Department of Surgery
Division of Digestive Surgery

Katsuhiko Yanaga, *Professor*
Norio Mitsumori, *Professor*
Hideyuki Kashiwagi, *Visiting Professor*
Masahiko Otsuka, *Visiting Professor*
Tetsuji Fujita, *Associate Professor*
Yoshio Ishibashi, *Associate Professor*
Satoru Yanagisawa, *Associate Professor*
Yuichi Ishida, *Associate Professor*
Shuzo Kono, *Assistant Professor*
Masaichi Ogawa, *Assistant Professor*
Katsunori Nishikawa, *Assistant Professor*
Shuichi Fujioka, *Assistant Professor*
Yasuro Futagawa, *Assistant Professor*
Katsuhito Suwa, *Assistant Professor*
Hiroaki Shiba, *Assistant Professor*
Kazuhiko Yoshida, *Professor*
Tomoyoshi Okamoto, *Professor*
Nobuyoshi Hanyu, *Visiting Professor*
Kenji Ikeuchi, *Visiting Professor*
Takeyuki Misawa, *Associate Professor*
Noburo Omura, *Associate Professor*
Kouji Nakada, *Associate Professor*
Hidejirou Kawahara, *Associate Professor*
Yoshiyuki Hoya, *Assistant Professor*
Naoto Takahashi, *Assistant Professor*
Shigeki Wakiyama, *Assistant Professor*
Ken Eto, *Assistant Professor*
Fumiaki Yano, *Assistant Professor*
Teruyuki Usuba, *Assistant Professor*
Atsuo Shida, *Assistant Professor*

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 evaluate the pathogenesis of primary esophageal motor functional disorders, especially achalasia and gastroesophageal reflux disease, using high-resolution manometry and multichannel intraluminal impedance pH monitoring. We have performed many laparoscopic operations and obtained good results. Recently, we introduced reduced port surgery and needlescopic surgery for minimally invasive surgery.
Basic research in esophageal cancer led us to find molecular markers that indicate patients' prognoses. We aimed to investigate the significance of small ubiquitin-like modifier 1 (SUMO-1) expression in esophageal cancer as a prognostic factor. We found that overexpression of SUMO-1 correlated with malignancy-associated pathological findings and poor prognoses.
We continue to assess the viability of the gastric tube with an intraoperative thermal imaging system during esophagectomy. The correlation between suitable graft construction and postoperative complications of a graft has been investigated. We also continue to

examine intraoperative recurrent nerve monitoring to prevent postoperative recurrent nerve palsies and to predict the degree of paralysis after surgery.
Limited surgery for gastric cancer may be aided by a search for sentinel lymph nodes, which are thought to be the first site of cancer cell metastasis. Lymphatic vessels and lymph nodes can easily be identified with an infrared endoscope. We were the first in the world to develop this procedure in 2001 and have used this technique for more than 300 patients with early gastric cancer. Regarding this procedure using an infrared endoscope, we have published 9 original or review articles in English. In addition, we have surveyed immunohistochemical staining and the expression of messenger RNA in tumor cells and evaluated the relationship between these expressions and clinicopathological findings. Such research revealed that zinc finger protein (ZNF) 217 is an independent prognostic factor for relapse-free survival and a novel prognostic biomarker in 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, after patients have undergone gastrectomy, multiple tests of postoperative gastrointestinal function are performed to evaluate various gastrectomy procedures and to inform the patients of the appropriate management.

Lower gastrointestinal surgery
We have reported the beneficial cosmetic outcomes of a novel and patient-friendly ileostomy procedure. This procedure uses the umbilical fossa for placement of a defunctioning ileostomy followed by a simple umbilicoplasty for ileostomy closure. In collaboration with the Department of Internal Medicine we have started to register chemotherapy to develop a database. Together with the Department of Biochemistry we are committed to constructing 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. 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 manifestation of DYRK2 and associated genes is investigated. When chemoradiation therapy is performed for rectal cancer, radiation causes microenvironmental inflammation around cancer cells and promotes the secretion of matrix metalloproteinase (MMP) and nuclear factor kapp B (NF-κB). In addition, NF-κB is reported to directly induce MMP. The basement membrane is dissolved by MMP, and cancer cells enter the bloodstream and metastasize to another organ. Therefore, suppression of MMP might prevent metastasis after surgery. We will examine whether NF-kB 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 on February 9, 2007. Our first blood type ABO-incompatible LDLT (15th LDLT) was performed for a patient with primary biliary cirrhosis on June 5, 2015. Our 18th LDLT was performed for a patient with primary biliary cirrhosis on November 6, 2015. All 18 recipients were discharged in good condition on postoperative day 15 to 70 , 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 75%, 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 are evaluating 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. 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 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 thrombocytonpenic purpura. Also, we have started to apply molecularly targeted therapy to advanced HCC and to analyze new biological markers for HCC.

Publications

Matsumoto A, Watanabe M, Shigaki H, Nishida K, Mine S, Sano T, Yanaga K. Efficacy of staged treatment strategy for patients with synchronous double cancers of the esophagus and

head and neck: a retrospective study. *World J Surg.* 2016; **40:** 388–94.

Yamamoto SR, Yano F, Omura N, Tsuboi K, Hoshino M, Kashiwagi H, Yanaga K. Efficacy of laparoscopic Toupet fundoplication for non-erosive reflux disease assessed by combined multichannel intraluminal impedance-pH monitoring. *Esophagus.* 2015; **12:** 219–24.

Fujisaki M, Takahashi N, Yanaga K. Analysis of epidermal growth factor receptor expression and KRAS mutations in gastric cancer: a single-institution retrospective analysis. *Jikeikai Medical Journal.* 2015; **62:** 79–87.

Tsuboi K, Omura N, Yano F, Hoshino M, Yamamoto SR, Akimoto S, Masuda T, Kashiwagi H, Yanaga K. Identification of risk factors for mucosal injury during laparoscopic Heller myotomy for achalasia. *Surg Endosc.* 2016; **30:** 706–14.

Kawahara H, Watanabe K, Enomoto H, Tomoda M, Akiba T, Yanaga K. Sentinel node navigation surgery for lower rectal cancer. *Anticancer Res.* 2015; **35:** 3489–93.

Kawahara H, Misawa T, Wanatabe K, Hojo S, Ishida K, Akiba T, Yanaga K. Feasibility of single-incision laparoscopic surgery plus one assist port for anterior resection. *Anticancer Res.* 2016; **36:** 467–70.

Ogawa M, Ichiba N, Watanabe M, Yanaga K. The usefulness of diffusion MRI in detection of lymph node metastases of colorectal cancer. *Anticancer Res.* 2016; **36:** 815–9.

Suzuki T, Suwa K, Ogawa M, Eto K, Kawahara H, Fujita T, Ikegami M, Yanaga K. Adjuvant chemotherapy for the perineural invasion of colorectal cancer. *J Surg Res.* 2015; **199:** 84–9.

Nakamura M, Wakabayashi G, Miyasaka Y, Tanaka M, Morikawa T, Unno M, Tajima H, Kumamoto Y, Satoi S, Kwon M, Toyama H, Ku Y, Yoshitomi H, Nara S, Shimada K, Yokoyama T, Miyagawa S, Toyama Y, Yanaga K, Fujii T, Kodera Y; Study Group of JHBPS.; JSEPS., Tomiyama Y, Miyata H, Takahara T, Beppu T, Yamaue H, Miyazaki M, Takada T. Multicenter comparative study of laparoscopic and open distal pancreatectomy using propensity score-matching. *J Hepatobiliary Pancreat Sci.* 2015; **22:** 731–6.

Toyama Y, Yoshida S, Saito R, Iwase R, Haruki K, Okui N, Shimada J, Kitamura H, Matsumoto M, Yanaga K. Efficacy of a half-grip technique using a fine tip LigaSure™, Dolphin Tip Sealer/Divider, on liver dissection in swine model. *BMC Res Notes.* 2015; **8:** 362.

Shiba H, Wakiyama S, Futagawa Y, Iida T, Matsumoto M, Haruki K, Ishida Y, Misawa T, Yanaga K. Assessment of graft selection criteria in living-donor liver transplantation: the Jikei experience. *Int Surg.* 2015; **100:** 1229–32.

Funamizu N, Lacy CR, Kamada M, Yanaga K, Manome Y. MicroRNA-203 induces apoptosis by upregulating Puma expression in colon and lung cancer cells. *Int J Oncol.* 2015; **47:** 1981–8.

Furukawa K, Shiba H, Shirai Y, Horiuchi T, Iwase R, Haruki K, Fujiwara Y, Misawa T, Yanaga K. Negative impact of preoperative endoscopic biliary drainage on prognosis of pancreatic ductal adenocarcinoma after pancreaticoduodenectomy. *Anticancer Res.* 2015; **35:** 5079–83.

Haruki K, Shiba H, Horiuchi T, Shirai Y, Iwase R, Fujiwara Y, Furukawa K, Misawa T, Yanaga K. Preoperative change in peripheral blood monocyte count may predict long-term outcomes after pancreaticoduodenectomy for bile duct cancer. *Anticancer Res.* 2015; **35:** 4961–6.

Haruki K, Shiba H, Horiuchi T, Shirai Y, Iwase R, Fujiwara Y, Furukawa K, Misawa T, Yanaga K. Neutrophil to lymphocyte ratio predicts therapeutic outcome after pancreaticoduodenectomy for carcinoma of the ampulla of Vater. *Anticancer Res.* 2016; **36:** 403–8.

Shirai Y, Shiba H, Sakamoto T, Horiuchi T, Haruki K, Fujiwara Y, Futagawa Y, Ohashi T, Yanaga K. Preoperative platelet to lymphocyte ratio predicts outcome of patients with pancreatic ductal adenocarcinoma after pancreatic resection. *Surgery.* 2015; **158:** 360–5.

Shirai Y, Shiba H, Iwase R, Haruki K, Fujiwara Y, Furukawa K, Uwagawa T, Ohashi T, Yanaga K. Dual inhibition of nuclear factor kappa-B and Mdm2 enhance the antitumor effect of radiation therapy for pancreatic cancer. *Cancer Lett.* 2016; **370:** 177–84.

Shiba H, Hashimoto K, Kelly D, Fujiki M, Quintini C, Aucejo F, Uso TD, Yerian L, Yanaga K, Matsushima M, Eghtesad B, Fung J, Miller C. Risk stratification of allograft failure secondary to hepatitis C recurrence after liver transplantation. *Hepatol Res.* 2016; **46:** 1099–106. Epub 2016 Mar 6.

Reviews and Books

Okamoto T, Onda S, Yanaga K, Suzuki N, Hattori A. Clinical application of navigation surgery using augmented reality in the abdominal field. *Surg Today.* 2015; **45:** 397–406.

Tsuboi K, Omura N, Yano F, Hoshino M, Yamamoto SR, Akimoto S, Masuda T, Kashiwagi H, Yanaga K. Data analyses and perspectives on laparoscopic surgery for esopahgeal achalasia. *World J Gastroenterol.* 2015; **21:** 10830–9.