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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 effects of preoperative chemotherapy with fluorouracil, cisplatin, and docetaxel for resectable advanced esophageal cancer on postoperative outcomes and long-term survival. We continue to study how to reduce complications after esophagectomy. An intraoperative thermal imaging system and recurrent nerve integrity monitoring are used to assess the viability of the gastric tube to prevent anastomosis-related complications and postoperative recurrent nerve palsy, retrospectively. Clarifying the usefulness of a near-infrared fluorescence imaging system for the viability of the gastric tube is also planned. We had performed many laparoscopic operations for esophageal motor disorders and performed per-oral endoscopic myotomy for achalasia. The preoperative and postoperative pathophysiology and the effects of these treatments were investigated with high-

resolution manometry and multichannel intraluminal impedance pH monitoring. The significance of completely circumferencial myotomy for achalasia with severe chest pain is being evaluated.
We developed sentinel node navigation surgery using an infrared ray endoscopic system for the first time in the world. By means of this system, minimally invasive surgery with curability became possible.
Postgastrectomy syndrome comprises specific symptoms 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, such as the Postgastrectomy Syndrome Assessment Study 37, are performed to evaluate the postgastrectomy gastrointestinal function of various gastrectomy procedures.
In basic research on esophageal cancer and gastric cancer, we have surveyed biological cancer behavior by means of DNA chips and immunohistochemical and reverse transcriptase-polymerase chain reaction methods.
Treatment for obesity is performed by a team (dietician, pharmacist, and physicians), and patients with resistant morbid obesity undergo surgery. The change of gastroesophageal reflux between presleeve and postsleeve gastrectomy is assessed with 24-hour pH monitoring.

Lower gastrointestinal surgery
In collaboration with the Department of Internal Medicine we hold conferences regularly and examine multimodal therapy for colorectal cancer. We have been investigating operative methods, complications, and histopathological factors with a database of patients with colorectal cancer. We started studies of anal function by means of stationary 3-dimensional manometry and aim at specific treatment for anal disease and postoperative complications. We are developing a complementary DNA library from surgical specimens and preparing a database for basic research.
Together with the Department of Biochemistry, we analyzed the expression of intracellular signal molecules that are associated with the progression and growth of cancer. We analyzed dual-specificity tyrosine-(Y)-phosphorylation-regulated kinase 2 (DYRK2) involved in the induction of apoptosis and the control of the cell cycle. By correlating with the database, we investigated the relationship of the expression of DYRK2 with associated genes. We prepared 3-dimensional cultures with colorectal cancer specimens to form so-called "organoid," with which we started basic research on the mechanism of drug action. Our aim is to develop methods to choose the appropriate medicines before treatment.
When chemoradiation therapy is given to patients with colon cancer, radiation causes microenvironmental inflammation around cancer cells and promotes the secretion of nuclear factor kappa B (NF-κB), which is associated with the growth and invasion of tumor cells and with angiogenesis. Recombinant thrombomodulin is known to have antitumor effects by inhibiting NF-κB for pancreas cancer cell lines in previous studies. We examined whether recombinant thrombomodulin has antitumor effects on colorectal cancer cell lines that are resistant to chemotherapy by inhibiting activation of NF-κB.

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 cancers
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 treatment with eltrombopag before splenectomy for idiopathic thrombocytopenic purpura
10. Molecular-targeting therapy for advanced HCC
11. Analyses of new biological tumor markers for HCC

Since 2007 we have performed LDLT for 22 patients, including 3 patients who underwent ABO-incompatible LDLT. All 22 recipients were discharged in good condition on postoperative days 15 to 146, the donors were discharged on postoperative days 7 to 26, and all donors have returned to preoperative status. We are planning to extend the indications of LDLT to acute hepatic failure. The outcome of patients who undergo HCC resection at our institution is much better than the national average. To reduce postoperative complications, we investigated the risk factors and effective treatments for postoperative portal vein thrombosis and venous thromboembolism. 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. Current trials for advanced biliary tract cancer include chemotherapy with S-1 every other day in combination with gemcitabine/cisplatin. We have also performed extended liver resection 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 surgery, i.e., hybrid surgery, has gradually been expanded for hepatobiliary, pancreatic, and splenic diseases because of its lower invasiveness. We have used the SYNAPSE VINCENT medical imaging system (Fujifilm Medical Systems) for 3-dimensional visualization and preoperative planning for operative safety. Furthermore, hepatobiliary and pancreatic navigation surgery using augmented reality for either open or laparoscopic surgery is performed at Daisan Hospital in collaboration with the Institute for High Dimensional Medical Imaging Research Center. With regard to nutritional therapy for patients with 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 4 affiliated university hospitals. Since 2014,

we have had 6 articles published in English.
Because surgical infection is a common problem that is important to control, we have assigned members of the staff to be in charge of surgical infection at each university hospital and are encouraging the reduction of surgical infection. Three of the 4 hospitals are participating in the Japan Nosocomial Infections Surveillance program supervised by the Japanese Ministry of Health, Labour and Welfare, and 3 of the 4 hospitals are teaching-hospitals approved by the Japan Society for Surgical Infection. Although we are active in presentations at national conferences, we must publish articles other than case reports.

Publications

Eto K, Kosuge M, Ohkuma M, Noaki R, Neki K, Ito D, Sugano H, Takeda Y, Yanaga K. Defunctioning ileostomy is a key risk factor for small bowel obstruction after colorectal cancer resection. *Anticancer Res.* 2018; **38:** 1789-95.

Kawahara H, Mouri T, Ishida K, Matsumoto N, Akiba T, Yanaga K. Usefulness of TAS-102 as third-line chemotherapy for metastatic colorectal cancer. *Anticancer Res.* 2018; **38:** 2419-22.

Takeda Y, Akiyoshi T, Matsueda K, Fukuoka H, Ogura A, Miki H, Hiyoshi Y, Nagasaki T, Konishi T, Fujimoto Y, Fukunaga Y, Ueno M. Skeletal muscle loss is an independent negative prognostic factor in patients with advanced lower rectal cancer treated with neoadjuvant chemoradiotherapy. *PLoS One.* 2018; **13:** e0195406.

Kawahara H, Hiramoto Y, Takeda M, Matsumoto T, Misawa T, Yanaga K. Long-term outcome of adjuvant chemotherapy with S-1 consisting of 3-week administration followed by 1-week rest for stage III colorectal cancer. *Surg Gastroenterol Oncol.* 2018; **23:** 330-5.

Sugano H, Shirai Y, Horiuchi T, Saito N, Shimada Y, Eto K, Uwagawa T, Ohashi T, Yanaga K. Nafamostat mesilate enhances the radiosensitivity and reduces the radiation-induced invasive ability of colorectal cancer cells. *Cancers.* 2018; **10.** pii: E386.

Suwa K, Okamoto T, Yanaga K. Is fascial defect closure with intraperitoneal onlay mesh superior to standard intraperitoneal onlay mesh for laparoscopic repair of large incisional hernia? *Asian J Endosc.* 2018; **11:** 378-84.

Narihiro S, Suwa K, Ushigome T, Ohtsu M, Ryu S, Shimoyama Y, Okamoto T, Yanaga K. Safety and efficacy of trifluridine-tipiracil hydrochloride oral combination (TAS-102) in patients with unresectable colorectal cancer. *In Vivo.* 2018; **32:** 1643-6.

Omura N, Yano F, Tsuboi K, Hoshino M, Yamamoto SR, Akimoto S, Masuda T, Kashiwagi H, Yanaga K. Surgical results of laparoscopic Toupet fundoplication for gastroesophageal reflux disease with special reference to recurrence. *Esophagus.* 2018; **15:** 217-23.

Nishikawa K, Fujita T, Hasegawa Y, Tanaka Y, Matsumoto A, Mitsumori N, Yanaga K. Association of level of anastomosis and anastomotic leak after esophagectomy in anterior mediastinal reconstruction. *Esophagus.* 2018; **4:** 231-8.

Takahashi N, Kanda M, Yoshikawa T, Takiguchi N, Fujitani K, Miyamoto K, Ito Y, Takayama O, Imano M, Mitsumori N, Sakamoto J, Morita S, Kodera Y. A randomized phase II multicenter trial to explore efficacy of weekly intraperitoneal in comparison with intravenous paclitaxel administered immediately after gastrectomy to the patients with high risk of peritoneal recurrence: final results of the INPACT trial. *Gastric Cancer.* 2018; **21:** 1014-23.

Tsuboi K, Omura N, Yano F, Hoshino M, Yamamoto SR, Akimoto S, Masuda T, Kashiwagi H, Yanaga K. Impact of preoperative balloon dilatation on outcomes of laparoscopic surgery in young patients with esophageal achalasia. *Esophagus.* 2018; **15:** 39-46.

Matsumoto A, Kanaoka Y, Baba T, Takizawa R, Hara M, Maeda K, Nishikawa K, Suzuki Y, Yanaga K, Ohki T. Result of thoracic endovascular aortic repair for patients with esophageal cancer. *World J Surg.* 2018; **42:** 1551-8.

Yuda M, Nishikawa K, Takahashi K, Kurogochi T, Tanaka Y, Matsumoto A, Tanishima Y, Mitsumori N, Yanaga K. A strategy for using intraoperative nerve monitoring during esophagectomy to prevent recurrent laryngeal nerve palsy. *Anticancer Res.* 2018; **38:** 1563-7.

Uno K, Seki Y, Kasama K, Wakamatsu K, Hashimoto K, Umezawa A, Yanaga K, Kurokawa Y. Mid-term results of bariatric surgery in morbidly obese Japanese patients with slow progressive autoimmune diabetes. *Asian J Endosc Surg.* 2018; **11:** 238-43.

Kurogochi T, Honda M, Yamashita K, Hayami M, Okamura A, Imamura Y, Mine S, Watanabe M. Safety and efficacy of preoperative chemotherapy followed by esophagectomy versus upfront surgery for resectable esophageal squamous cell carcinoma. *Surg Today.* 2019; **49:** 150-7.

Funamizu N, Okamoto T, Kumamoto T, Kazama T, Watanabe A, Fujioka S, Yanaga K. Effective method of gallbladder retraction for single incision laparoscopic cholecystectomy. *Asian J Endosc Surg.* 2019; **12:** 222-6. Epub 2018 Dec

13.
Funamizu N, Lacy CR, Kamada M, Yanaga K, Manome Y. MicroRNA-200b and -301 are associated with gemcitabine response as biomarkers in pancreatic carcinoma cells. *Int J Oncol.* 2019; **54:** 991-1000.
Matsumoto M, Wakiyama S, Shiba H, Haruki K, Futagawa Y, Ishida Y, Misawa T, Yanaga K. Usefulness of aspartate aminotransferase to platelet ratio index as a prognostic factor following hepatic resection for hepatocellular carcinoma. *Mol Clin Oncol.* 2018; **9:** 369-76.
Suzuki F, Fujiwara Y, Hamura R, Haruki K, Sakamoto T, Shiba H, Yanaga K. Combination of distance from superior mesenteric artery and serum CA19-9 as a novel prediction of local recurrence in patients with pancreatic cancer following resection. *Anticancer Res.* 2019; **39:** 1469-78.
Fujiwara Y, Sun Y, Torphy RJ, He J, Yanaga K, Edil BH, Schulick RD, Zhu Y. Pomalidomide inhibits PD-L1 to promote anti-tumor immunity. *Cancer Res.* 2018; **78:** 6655-65.
Fujiwara Y, Haruki K, Shiba H, Hamura R, Shirai Y, Furukawa K, Gocho T, Yanaga K. The comparison of inflammation-based prognostic scores in patients with extrahepatic bile duct cancer after pancreaticoduodenectomy. *J Surg Res.* 2019; **238:** 102-12.
Okui N, Kamata Y, Sagawa Y, Kuhara A, Hayashi K, Uwagawa T, Homma S, Yanaga K. Claudin 7 as a possible novel molecular target for the treatment of pancreatic cancer. *Pancreatology.* 2019; **19:** 88-96.
Abe K, Uwagawa T, Haruki K, Takano Y, Onda S, Sakamoto T, Gocho T, Yanaga K. Effects of ω-3 fatty acid supplementation in patients with bile duct or pancreatic cancer undergoing chemotherapy. *Anticancer Res.* 2018; **38:** 2369-75.
Yasuda J, Okamoto T, Onda S, Futagawa Y, Yanaga K, Suzuki N, Hattori A. Novel navigation system by augmented reality technology using a tablet PC for hepatobiliary and pancreatic surgery. *Int J Med Robot.* 2018; **14:** e1921.
Haruki K, Shiba H, Saito N, Horiuchi T, Shirai Y, Fujiwara Y, Furukawa K, Sakamoto T, Yanaga K. Risk stratification using a novel liver functional reserve score of combination PT-INR and albumin in patients with hepatocellular carcinoma. *Surgery.* 2018; **164:** 404-10.
Haruki K, Shiba H, Shimada Y, Shirai Y, Iwase R, Fujiwara Y, Uwagawa T, Ohashi T, Yanaga K. Glycogen synthase kinase-3β activity plays a key role in the antitumor effect of nafamostat mesilate in pancreatic cancer cell. *Ann Gastroenterol Surg.* 2018; **2:** 65-71.
Iwase R, Suzuki Y, Yamanouchi E, Suzuki N, Imakita T, Tsutsui N, Odaira H, Yanaga K. Double percutaneous transesophageal gastrotubing (dPTEG) for gastric cancer: a pilot study. *J Surg Res.* 2018; **232:** 470-4.
Nakaseko Y, Haruki K, Shiba H, Horiuchi T, Saito N, Sakamoto T, Gocho T, Yanaga K. Impact of FFP transfusion on postoperative inflammation and prognosis of colorectal liver metastases. *J Surg Res.* 2018; **226:** 157-65.
Shirai Y, Saito N, Uwagawa T, Shiba H, Horiuchi T, Iwase R, Haruki K, Ohashi T, Yanaga K. Pomalidomide promotes chemosensitization of pancreatic cancer by inhibition of NF-κB. *Oncotarget.* 2018; **9:** 15292-301.
Saito N, Shirai Y (equal to first author), Uwagawa T, Horiuchi T, Sugano H, Haruki K, Shiba H, Ohashi T, Yanaga K. Pomalidomide enhanced gemcitabine and nab-paclitaxel on pancreatic cancer both in vitro and in vivo. *Oncotarget.* 2018; **9:** 15780-91.

Reviews and Books

Nakaseko Y, Ishizawa T, Saiura A. Fluorescence-guided surgery for liver tumors. *J Surg Oncol.* 2018; **118:** 324-31.