

Department of Internal Medicine

Division of Gastroenterology and Hepatology

Masayuki Saruta, *Chairman and Professor*
 Atushi Hokari, *Associate Professor*
 Kazuhiko Koike, *Assistant Professor*
 Kan Uchiyama, *Assistant Professor*
 Akiyoshi Kinoshita, *Assistant Professor*
 Makoto Mitsunaga, *Assistant Professor*

Shigeo Koido, *Associate Professor*
 Tomohisa Ishikawa, *Associate Professor*
 Seiji Arihiro, *Assistant Professor*
 Mikio Kajihara, *Assistant Professor*
 Yuichi Torisu, *Assistant Professor*
 Tsunekazu Oikawa, *Assistant Professor*

Research Activities

Alimentary Tract

1. Examination of new biomarkers to assess disease activity in inflammatory bowel disease

(1) Prostaglandin E-major urinary metabolite as a reliable surrogate marker for mucosal inflammation in ulcerative colitis

We evaluated whether prostaglandin E-major urinary metabolite (PGE-MUM) can be used as a biomarker for ulcerative colitis (UC). Areas under the receiver operating characteristic curves of a simple clinical colitis activity index, the Mayo Endoscopic Score, and the Matts' grade (histologic activity) were each higher for PEG-MUM than for C-reactive protein.

The main advantage of PGE-MUM appears to be the differentiation of colonoscopic or histologic remission from active disease in UC. On the other hand, this marker was lower in patients with UC in remission than in healthy volunteer subjects. Compared with the C-reactive protein level, the PGE-MUM level demonstrated greater sensitivity for reflecting UC activity, especially in cases of histologic inflammation, and, thus, seems to be a better evaluator of mucosal healing.

On the basis of this result, we have performed a comparative trial to identify the most reliable marker among the immunochemical fecal occult blood test, fecal calprotectin, and PGE-MUM for detecting endoscopic mucosal healing in patients with UC.

(2) The clinical benefit of serum and tissue interleukin 6 to assess disease activity and severity in inflammatory bowel disease

Levels of serum interleukin 6 are relevant to UC, Crohn's disease, and systemic inflammatory responses. Herein, we hypothesize that serum and tissue levels of interleukin 6 are helpful for predicting treatment efficacy in UC and Crohn's disease, especially for the evaluation of anti-tumor necrosis factor (TNF) α antibody treatment.

2. Examination of the efficacy of anti-TNF- α antibodies for treating intestinal Behçet's disease

We reviewed the clinical background, effects, and outcome of treatment with an anti-TNF- α antibody for intestinal Behçet's disease at our hospital. The anti-TNF- α antibody was administered to 9 patients, who had been previously treated with infliximab (6 patients), adalimumab (2 patients), and infliximab followed by adalimumab (1 patient). All patients had ulcers surrounding the ileocecal region; treatment with prednisolone was

ineffective in all patients, but a secondary treatment with infliximab was effective in 6 of 7 patients. Treatment with infliximab eventually became secondarily ineffective in 5 patients, but 2 of the 2 other patients responded to treatment with adalimumab and were able to remain in remission.

3. The development of molecular-specific cancer theranostics

We have developed a method for molecular-specific phototherapy based on near-infrared fluorescence molecular imaging.

4. Examination of characteristics of primary gastrointestinal malignant lymphoma

Primary gastrointestinal malignant lymphomas account for 3% to 4% of extranodal lymphomas. We reviewed the clinical features (histotype, localization, and stage) of 166 cases that were histologically diagnosed as primary gastrointestinal malignant lymphoma in our hospital from October 2007 through September 2017. The types of lymphoma identified in these cases were mucosa-associated lymphoid tissue lymphoma, 49.4%; diffuse large B-cell lymphoma, 28.9%; follicular lymphoma, 14.5%; mantle cell lymphoma, 3.0%; Burkitt's lymphoma, 1.8%; and T-cell lymphoma, 2.4%. Twenty-one cases (13%) had lesions in multiple organs of the digestive tract, and duplication rate was significantly higher for mantle cell lymphoma, follicular lymphoma, diffuse large B-cell lymphoma than for mucosa-associated lymphoid tissue. In the case of these tumors, careful examination of the entire digestive tract is necessary.

5. Examination of biological malignancy analyzed from the rate of vascular invasion positivity in resected gastrointestinal tract neuroendocrine tumors

Gastrointestinal neuroendocrine tumors and neuroendocrine cancers are rare, but the number of patients is increasing. Gastrointestinal neuroendocrine tumors or neuroendocrine cancer was diagnosed in 144 patients (156 lesions), who underwent endoscopic or surgical resection in our hospital from February 2008 through October 2017. The degree of malignancy and the presence of vascular invasion and distant metastasis were examined, and the presence or absence of vascular invasion according to the tumor diameter was analyzed. The lesion was most often in the rectum (65.4%), followed by the duodenum (16.7%), the stomach (12.8%), the appendix (3.2%), the colon (1.3%), and the jejunum and ileum (0.6%). The treatments were 71.8% for endoscopic resection, 18.6% for surgical resection, 57.1% for Grade 1 (G1) neuroendocrine tumors, 8.3% for G2, 0.6% for G3, and others unknown. Vascular invasion occurred at a high rate, even for G1 neuroendocrine tumors with a diameter less than 10 mm, and included venous infiltration (15.6%) and lymphatic vessel infiltration (7.8%).

6. Comparison of endoscopic hemostasis and percutaneous arterial embolization re-bleeding rate for colonic diverticulum hemorrhage and retrospective examination of risk factors for re-bleeding

We compared the results of emergency endoscopy and percutaneous arterial embolization with interventional radiology (IVR) in 207 patients hospitalized for diverticulum hemorrhage from November 2012 through December 2017 and examined risk factors for re-bleeding. Of the 207 cases of diverticulum hemorrhage, 93 cases with massive hemorrhage were subjected to abdominal enhanced dynamic computed tomographic imaging, 34 cases showed active extravasation, and 14 cases were conducted prior to IVR. Endoscopy was performed prior to IVR in 193 of 207 cases, and IVR was also performed owing

to hemostasis difficulties in 12 cases. Re-bleeding was observed in 1 (3.8%) of 26 patients who underwent IVR and in 27 (14.8%) of 181 patients who underwent hemostasis or were follow-up with endoscopy alone. Risk factors for re-bleeding included hypertension, diabetes, renal failure, smoking history, and the administration of nonsteroidal anti-inflammatory, antithrombotic, or anticoagulant drugs; however, multivariate analysis showed that hypertension ($p = 0.0423$) and smoking ($p = 0.0486$) were independent risk factors.

7. Examination of irregular change of gastric mucosa newly generated after *Helicobacter pylori* eradication

After *H. pylori* is eradicated, although the development of gastric cancer is suppressed, irregular changes are generated in some cases, which makes the endoscopic diagnosis of gastric cancer difficult. From 2005 through 2017, 352 cases who received eradication therapy were reviewed, in which the eradication history was clear and gastric mucosal changes before and after eradication were able to be analyzed temporally and histologically with endoscopic images. Temporal changes in gastric mucosa after *H. pylori* eradication were classified into 3 groups based on the ease of endoscopic observation: Easy group (175 of 352 cases, 49.7%), Invariant group (87 of 352 cases, 24.7%), and Difficult group (90 of 352 cases, 25.6%). The groups did not differ significantly in patient age, sex, or gastric mucosal atrophy before *H. pylori* eradication. An increase of crypt epithelia was observed in 51.9% of cases, which is the main reason for the Difficult group, in the process of eliminating inflammation after *H. pylori* eradication and the mechanisms of repair and regeneration. On the basis of these results, we believe that gastric cancers will be more difficult to detect after eradication than before eradication in approximately one-fourth of the stomach and that careful endoscopy, similar to that of an infected stomach, is required.

8. Nutrition treatment for inflammatory bowel disease

We have found that an omega 3 diet, in which omega-3 polyunsaturated fatty acids are consumed, can maintain the remission of inflammatory bowel disease (IBD).

9. Study of fatty acids in Crohn's disease

In patients with Crohn's disease, various fatty acids were specifically altered in both plasma and erythrocytes, and plasma palmitic acid and the plasma Crohn's disease fatty acid index are potentially useful as new serological markers for Crohn's disease.

10. The study of mutations of the genes nudix hydrolase 15 (NUDT15) and inosine triphosphatase (ITPA) in patients with IBD

Although mutations of both the nudix hydrolase 15 and inosine triphosphatase genes are strongly associated with myelosuppression due to azathioprine in Japanese patients with IBD, metabolite concentrations are not changed.

11. Examination of a smoking habit and intestinal flora in patients with IBD

The effects of smoking habits on patients with IBD were examined and found to alter the intestinal flora.

12. Examination of the efficacy of indigo naturalis (*qing-dai*) in ulcerative colitis

The administration of indigo naturalis (*qing dai*) for 2 weeks significantly improves the clinical activity of ulcerative colitis.

Liver

1. The development of targeting therapy for cancer stem cells in liver cancers

The only curative treatments for primary liver cancers are surgical resection at an early stage. However, most cancers are diagnosed at advanced stages, when extant therapies are ineffective. Therefore, novel molecules that can become targets for future therapies are urgently needed to be identified. We have reported that spalt-like transcription factor 4 (SALL4) regulates the cell fate decision in hepatic stem/progenitor cells during normal liver development, is indicative of aggressiveness and poor prognosis, and maintains the stemness of cancer stem cells in liver cancers. Further analyses of cancer stem cell-mediated mechanisms might provide a novel future therapeutic strategy against liver cancers.

2. Pathogenesis and messenger RNA and micro RNA expression profiling of primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH)

The pathogenesis of autoimmune liver disease such as PBC and AIH is unknown. To investigate the pathogenesis and identify novel therapeutic targets, we performed microarray analysis of messenger (m) RNA and micro (mi) RNA expression in CD4+ T cells derived from 14 patients with primary biliary cholangitis (PBC). We found decreased expression of 4 miRNAs (miR-425, -181a, -181b, and -374b), which dysregulate T-cell antigen receptor signaling in PBC-CD4 T+ cells. In particular, the decreased expression of miR-425 strongly induced inflammatory cytokines via N-Ras upregulation in the T-cell antigen receptor signaling pathway, suggesting that the restoration of decreased miR-425 or the suppression of N-Ras is a promising immunotherapeutic strategy against PBC.

3. The relationship of nutritional condition and neuropsychological test results in patients with liver cirrhosis

Cases of liver cirrhosis complicate minimum hepatic encephalopathy and have caused traffic accidents and communication problems. Neuropsychological disturbance is typical of minimum hepatic encephalopathy. However, the diagnostic criteria for minimum hepatic encephalopathy have not been clarified. We studied the pathophysiological findings of minimum hepatic encephalopathy using a neuropsychological test and a food frequency questionnaire. Of patients with liver cirrhosis, 17% had abnormal results of the Digit Symbol Test. Such abnormal results are related to the Child-Pugh score, the serum albumin level, the branched chain amino acid and tyrosine ratio, nutrient intake as usual energy intake, and the fat energy ratio. Thus, nutrition support using the food frequency questionnaire might be a useful method to prevent minimum hepatic encephalopathy.

4. Investigation of the Frailty index in elderly patients with digestive disease

We evaluated whether simplified Frailty scores are associated with clinical outcomes or adverse outcomes after treatment in patients 80 years or older with digestive disease.

5. Examination of the dynamics of blood cholesterol levels before and after treatment with sofosbuvir and ribavirin for hepatitis C virus genotype 2

In its life cycle, hepatitis C virus (HCV) uses and affects the host's lipid metabolism. Infection with HCV reduces the total cholesterol level, but the change varies in degree depending on genotype, can be improved by elimination of HCV, and is reversible.

We investigated blood lipid dynamics before and after treatment of HCV genotype 2 with sofosbuvir and ribavirin. Levels of total cholesterol and low-density lipoprotein chole-

terol did not change during the treatment period but increased significantly 4 weeks after the end of treatment.

On the other hand, levels of high-density lipoprotein cholesterol increased 4 weeks after the start of treatment and remained elevated for 24 weeks after the end of treatment. In the group of patients in whom the hemoglobin level at the end of treatment had decreased from the baseline level by 2 g/dl or more, the total cholesterol level decreased during treatment but recovered to the same level as in the group in which hemoglobin had not decreased 4 weeks after the end of treatment.

6. Study of characteristics of acute-onset autoimmune hepatitis presenting central lobular zone and band necrosis and its fine classification

Because acute-onset autoimmune hepatitis (AIH) may lead to acute liver failure, it should be promptly diagnosed and treated. Recently, unlike typical AIH with interface hepatitis, AIH that causes central lobular zone and band necrosis (CZN) in the central vein area has been reported, and its laboratory findings and immunogenetic factors have been shown to differ from those of typical AIH. Therefore, we examined the clinical features of acute-onset AIH exhibiting CZN and found that this type of AIH was frequently associated with inflammation in the portal region with low levels of alkaline phosphatase and γ guanosine triphosphate and with low levels of immunoglobulin G, immunoglobulin M, and total bilirubin. In addition, we found that the frequency of HLA-DR9 was higher in cases of acute AIH with CZN than in cases without CZN and that the frequency of HLA-DR 13 tended to be higher in pure AIH phenotype than in mixed AIH phenotypes.

Gall bladder and Pancreas

1. The mechanistic effects of cigarette smoking on the development of pancreatic cancer
Pancreatic cancer is extremely aggressive, and the results of even advanced medical treatment remain unsatisfactory. Smoking is a major risk factor for various malignancies, including pancreatic cancer. Clarifying the mechanism of how smoking enhances the development of pancreatic cancer can be a useful tool for decreasing its incidence and developing effective treatments. Therefore, we are studying the effects of smoking on the autophagy mechanism in patients who have pancreatic cancer.

2. Clinical trial of a surveillance-targeted intraductal papillary mucinous neoplasm with endoscopic ultrasonography for early detection of pancreatic cancer

In patients with an intraductal papillary mucinous neoplasm (IPMN), frequent are both the canceration of an IPMN and the coexistence of normal-type pancreatic ductal carcinoma. Furthermore, pancreatic cancer has an extremely poor prognosis, and detection of a tumor at a diameter of 10 mm or less is reportedly necessary to expect a long-term survival. Because endoscopic ultrasonography is the most sensitive method for detecting small pancreatic cancers, it is considered to be the main strategy for early diagnosis. However, because pancreatic cancer progresses rapidly and has no effective biomarkers for early detection, periodic surveillance under a high-risk group enclosure is needed for early diagnosis. We are examining whether periodic surveillance with endoscopic ultrasonography in patients with an IPMN contributes to early detection of pancreatic cancer. We are also attempting to establish a more effective and executable surveillance strategy.

3. Study of the effect of corticosteroid treatment on diabetes management for autoimmune pancreatitis

Autoimmune pancreatitis (AIP) is an immunoglobulin G4-related disease for which a corticosteroid (prednisolone) is effective for treating pancreatic lesions and whose onset involves autoimmune mechanisms. Generally, AIP frequently complicates diabetes mellitus, but because the effect of prednisolone treatment on the management of diabetes mellitus is unclear, the medium- and long-term effects on diabetes mellitus management were examined. Of the 28 cases of AIP at our hospital, 18 were associated with diabetes mellitus. We divided the cases into 3 groups on the basis of the time of diabetes mellitus onset — before prednisolone introduction (pre-existing group), at AIP diagnosis (new-onset group), and after prednisolone introduction (after prednisolone group) — and retrospectively analyzed changes of HbA1c values and the contents of diabetes mellitus treatment. Prednisolone was introduced in 14 cases (77.8%), and imaging findings and blood biochemical responses were obtained in all cases. The HbA1c value improved 1 month after prednisolone administration in 2 cases (14.3%), but improved after 12 months in 7 cases (50.0%). The patient's age when AIP developed in the group in which the HbA1c level improved after 12 months was lower than in the group without improvement. In the pre-existing group ($n = 7$), diabetes mellitus did not improve 24 months after prednisolone introduction. Treatment with diet alone was difficult in the pre-existing group, but diet alone was effective in the new-onset and post-prednisolone groups, and doses of insulin could be reduced. The patients in whom prednisolone was not introduced were older (72 ± 8.7 years old) than those in the prednisolone administration group (74 ± 9.2 years old).

4. Clinical analysis of long-term management of AIP

Whether administration of a low corticosteroid dosage must be continued to maintain remission of AIP remains controversial.

Considering the side effects of corticosteroids, the minimum dosage required to maintain remission and the predictors of recurrence due to corticosteroid withdrawal must be clarified. We analyze the clinical data of cases of AIP at our hospital and are aiming to construct a treatment strategy for long-term management.

5. Clinical research about the relationship of gut microbiota and oxidative stress with pancreatic cancer

Gut microbiota have received substantial attention as a research topic in various diseases, including malignant tumors. In particular, the effects of short-chain fatty acids (SCFAs) in several cancers have been reported. Oxidative stress, which is a risk factor of senescence, is also a recent subject of cancer research. However, the effects of SCFAs and oxidative stress in pancreatic cancer growth are still unknown. Therefore, we will assess the clinical usefulness of several SCFAs and oxidative stress markers as potential markers of diagnosis and prognosis in patients with pancreatic cancer.

6. The investigation of Wilm's tumor protein 1-pulsed dendritic cell vaccines for patients with advanced pancreatic cancer

Wilm's tumor protein 1-targeted cancer vaccine might be effective for treating patients who have pancreatic ductal adenocarcinoma.

Chemotherapy

1. Optimized and personalized treatments for elderly patients with cancer

New chemotherapy drugs have recently been developed, and considerable improvement was observed in the prognosis of advance and recurrent malignancies of the digestive system. Owing to the rapid aging of the population, many patients who have cancer are 80 years or older. The management of cancer in elderly patients is challenging because of the difficulty of assessing the benefits of treatment and the decreased tolerance of anticancer therapy. We analyzed the prognosis, adverse effects, and treatment regimen of elderly patients with cancer at our hospital and have developed optimized and personalized treatments.

2. Cancer associated venous thromboembolic disease and systemic chemotherapy

Venous thromboembolic (VTE) disease is often found in patients who have cancer. Such VTE disease is life-threatening and is the second most common cause of death in patients with cancer. Bleeding from the alimentary tract is frequently observed in patients who have malignancies in the digestive system; thus, the possibility of VTE disease should be evaluated in all patients, and the risks associated with anticoagulant therapy should be assessed. We analyzed the risk of VTE, the chemotherapy regimen, and the treatment of VTE in patients of our hospital and then optimized cancer and VTE treatment.

3. Search for biomarkers of the efficacy and safety of nivolumab for advanced and recurrent gastric cancer

Nivolumab is a newly developed immune checkpoint inhibitor that enhances antitumor activity through programmed death 1 receptor. Despite severe adverse reactions having occurred in 18% of patients treated with nivolumab, the response rate with nivolumab was only 11%. Considering the cost and benefits of nivolumab, biomarkers that predict the efficacy and safety of nivolumab are desired. We are working with National Cancer Center of Japan to achieve this aim.

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