

## Department of Surgery

### Division of Digestive Surgery

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### General Summary

The delivery of research papers is supported by writing skills in addition to the ability to accomplish the study. More efforts to read scientific papers are necessary to improve writing skills and to ensure patient safety. All surgeons should keep in mind that research based on anatomic, pathologic, and physiologic principles, in combination with animal experimentation, makes it possible to develop complex operative procedures and to become the consummate surgeon, as stated in the last Southern Surgical Association Presidential Address (J Am Coll Surg 2015; 220(4); 387-395).

### Research Activities

#### *Upper gastrointestinal surgery*

We evaluated the effect of neoadjuvant chemotherapy for advanced esophageal cancer, and also considered the second best treatment for refractory cases. We continue to investigate how to reduce the postoperative complications after esophagectomy. Intraoperative thermal imaging system and recurrent nerve monitoring are used to assess the viability of the gastric tube and recurrent nerve, respectively to prevent anastomosis-related complications and postoperative recurrent nerve palsy. We also started to analyze upper esophageal sphincter and residual esophageal motility with High Resolution Manometry (HRM). Basic research for new molecular markers specific in esophageal cancer using DNA chips is now under investigation.

We had performed many laparoscopic operations for esophageal motor disorders and Per-

Oral Endoscopic Myotomy (POEM) for achalasia. The pre- and post-operative pathophysiology and the effect of these therapies were investigated using HRM and multichannel intraluminal impedance pH monitoring. All circumferential myotomy was introduced for achalasia with severe chest pain since 2017. The treatment for patients with achalasia is selected case-by-case with informed consent.

We developed SNNS using infrared ray endoscopic system for the first time in the world. Minimum invasive surgery with curability became possible under this system. In basic research of gastric cancer, we had conducted surveying biological cancer behavior using immunohistochemical and RT-PCR methods, which revealed that ZKSCAN3 was an independent prognostic factor for relapse-free survival and a novel prognostic biomarker for patients with gastric cancer. Postgastrectomy syndrome comprises specific symptoms after gastrectomy and is a target for treatment. To decrease the incidence and severity of postgastrectomy syndrome and to maximize residual gastric function, several types of limited gastric resection with refined techniques of reconstruction have been attempted. In addition, multiple tests of post-gastrectomy gastrointestinal function are performed to evaluate various types gastrectomy procedures.

In 2017 we conducted five sleeve gastrectomies for morbid obesity, for which the surgical outcome was satisfactory.

#### *Lower gastrointestinal surgery*

In collaboration with the Department of Internal Medicine we hold conference regularly and update the database of chemotherapy to examine combined therapy for colorectal cancer. We started studies on anal function using Stationary 3D-manometry. Together with the Department of Biochemistry, we are committed to construct a complementary DNA library from the surgical specimens of colorectal cancer to analyze the expression of intracellular signal molecules that are associated with progression and growth of cancer. As a first step of the project, the following basic research will be started: analysis of the cell-cycle regulation and dual-specificity tyrosine-(Y)-phosphorylation-regulated kinase 2 (DYRK2) in relation to c-jun/c-myc phosphorylation. By correlating with the clinical database, the relationship between the stage of colorectal cancer and the expression of DYRK2 and associated genes is investigated. We performed three-dimensional culture with a colorectal cancer specimen to form so-called 'organoid'. We started the basic research on the mechanism of drug action using the 'organoid'. Our aim is to develop methods to identify factors associated chemo-resistance and to choose appropriate anticancer drugs for each patient. When chemoradiation therapy is given to patients with rectal cancer, radiation causes microenvironmental inflammation around cancer cells and promotes the secretion of matrix metalloproteinase (MMP) and nuclear factor kappa B (NF- $\kappa$ B). In addition, NF- $\kappa$ B is reported to directly induce MMP. The basement membrane is dissolved by MMP, and then cancer cells enter the bloodstream and metastasize to other organs. Therefore, suppression of MMP might prevent metastasis after surgery. We will examine whether down-regulation of NF- $\kappa$ B decreases the recurrence and metastasis of colon cancer.

*Hepatobiliary and pancreatic surgery*

The outlines of our main research activities are as follows:

- 1) Living donor liver transplantation (LDLT) and regenerative medicine
- 2) Treatment for hepatocellular carcinoma (HCC) and control of recurrence
- 3) Chemotherapy for pancreatic and biliary cancer
- 4) Expansion of surgical indications for multiple hepatic tumors
- 5) Laparoscopic surgery for the liver, biliary tree, pancreas, and spleen
- 6) Navigation surgery for hepatobiliary and pancreatic diseases
- 7) Nutritional therapy for patients with cancer (enhanced recovery after surgery)
- 8) Control of surgical site infection
- 9) Effect of preoperative treatment of eltrombopag on splenectomy for idiopathic thrombocytopenic purpura
- 10) Molecular-targeting therapy for advanced HCC
- 11) Analyses of new biological tumor markers for HCC

The first LDLT was successfully performed for a patient with postnecrotic cirrhosis and HCC in February 2007. Our first blood type ABO-incompatible LDLT (15th LDLT) was performed for a patient with primary biliary cirrhosis in June 2015. Our 22th LDLT was performed for a patient with primary sclerosing cholangitis in October 2017. All 22 recipients were discharged in good condition on postoperative day 15 to 146, and donors were discharged on postoperative day 7 to 26 and returned to preoperative status. We are planning to extend the indication of LDLT to acute hepatic failure. The 5-year cumulative overall survival rate of HCC after hepatic resection in our department is 71.5%, which is significantly better than the mean survival rate in Japan (56.8%). We have performed clinical trials for pancreatic cancer and biliary tract cancer. Ongoing trials for pancreatic cancer evaluate combination chemotherapy with gemcitabine, S-1 with regional arterial infusion of nafamostat mesilate for advanced pancreatic cancer, and gemcitabine in combination with regional arterial infusion of nafamostat mesilate as an adjuvant chemotherapy after pancreatectomy. A current trial for advanced biliary tract cancer is evaluating chemotherapy with S-1 every other day in combination with gemcitabine/cisplatin. We have also performed extended liver resections as a conversion therapy for multiple metastatic tumors of the liver, mainly originating from colorectal cancers. Furthermore, laparoscopic surgery, including hand-assisted laparoscopic surgery and laparoscopy-assisted, i.e., hybrid surgery, has gradually been expanded for hepatobiliary, pancreatic, and splenic diseases because of its lower invasiveness. Navigation for liver resection has been paid for by national health insurance since April 1, 2012, and the Vincent navigation system was introduced in July 2012. Biliary and pancreatic navigation surgery for either open or laparoscopic surgery is performed with the Institute for High Dimensional Medical Imaging Research Center. With regard to nutritional therapy for patients who have cancer, clinical and experimental studies are examining enhanced recovery after surgery, surgical site infection, and the use of eltrombopag before laparoscopic splenectomy for idiopathic thrombocytopenic purpura.

*Digestive surgery (comprehensive)*

We have been pursuing clinical research at four university hospitals. Since 2014, 6 origi-

nal articles in English have been published.

Also, since the control of surgical infection is a common and important issue, we have assigned staff in charge of surgical infection at each university hospital and are encouraging reduction of surgical infection. Three of the 4 hospitals are participating in JANIS supervised by the Japanese Ministry of Health, Labor and Welfare, and three of the 4 hospitals are teaching hospitals approved by the Japan Society for Surgical Infection. Although active in presentations at national conferences, publications are limited to case reports, and introduction of good clinical protocols and publication of original articles are needed.

## Publications

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