Department of Endoscopy

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General Summary

Our main fields of research are clinical studies of endoscopic diagnosis and treatment of gastrointestinal (GI), hepatobiliary, and pancreatic diseases. In addition, we performed basic research for the development of novel instrumentation, image processing and analysis, and optical devices, such as autofluorescence imaging (AFI), narrow band imaging (NBI), supermagnified imaging, confocal endoscopy, 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 esophagogastric premalignant and malignant lesions are essential for selecting the most appropriate therapeutic strategy for each patient. At our institution, the following novel optical technologies are used in addition to conventional white-light endoscopy.

1) Magnifying endoscopic observation using an NBI system: This new diagnostic system consists of a magnifying ($\times$80) endoscope and an NBI light source and provides detailed morphological information about capillaries on the mucosal surface. Our present goal is to develop algorithms for NBI technology, which may allow accurate analysis of the histological type of gastric carcinoma and the tumor extent without biopsy and allow the early detection of precancerous changes in the specialized columnar epithelium of Barrret's esophagus. The preliminary achievements have already been published and reported at several conferences.

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

3) AFI

AFI is a technology to visualize autofluorescence emitted from the GI mucosa. AFI is

expected to enable early detection of GI tumors. We are comparing regular endoscopy, NBI, and AFI in prospective clinical studies to determine the features of each modality.

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 increasing. Research on the following endoscopic therapeutic modalities are now under way to standardize these endoscopic techniques as treatments for upper GI tumors.

1) New indications for endoscopic mucosal resection: Current indications for mucosal resection (EMR) are limited by the size, depth, and histological type of the lesions. Our recent efforts have been focused on expanding the indications of EMR for early gastric cancer on the basis of the histopathological analysis. Being evaluated as new EMR indications for gastric cancer are small, poorly differentiated adenocarcinomas without ulceration, well-differentiated adenocarcinomas 30 mm or larger confined to the mucosa, and carcinomas with microinvasion to the submucosal layer. In esophageal cancer the current indications for EMR are epithelial cancer (m1) and cancer partially invading the lamina propria mucosae (m2) with negligible risk of lymph node metastasis. Being evaluated as new indications are mucosal cancer invading the lamina muscularis mucosae (m3) and lesions with slight submucosal invasion within the first third of the submucosal layer (sm1).

2) Therapeutic interventions with innovative endoscopy systems

The multibending endoscope (M-scope) is a new type of endoscope with a higher degree of freedom. We have previously reported that the M-scope is useful for treating tumors in the lesser curvature, greater curvature, posterior wall of the gastric body, and the cardiac region, which are poorly accessible with a conventional endoscope. Studies using an M-scope with magnifying capability are now under way to develop safer and more accurate 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 under way to advance endoscopic therapy.

3. The role of *Helicobacter pylori* (*H. 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 aspects of this association remain unclear. Therefore, it is imperative to clarify this association in our department, in which endoscopic treatment of gastric cancer is routinely performed. The experiments on this topic, especially on DNA methylation due to *H. pylori* infection, have been performed in cooperation with Department of Gastroenterology, Toshiba General Hospital. We have also been exploring the roles of inducible nitric oxide synthase in the pathogenesis of *H. pylori*-associated diseases and have found that the treatment to eradicate *H. pylori* plays an important role in the repair of methylated DNA. The interim results have already been reported at several conferences and have been published in Japan and internationally. In addition, we have reported that the diverse topographical patterns of *H. pylori*-induced inducible nitric oxide synthase expression 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 has allowed esophageal cancer to be detected at an early stage and has improved prognoses. However, metachronous or synchronous cancer of the oropharynx or hypopharynx has become the main factor affecting the prognosis and quality of life of patients with esophageal cancer. Although detecting such cancers at early stage is, of course, important, performing chromoendoscopy is difficult because of their locations, unlike in cases of esophageal cancer. Magnifying endoscopy performed in combination with the NBI system has enabled us to detect hard-to-find cancers at an early stage without performing chromoendoscopy. A multicenter randomized, controlled study on the clinical value of this new combination endoscopy is now under way.

Functional disorders of the upper GI tract
The etiology of gastroesophageal reflux diseases, including nonerosive reflux disease and GI motility disorders, is difficult to determine. Methods must be established to evaluate hypersensitivity and dysmotility disorders of the GI tract to understand the pathophysiology of these disorders and treat them.
We developed a new method for evaluating esophageal functions using a small-caliber endoscope. We started basic experiments for analyzing the motility and sensitivity of the esophagus with the goal of applying this technique to clinical practice.

Diagnosis and treatment of esophagogastric varices
Recently, we have been involved in color-Doppler endoscopic ultrasonography (CD-EUS) studies of 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 recurrence of esophagogastric varices after endoscopic treatment. When all the factors are 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 gastrorenal shunts and can clearly delineate shunt status 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 therapeutic effects.

Enteroscopy and colonoscopy
1. Diagnostic techniques
Capsule endoscopy is a breakthrough modality that allows the detection of diseases in the small intestine that are inaccessible with ordinary endoscope systems. In western countries, capsule endoscopy has been performed in 300,000 cases and is recommended as a first-line examination for detecting diseases of the small intestine. Our department is 1 of 12 major endoscopy centers participating in a multicenter study to evaluate the usefulness of capsule endoscopy. Accurate preoperative evaluation of tumor invasion is essential for selecting the most appropriate and effective therapeutic strategy. To

improve diagnostic accuracy, we use a magnifying endoscope with NBI/AFI technology.

2. Treatment using colonoscopic techniques

Surgical resection has been the first choice of treatment for large sessile tumors in the colon. Endoscopic *en bloc* resection, which has become a standard treatment for gastric lesions, might also be a treatment option for colonic lesions. However, endoscopic resection of large lesions in the narrow colonic lumen is technically challenging and is accompanied by a higher risk of severe complications, such as perforation and bleeding. Our present efforts are focused on establishing safe and reliable methods to remove large colonic lesions endoscopically. Accordingly, we have started to apply endoscopic submucosal dissection to colonic lesions. Additionally, we have used an infrared endoscopy system to evaluate potentially troublesome vessels on the ulcer base to prevent postoperative bleeding after endoscopic submucosal dissection.

Pancreatobiliary endoscopy

1. Diagnosis of biliary and pancreatic diseases

Due to the recent introduction of duodenopancreatectomy the establishment of standardized systematic diagnostic algorithms for biliary and paricreatic diseases has become more important than ever. We are clinically comparing diagnostic accuracy for hepatopancreatic diseases among EUS-FNA, multidetector computed tomography, magnetic resonance cholangiopancreatography, and endoscopic retrograde cholangiopancreatography. We are also evaluating the usefulness of immunohistological examination of EUS-FNA samples to determine prognosis in cases of hepatopancreatic malignancy. Aiming to improve diagnostic accuracy of EUS-FNA and reducing sampling errors, we have started to compare 22-G and 25-G needles for tissue sampling. In the diagnosis of ampullary tumors of the duodenum, we perform detailed characterization of the mucosal surface structures by means of NBI with magnifying capabilities to determine if the lesion is benign or malignant. In addition, a convex-array EUS study is being performed to evaluate the depth of tumor invasion. On the basis of these findings, indications for endoscopic papillectomy are determined. Favorable clinical outcomes have been obtained so far.

2. Treatment using endoscopic techniques of pancreatobiliary diseases

A randomized, controlled study was conducted to compare the usefulness of endoscopic sphincterotomy and endoscopic papillary balloon dilation for the removal of stones from the common bile duct. Data obtained from the comparative study are used for selecting the most appropriate treatment for patients with common bile duct stones. The appropriateness of the procedure selection has also been reviewed and examined, for further improvement of the therapeutic results. Now studies of the long-term results, such as the recurrence rate and long-term complications, are under way. External biliary drainage, or endoscopic nasobiliary drainage, and internal biliary drainage using a plastic stent (endoscopic biliary drainage) have been widely adopted for the treatment of obstructive jaundice. No criteria, however, have been established to facilitate the selection of the most appropriate treatment for individual patients. We are now conducting a randomized, controlled study to compare the two different endoscopic treatment methods. For cases of inoperable cancers of the bile duct and pancreatic

head, we employ a metallic stent made of shape-memory alloy and performed historical comparison with standard stents. Although EUS-guided celiac plexus block has been performed to control benign but persistent pain due to chronic pancreatitis, the pain relief was short-lived. Therefore, we have applied EUS-guided celiac plexus neurolysis with injections of small amounts of ethanol and are evaluating its feasibility.

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, 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 usually not indicated for patients who have undergone gastric surgery, we have extended the use of this procedure to include such patients since 1994 and have investigated its clinical usefulness. Kits developed by us for placing percutaneous endoscopic gastrostomies have reduced the frequency of complications associated with percutaneous endoscopic enterostomy placement. To alleviate stenosis attributable to tumors of the digestive tract and bile ducts, 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 improve the quality of life of patients who are not candidates for radical surgery. The cost-effectiveness of these interventions is an additional benefit.

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