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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.

A boy who underwent surgery at a university hospital died in February 2014 after removal of a cervical lymphangioma due to acute circulatory failure 3 days after he had been transferred to the intensive care unit (ICU) and given propofol intravenously for approximately 70 hours. After the boy's death, the hospital admitted the use of propofol, which was prohibited to be used in children, and that from 2008 through 2013, 11 of their pediatric patients 14 years or younger had died during the treatment or within 30 days after leaving the ICU.

If the surgeons and anesthesiologists who treated the boy in the ICU had read a brief review article and statement in the *Canadian Medical Association Journal*, they would not have treated children with propofol. According to the article, published in 2002, the problem of propofol in children was first noted in 1992, when a report was published about 5 children with croup or bronchiolitis who were sedated with propofol and subsequently in an ICU and died of metabolic acidosis and myocardial failure. Sporadic cases of subsequently termed "propofol syndrome" were described in the literature, including a report in 1998 of 18 critically ill pediatric patients who had bradycardia, asystole, severe metabolic acidosis, lipemia, hepatomegaly, and rhabdomyolysis. Canadian product monographs of propofol infusions are now being updated to indicate that the agent is contraindicated for the sedation of children receiving intensive care.

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): 387-95).

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) expressions 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 are comparing the observation methods of fluorescence imaging and infrared absorption imaging. 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 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 assessed the stress of surgeons during laparoscopic surgery for colorectal cancer by measuring serum levels of adrenaline, noradrenaline, dopamine, adrenocorticotropic hormone, and cortisol. We are analyzing the data to clarify which factors are related to the stress of surgeons during an operation. We have published the cosmetic outcome of a novel and patient-friendly ileostomy procedure. In this procedure the umbilical fossa is used to place a defunctioning ileostomy, and a simple umbilicoplasty is used for ileostomy closure. A collaborative study with the Department of Urology to identify novel

cancer-related proteins in the gastrointestinal tract is still in progress. The relationships of copy number variation to recurrence and prognosis are evaluated after DNA is extracted from frozen specimens of colorectal cancer tissue, because copy number variation is likely to influence gene function. 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. We will also use a model of liver metastasis through the spleen with a colon carcinoma cell line in mice. Using this model, we plan to analyze factors involved in the development of metastasis. Cancer cells that cause epithelial-mesenchymal transition lose their cellular adhesion and escape into the blood flow by invading blood vessels before reaching the sites of metastasis as circulating cells. We therefore speculate that the control of epithelial-mesenchymal transition inhibits postoperative metastasis to distant sites. We will focus on signal transducer and activator of transcription 3(STAT3) and nuclear factor kappa B(NFKB), which cause inflammation in the cancer microenvironment, and investigate the inhibitory effect of epithelial-mesenchymal transition on recurrence and metastasis.

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 was performed for a patient with primary biliary cirrhosis on June 5, 2015 (15th LDLT). Our 16th LDLT was performed for a patient with nonalcoholic steatohepatitis on July 10, 2015. All 16 recipients were discharged in good condition on postoperative day 15 to 55, and all donors were returned to preoperative status and discharged on postoperative day 7 to 26. 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

76.7%, 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 had its indications gradually 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. Clinical and experimental studies are now evaluating nutritional therapy for patients with cancer, enhanced recovery after surgery, surgical site infection, and the use of eltrombopag before laparoscopic splenectomy for idiopathic thrombocytopenic purpura. Also, we have started to apply molecularly targeted therapy to advanced HCC and to analyze new biological markers for HCC.

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