AFI would allow the detection of premalignant lesions or early-stage malignant lesions that do not have a distinct endoscopic appearance on conventional white-light endoscopy. Although AFI still has a high false-positive rate, we found that AFI, in combination with conventional white-light imaging and NBI, can improve specificity.

3) Ultrathin endoscopy (transnasal endoscopy)

An ultrathin endoscope can reduce discomfort during endoscopic examination. However, the ultrathin endoscope has a lower image resolution than do conventional endoscopes, and, therefore has a higher risk of false-negative results. Accordingly, we found that rate of detection of gastric lesions was lower with ultrathin endoscopy than with high-resolution endoscopy. We are attempting to develop a method for 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 with endoscopic examination. These include lesions within the GI walls, such as submucosal tumors of the esophagus and stomach, and mediastinal and lymph-node lesions. In EUS-FNA, the real-time ultrasonographic images are used to precisely guide the biopsy needle into lesions. The tissues obtained with EUS-FNA are immediately examined for malignant cells by a cytologist or pathologist. We are now evaluating the 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, the indications for endoscopic therapy in early gastric and esophageal carcinomas have expanded. Research on the following endoscopic therapeutic modalities is now under way to standardize the use of these techniques for treating upper GI tract tumors.

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, based on 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. The 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 via ESD is considered necessary for the further development of endoscopic treatment. The 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 also evaluated the effectiveness of gastric acid-suppressing agents, which have been used empirically following endoscopic treatment, by monitoring intragastric pH after endoscopy. A blood culture study to evaluate the risk of sepsis and endotoxemia following ESD is now underway.

2) Treatments with 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 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, regions that are not accessible with a conventional endoscope. Studies with an M-scope with magnifying capability are now underway to develop more accurate and safer procedures. Furthermore, clinical studies using a newly developed therapeutic endoscope (R-scope), with 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 translumenal endoscopic surgery, including full-thickness resection, as 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 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 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 important roles 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 using iodine staining, or Lugol chromoendoscopy, has enabled endoscopists to detect esophageal cancer at an early stage, thus improving patient prognosis. However, this technique is difficult to perform in such locations as the oropharynx and hypopharynx. The presence of metachronous or synchronous cancer in 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 the combination of magnifying endoscopy and the NBI system can be used to detect hard-to-find cancers at an early stage without the need for Lugol chromoendoscopy. A multicenter randomized, controlled study has examined the clinical value of this new combination endoscopy. In addition, we performed a study at our institution to evaluate the endoscopic characteristics of superficial carcinoma in the pharyngeal region. The results have reported at medical congresses and in English-language medical journals.

Functional disorders of the upper GI tract

The causes of gastroesophageal reflux diseases, including nonerosive reflux disease, and GI motility disorders are difficult to identify. To understand disease pathophysiology and choose effective treatments, it is important to establish methods to evaluate the hypersensitivity and dysmotility of the GI tract. Hence, we have developed a new method of evaluating esophageal function using a small-caliber endoscope. We have started basic experiments on esophageal motility and sensitivity to transform this technique from a research tool into a clinical tool.

Diagnosis and treatment of esophagogastric varices

We have recently used color-Doppler endoscopic ultrasonography (CD-EUS) to study the hemodynamics of the portal venous system in patients with esophagogastric varices. These studies have clarified several factors associated with an increased risk of recurrence of esophagogastric varices after endoscopic treatment. When all such factors are identified, we will be able to predict and prevent the early recurrence of varices after treatment. We have also started a study to confirm factors that exacerbate hemorrhagic gastritis and cardiac varices. CD-EUS is also highly accurate for detecting gastrorenal shunts, which can complicate the treatment of esophagogastric varices, and can visualize shunts in detail. Therefore, this diagnostic system would be extremely useful for selecting patients with esophagogastric varices who are candidates for interventional radiology and for predicting the efficacy of this treatment.

Enteroscopy and colonoscopy

1. Diagnostic techniques

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

Recently, the prevalence of colon cancer has markedly increased, particularly in Japan. In Europe and the United States, several reports of capsule endoscopy for examining the large intestine have been published. In Japan, we are collaborating with 6 hospitals to perform studies of capsule endoscopy to screen patients for neoplasms of the

colon.
Accurate preoperative evaluation of the degree of tumor invasion into the deep layers of the colon is essential for appropriate decision-making and determining the optimal therapy. Hence, to maximize diagnostic accuracy, we use 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 first choice for treating large, flat, elevated tumors in the colon. Recently, endoscopic en bloc resection performed by means of ESD (a standard treatment for gastric lesions) has been used for some 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 current 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 at the base of an ulcer made with ESD.
3. Capsule endoscopy and enteroscopy
Capsule endoscopy is a minimally invasive endoscopic modality that can be used to detect lesions in areas of the small intestine unreachable with traditional push enteroscopy. Recently, particularly in Western countries, capsule endoscopy has been recommended as the first-line endoscopic examination for evaluating and managing obscure GI bleeding. We have performed capsule endoscopy for 109 patients since Japanese health insurance began covering the examination in April 2007. Our study, which was published in scientific journals, 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 for evaluating obscure GI bleeding by reevaluating 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), 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 EUS diagnosis.
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 to reduce unplanned pancreatic injection of contrast medium, which is considered a major cause of a common complication, post-ERCP pancreatitis.
For the diagnosis of ampullary tumors of the duodenum, we have characterized mucosal surface structures in detail using NBI to magnify microstructures and to help determine whether a lesion is benign or malignant. Furthermore, convex array EUS examination 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 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 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 placing 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 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 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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