

Department of Innovative Interventional Endoscopy Research

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General Summary

This department was established in April 2015, with the aims of establishing new methods of endoscopic diagnosis and treatment and developing new apparatuses and with the purposes of supporting and teaching to standardize endoscopic medicine in Japan and in foreign facilities.

Research Activities

Endoscopic submucosal dissection (ESD), which was developed in Japan, has been followed by various improvements for safety, promptness, and accuracy. Following ESD, new minimally invasive endoscopic treatments, such as endoscopic full thickness resection and endoscopic treatment applying robotic technology, are being developed. Minimally invasive endoscopic treatments, which are less of a burden to patients, make a substantial contribution. As the social demands for endoscopic medicine grow, new endoscopic treatment methods and new instruments are being developed. This department plays several roles, such as performing relevant research studies and developing new educational methods for training physicians to perform endoscopy in Japan, other parts of Asia, Russia, the Middle East, and South America.

Endoscopic optical molecular imaging for cancer

Molecularly targeted therapies, such as monoclonal antibodies, have been widely used for various cancers and have improved patient outcomes. Photoimmunotherapy (PIT) is a new class of molecularly targeted cancer theranostics which employs monoclonal antibodies conjugated to a photosensitizer, IRDye 700DX (IR700). The photosensitizer is activated by focal near-infrared (NIR) light irradiation, leading to necrotic cell death by cell membrane rupture, where antibody-IR700 conjugates bind to target membrane proteins specifically. A global phase 3 clinical trial of PIT for patients with recurrent cancer of the head and neck has been conducted with a monoclonal antibody (mAb) against epidermal growth factor receptor, a cetuximab-IR700 conjugate. In this study, we developed a new type of PIT agent targeting vascular endothelial growth factor receptor 2 (VEGFR-2), which is expressed on the vascular endothelium in a tumor, and evaluated the feasibility by comparing conventional membrane-targeted PIT in vitro and in vivo. Human epidermal growth factor receptor 2 (HER2)-positive human gastric cancer cells of the NCI-N87 cell line were used for the experiments. Conjugated to IR700 were HER2-targeting trastuzumab and VEGFR-2-targeting DC101. Cells were treated with mAb-IR700 conjugates and then, after being washed, with NIR light irradiation. A mouse model of a tumor xenograft was created for in vivo PIT. Tumor-bearing mice were randomized and treated

under anesthesia with mAb-IR700 conjugates followed by NIR light irradiation. The PIT utilizing DC101-IR700 conjugates did not induce a phototoxic effect in vitro because of the absence of membranous expression of VEGFR-2 in NCI-N87 cells, whereas PIT utilizing trastuzumab-IR700 conjugates induced a rapid phototoxic effect because of the strong membranous expression of HER2 in NCI-N87 cells. In contrast, antitumor effects were observed in NCI-N87 xenograft tumors in vivo utilizing both DC101- and trastuzumab-IR700 conjugates followed by NIR light irradiation. Because VEGFR-2 is upregulated in many types of solid cancer, this method might be considered as applicable to various types of cancer.

Evaluation of 0.6% sodium alginate as an endoscopic submucosal injectant for esophageal and gastric ESD

Because ESD requires a high level of skill and is targeted at larger lesions, the risks of prolonged treatment and increased bleeding and perforation might increase. From these points of view, to perform ESD more easily and safely, maintaining a sufficient mucosal raise for the lesion and its surroundings is important. Currently, 0.4% sodium hyaluronate solution is widely used as an endoscopic submucosal injectant, but a problem is that the price of insurance coverage is high. Therefore, we have focused on sodium alginate with viscosity as an endoscopic submucosal injectant that is less expensive and does not impair mucosal raise as much as the 0.4% sodium hyaluronate solution does. In conducting ESD for patients with neoplastic lesions in the esophagus and gastric mucosa, we participated in a multicenter study as a control group using 0.4% sodium hyaluronate solution for the efficacy, safety, and usefulness as an endoscopic submucosal injectant. In this study, as an advisor to clinical trials, Tajiri has taught much from protocol construction to publication of the articles. Of a total of 130 cases, 65 were in the test group and 65 were in the control group. Sodium alginate is an inexpensive natural material widely used in various fields, and it became clear that the 0.6% sodium alginate solution, whose physical properties were adjusted in this study, has excellent mucosal raising ability without interfering with catheter passage.

Development of automatic insertion endoscope equipment

We are developing a motorized spiral enteroscope. This enteroscope is unique because it incorporates a user-operated motor to rotate the power spiral tube, which is mounted on the endoscope's insertion tube and relies primarily on the pleating of the small bowel onto the scope with minimal pushing.

Representatives from Japan, Europe, and the United State repeated experiments in vivo and in vitro with medical device manufacturers, and clinical trials were conducted for the first time in Europe. As a representative of Japan, Tajiri was in charge of animal experiments and has participated as an advisor to clinical trials in Europe. This instrument is a safe and effective tool for the diagnosis and treatment of small bowel disease and has been available in Europe since 2018. We believe this instrument will become a standardized enteroscope. In addition, the procedure time is shorter than that of the conventional scope, and we anticipate that this technology will be applied to colonoscopy.

Educational Activity

Since 2014 the Japan Gastroenterological Endoscopy Society has been leading hands-on courses in China, and in 2018 we visited Dairen and Xiamen, where we gave lectures and performed therapeutic manipulation with animal models and live demonstrations. The young physicians being trained made remarkable progress in early cancer detection and diagnosis and endoscopic treatment. In Russia, Vietnam, Myanmar, Indonesia, and Brazil, we have been conducting similar activities. Hands-on courses have already been held in rural regions of Japan. We have visited and will visit the regions, to develop facilities where endoscopic diagnosis and treatment can be standardized. We will continue to conduct these supportive activities.

Publications

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