

Department of Endoscopy

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General Summary

Our main research activities are clinical studies of endoscopic diagnosis and the treatment of gastrointestinal and hepatobiliary-pancreatic diseases. In addition, we performed basic research on the development of novel instruments, image processing and analysis, and optical apparatuses, such as auto fluorescence imaging (AFI), narrow-band imaging (NBI), endocytoscopy, confocal laser endomicroscopy, 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 for esophagogastric neoplastic lesions

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. The following novel optical technologies are used clinically in addition to conventional white-light endoscopy. We have designed a series of prospective clinical studies to evaluate and validate the benefits of the following novel imaging technologies. Most recently we have introduced an ultrathin transnasal endoscope that is expected to improve patient cooperation, especially for screening at a nonreferral hospital by reducing discomfort during endoscopic examination.

1) Magnifying endoscopic observation using a NBI system

This new diagnostic system consists of a magnifying ($\times 90$) endoscope and an NBI light source and provides detailed morphological information about capillaries on the mucosal surface. Our current study focus is to develop algorithms for NBI technology that will allow prediction of the histological type of gastric carcinoma and the tumor extent without biopsies 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 gastric 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 endoscopically visualize autofluorescence emitted from the wall of the gastrointestinal (GI) tract. Theoretically, AFI may allow detection of premalignancies or early-stage malignancies without 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 the endoscopic examination. However, the image resolution of the ultrathin endoscope is poorer than that of conventional endoscopes, and therefore is associated with an inherent risk of a higher false-negative rate. Indeed, we found that for gastric lesions the false-negative rate was higher than with a high-resolution endoscope. We are trying to develop methods to study motility disorders of the esophagus with an ultrathin endoscope by assessing symptoms during examination. Details of this motility study are described later.

4) Endoscopic ultrasound-guided fine-needle aspiration biopsy

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

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 expanding. Research on the following endoscopic therapeutic methods is now under way to standardize them as treatments for upper GI tumors.

1) New indications for endoscopic treatment and endoscopic submucosal dissection
Current indications for endoscopic mucosal dissection (ESD) are limited by the size, depth, and histological type of the lesions. Our recent efforts have been focused on expanding indications for ESD for early gastric cancer based on histopathological analysis. We are evaluating small, poorly differentiated adenocarcinomas without ulceration, well-differentiated adenocarcinomas within 30 mm in size or over (> 30 mm) confined to the mucosa, and carcinomas with microinvasion into the submucosal layer as new indications for endoscopic mucosal resection (EMR) for gastric cancer. For esophageal cancer, current indications for EMR are epithelial cancer (m1) and cancer partially invading the lamina propria mucosae (m2) with a 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. The development of a series of endoscopic knives and long-lasting submucosal fluid successfully reduced the technical difficulty of ESD and the risks of complications. By monitoring intragastric pH after treatment, we also evaluated the effectiveness of acid-suppressive drugs that has been used empirically after endoscopic treatments. A study to evaluate with blood cultures the risk of sepsis and endotoxemia after ESD is underway.

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 treating tumors of the lesser curvature, greater curvature, 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 under way 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 proceeding with the goal of advancing the development of endoscopic therapy. We also performing several research studies related to natural orifice transluminal endoscopic surgery, including full-thickness resection, as technologies beyond current endoscopic treatments direct at mucosal diseases only.

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, many unknown factors remain concerning this topic. Therefore, it is imperative to clarify this relation in this department, where endoscopic treatment of gastric cancer is performed on a routine basis. The experiments on this topic, especially on DNA methylation due to *H. pylori* infection, have been performed in cooperation with the Department of Gastroenterology, Toshiba General Hospital. We have also been investigating the roles of inducible nitric oxide synthase (iNOS) in the pathogenesis of *H. pylori*-associated diseases and found that *H. pylori* eradication plays important roles in the repair process of methylated DNA and in the alteration of mucosal methylation during the 5 years after *H. pylori* eradication. The preliminary results have already been reported at several conferences and have been published in Japan and 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, *i.e.*, Lugol chromoendoscopy, has allowed esophageal cancer to be detected at an early stage and has improved prognoses. However, metachronous or synchronous cancer located in the oropharynx or hypopharynx has become the main factor adversely affecting the prognosis and quality of life of patients with esophageal cancer. Although detecting these cancers at an early stage is absolutely essential, Lugol chromoendoscopy is difficult to perform for these cancers, unlike esophageal cancer, 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 Lugol 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 gastroesophageal reflux diseases, including nonerosive reflux disease and GI motility disorders, are difficult to identify. It is important to establish methods to

evaluate the hypersensitivity and dysmotility of the GI tract to understand the pathophysiology of these disorders and to treat them.

We developed a new method to evaluate esophageal function using a small-caliber endoscope. We started basic experiments for the analysis of the motility and sensitivity of the esophagus with the aim of applying this technique to clinical practice.

Diagnosis and treatment of esophagogastric varices

Recently, we have been involved in studies of the hemodynamics of the portal venous system in patients with esophagogastric varices using color-Doppler endoscopic ultrasonography (CD-EUS); these studies have clarified several 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 of varices after treatment. 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 gastrosplenic shunts and can delineate shunt status in detail 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 effects.

Enteroscopy and colonoscopy

1. Diagnostic techniques

Capsule endoscopy is a breakthrough modality that enables the detection of diseases of the small intestine that were unreachable with ordinary endoscope systems. Capsule endoscopy had been performed for more than 1 million cases as of May 2009 and is recommended as a first-line examination for detecting diseases of the small intestine. We introduced a single-balloon enteroscope that allows procedures, such as biopsy and hemostasis, for small intestinal lesions.

Recently the incidence of colonic cancer has markedly increased. In particular, the incidence of colon cancer has increased in Japan. In Europe and the United States several studies have examined the use of capsule endoscopy as a screening examination of the large intestine. In Japan we are examining the use of capsule endoscopy as a screening examination for the large intestine at 6 hospitals.

Accurate preoperative evaluation of tumor invasion is essential for selecting the most appropriate therapeutic strategy for colonic lesions. To improve diagnostic accuracy, we use a magnifying endoscope with NBI and/or AFI technology involving conventional white-light observation.

2. Research on endoscopic interventions

Surgical resection has been performed as the treatment of first choice for large sessile tumors in the colon. Recently endoscopic en bloc resection with ESD, which is the standard treatment for gastric lesions, has been used to treat such colonic lesions. However, endoscopic resection of large intestinal lesions is technically difficult because of the narrow space and the much higher rate of complications, such as perforation and bleeding. Our current efforts are focused on establishing a safe and reliable method for

removing large colonic lesions endoscopically; we have just started to apply the ESD technique. Additionally, an infrared endoscopy system is being used to evaluate high-risk vessels on the ulcer base after ESD to prevent bleeding.

3. Capsule endoscopy as enteroscopy

Capsule endoscopy is a less-invasive endoscopic method that allows the detection of lesions in the small intestine which had been unreachable with traditional push enteroscopy. Recently, especially in Western countries, capsule endoscopy has been recommended as the first-line endoscopic examination for the evaluation and management of obscure GI bleeding. We have performed capsule endoscopy in 109 cases since it became covered by the Japanese health insurance system in April 2007. Our study clarified that capsule endoscopy should be performed as soon as possible after a patient visits the hospital with a complaint of melena. We published our results in scientific journals. We are aiming to improve the diagnostic accuracy of capsule endoscopy in the evaluation of obscure GI bleeding by reconsidering the traditional bowel preparation regimen.

Pancreatobiliary endoscopy

1. Diagnosis of biliary and pancreatic diseases

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

ERCP is well-established procedure but is associated with the risks of severe, possibly life-threatening complications. We designed a new catheter to reduce unplanned pancreatic injection of contrast medium, which is considered a major cause of post-ERCP pancreatitis.

In the diagnosis of ampullary tumors of the duodenum, we perform detailed characterization of the mucosal surface structures and the magnification of microstructures with NBI to determine whether a lesion is benign or malignant. Also, convex array EUS is performed to evaluate the depth of tumor invasion. On the basis of these findings, the indications for endoscopic papillectomy are determined. Favorable clinical outcomes have been obtained so far.

2. Treatment using endoscopic techniques of pancreatobiliary diseases

EUS-guided celiac plexus block has been performed to control persistent pain because of chronic pancreatitis despite the presence of benign disease. We applied EUS-guided celiac plexus neurolysis with the injection of small amounts of ethanol and are evaluating its feasibility.

We have also started experiments with animals to develop new interventional technologies to establish the local control pancreatic cancer and to diagnose gallbladder neoplasms.

Palliative care

Palliative care is attracting more and more attention. 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 is performed for patients who cannot maintain sufficient oral intake. Although percutaneous endoscopic enterostomy is conventionally not indicated for patients who have undergone gastric surgery, we have extended the use of this procedure for such patients since 1994 and have investigated its clinical usefulness. Kits developed by us for placing percutaneous endoscopic gastrostomies have reduced the frequency of associated complications. To relieve stenosis attributable to tumors of the digestive tract and bile duct, 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.

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