

Department of Innovative Interventional Endoscopy Research

Hisao Tajiri, *Professor*

Masato Mitsunaga, *Assistant Professor*

General Summary

This department was established in April, 2015, aiming at methodology of new endoscopic diagnosis and treatment, and also the development of apparatus, along with for the purpose of supporting and teaching to arrange the environment toward the standardization of endoscopic medicine not only in domestic but also in foreign facilities.

Research Activities

Endoscopic submucosal resection (ESD), which was developed in Japan, is followed by various improvements to conduct safely, promptly and accurately. Subsequently to ESD, new minimally invasive endoscopic treatments, such as endoscopic full thickness resection and endoscopic treatment applying robotic technology are being developed one after another. Now Japan is reaching an aging society at unprecedented speed among other countries, while its population is decreasing. Japanese world-class technology cultivated from experience of craftsmanship is a base for the development of endoscopy and even more growth is expected in the future. Especially minimally invasive endoscopic treatments with less burden to patients contribute significantly. While social demand for endoscopic medicine is growing, it is meaningful to propel new methodology for endoscopic treatment and development of instruments for it.

This department plays a role, in addition to the study of the above, to support formulation of educational structure of endoscopy for the doctors not only in Japan but in Asia, Russia, Middle East, and South America.

Endoscopic optical molecular imaging for cancer

Molecular targeted therapies, such as monoclonal antibodies, were widely used for various cancers recently, leading to improve patients' outcomes. Photoimmunotherapy (PIT) is a new class of molecular targeted cancer theranostics, which employs monoclonal antibody conjugated to a photosensitizer, IR700, that is activated by focal near-infrared (NIR) light irradiation leading to necrotic cell death by cell membrane rupture where antibody-IR700 conjugates binds to target membrane proteins specifically. In this study, we developed a new type of PIT agents targeting VEGFR-2 expressed on vascular endothelium in a tumor and evaluated the feasibility by comparing conventional membrane targeted PIT in vitro and in vivo. HER2-positive human gastric cancer cells, NCI-N87, were used for the experiments. HER2-targeting trastuzumab and VEGFR-2-targeting ramucirumab were conjugated to IR700. Cells were treated with mAb-IR700 conjugates followed by NIR light irradiation after washing the cells. Mouse tumor xenograft models were created for in vivo PIT. Tumor-bearing mice were randomized and treated with mAb-IR700 con-

jugates followed by NIR light irradiation under anesthesia. PIT utilizing ramucirumab-IR700 conjugates did not induce phototoxic effect in vitro because of the absence of membranous expression of VEGFR-2 in NCI-N87 cells, while PIT utilizing trastuzumab-IR700 conjugates induced rapid phototoxic effect because of the strong membranous expression of HER2 in NCI-N87 cells. By contrast, antitumor effects were observed in NCI-N87 xenograft tumors in vivo utilizing both ramucirumab- and trastuzumab-IR700 conjugates followed by NIR light irradiation. As VEGFR-2 is upregulated in many types of solid cancers, this method may be considered as being applicable to various types of cancers in future clinical settings.

Development of automatic insertion endoscope equipment

We are working on the development of a motorized spiral enteroscope. This is unique in that 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 pleating of small bowel onto the scope with minimal pushing. The system's control unit monitors the amount of torque which the rotating spiral assembly applies to the tissue by observing the system's force gauge. This display provides the operator with visual indication of the direction and the force of rotation throughout the examination.

Representatives from Japan, Europe, and the US repeated experiments in vivo and in vitro with medical device manufacturers, and clinical trials were conducted for the first time in Europe. As representative of Japan, Tajiri was in charge of animal experiments and have participated as advisor to clinical trials in Europe. In 132 cases using this device for 140 times, the success rate of insertion is 97% (137/140), the average insertion time is 29 minutes from the oral to the Treitz ligament, 416 minutes to the terminal end, and the average withdrawal time is 15 minutes. As for the complications, there were 17 cases (mucosal damage, epigastric pain, fever, etc.). There was a delayed perforation in one case, but it was a patient who had a treatment such as ablation therapy. This instrument is a safe and effective tool for the diagnosis and treatment of small bowel disease, and it is convinced that it will be an enteroscopy that is global standard in the future. In addition, the procedure time is also shorter than that of the conventional scope, and we anticipate in the future this technology can be applied for colonoscopy.

Educational Activity

In China, the Japan Gastroenterological Endoscopy Society has been leading the hands-on courses already since 2014, while in 2017, we visited the Sichuan Academy of Medical Science & Sichuan Provincial People's Hospital in Chengdu and the Cancer Hospital Chinese Academy of Medical Science in Beijing, giving lectures, therapeutic manipulation with animal models, and live demonstrations. The young doctors to be trained made remarkable progress in early cancer detection and diagnosis and also in endoscopic treatment. In Russia, Vietnam, Myanmar, Indonesia, and Brazil, we have been conducting similar activities. Domestically, hands-on courses have been already being held in rural regions. We have visited and will visit directly to the regions, to develop facilities where standardization of endoscopic diagnosis and treatment can be established. We are positively conducting these supportive activities continuously from now on.

Publications

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Reviews and Books

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