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Research Activities

Alimentary Tract

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. Areas under the receiver operating characteristic curves of the simple clinical colitis activity index, Mayo endoscopic score, and Matts' grade (histologic activity) for PEG-MUM were each higher than those for C-reactive protein. Compared with the C-reactive protein level, the PGE-MUM level demonstrated greater sensitivity for reflecting ulcerative colitis activity, especially in cases of histologic inflammation, and thus seems to be a better evaluator of mucosal healing.

2. Efficacy of infliximab in preventing restenosis after the endoscopic balloon dilatation therapy for Crohn's disease

The safety and efficacy of infliximab for preventing restenosis after endoscopic balloon dilatation were evaluated in 14 patients with Crohn's disease. Ten patients had no restenosies when infliximab was administered. Our results suggest that infliximab is useful for preventing restenosis after the endoscopic balloon dilatation therapy in patiens with Crohn's disease.

3. Photodymamic diagnosis of colitis-associated cancer or dysplasia withautofluorescent endoscopy following 5-animolevulinic acid sensitization

On the basis of previous animal experiments, we performed autofluorescent endoscopy after oral administration of 5-animolevulinic acid in 11 patients with ulcerative colitis. Of 21 lesions with the characteristic fluorescence signals, 14 received pathological diagnoses of colitis-associated cancer or dysplasia. The nethod of diagnosis showed good positive and negative predictive values and a sensitivity and specificity. Autofluorescent endoscopy following 5-animolevulinic acid sensitization would offer a useful method for diagnosing colitis-associated cancerous lesions.

4. Development of optical molecular imaging for gastrointestinal cancer and image-guided phototherapy

We have developed photoimmunotherapy, a type of molecular target-specific phototherapy that uses monoclonal antibodies conjugated to the near-infrared phthalocyanine dye.

We have established a molecular target-specific phototherapy that uses imaging-guided and fluorescence molecular imaging methods in a mouse model of human gastric cancer.
5. Clinical features of multiple early gastric cancer patients treated with endoscopic submucosal dissection
We examined clinical features of preoperatively diagnosed early gastric cancer treated with endoscopic submucosal dissection, particularly those with synchronous and metachronous multiple tumors.
6. Nutritional therapy for inflammatory bowel diseases
We demonstrated that understanding and using the omega-3 diet method, which emphasizes the intake of omega-3 polyunsaturated fatty acid, improves the efficacy of maintaining the remission of inflammatory bowel diseases.
7. A genetic factor associated with drug-induced leukopenia in Japanese patients with inflammatory bowel disease
We found that the 94C>A mutation of the inosine triphosphate pyrophosphatase gene (ITPA) is involved in the onset of thiopurine-induced leukopenia in Japanese patients with inflammatory bowel disease.

Pancreas
We demonstrated that a higher frequency of memory-phenotype Wilm's tumor protein 1 (WT1)-specific cytotoxic T lymphocytes could be a useful prognostic marker for a good response to the combination therapy with gemcitabine and WT1-pulsed dendritic cell vaccines in patients with advanced pancreatic cancer.

Liver
1. Pathogenesis of minimal hepatic encephalopathy
We found that psychometric testing was a useful method for the early diagnosis of minimal hepatic encephalopathy.
2. Nutritional imbalance of patients with liver cirrhosis
W e examined the nutritional status of patients with liver cirrhosis. The nutritional background was analyzed with a food frequency questionnaire based on food groups. We could easily evaluate the relation between nutritional imbalance and morbidity.
3. Nutritional evaluation in nonalcoholic fatty liver disease
The pathogenesis of nonalcoholic fatty liver disease resembles metabolic syndrome. We evaluated nutritional conditions in detail in nonalcoholic fatty liver disease. On the basis of the results, we are attempting to develop a new nutritional intervention for nonalcoholic fatty liver disease.
4. Clinical characteristics of primary biliary cirrhosis and autoimmune antibodies
Autoimmune antibodies against mitochondria, nuclei, or nuclear pore glycoprotein 210 (gp210) were examined in patients with primary biliary cirrhosis. The pattern of autoimmune antibodies was analyzed in association with the clinical course, outcome, and histological findings.
5. A useful prognostic factor in cases of hepatocellular carcinoma
The Glasgow Prognostic Score system, based on inflammation criteria and including only serum C-reactive protein and albumin, showed a correlation with prognosis in cases of

hepatocellular carcinoma.

6. Response to antiviral nucleic acid analogs in chronic hepatitis B virus infection

Resistant viral mutations are a urgent remedial problem in cases of chronic hepatitis B virus infection treated with antiviral nucleic acid analogues. We repeatedly analyzed viral gene sequences and followed up the treatment response rate. We consider the possibility of a new concurrent therapy for chronic hepatitis B virus infection. We found that the differences in clinical characteristics depend on the viral genotype. Cases of infection with the genotype A virus were more likely to be severe, to be prolonged, and to be treated with an antiviral nucleic acid analogue.

7. Immunological analyses in a mouse model of autoimmune hepatitis

Intrahepatic natural killer T-cell and several cytokine profiles were examined in a mouse model of autoimmune hepatitis.

8. Antiviral therapy against chronic hepatitis C virus infection

We investigated the efficacy of telaprevir-based combination therapy for genotype 1b chronic hepatitis C virus (HCV) infection in poor-responders to interferon (interleukin 28B minor). We found that the response to treatment is associated with serum HCV dynamics and the level of 25-hydroxyvitamin D3.

9. Abnormal lipoprotein kinetics in chronic HCV infection

We found that reduced serum levels of apolipoproteins CII and CIII are a common feature of chronic HCV infection regardless of HCV genotype although the kinetics of apolipoproteins E and A1 depends on the HCV genotype.

10. A biomarker for nonalcoholic steatohepatitis

We demonstrated that the serum level of cytokeratin 18 fragments is a useful marker for diagnosis and evaluation of activity for nonalcoholic steatohepatitis.

11. Clinical features of superelderly patients with hepatocellular carcinoma

We investigated clinical features and prognosis of superelderly patients with inoperable hepatocellular carcinoma.

Reviews and Books

Takakura K, Kajihara M, Ito Z, Ohkusa T, Gong J, Koido S. Dendritic-tumor fusion cells in cancer immunotherapy. *Discov Med*. 2015; **19:** 169-74.

Saruta M, Papadakis KA. Lymphocyte homing antagonists in the treatment of inflammatory bowel diseases. *Gastroenterol Clin North Am*. 2014; **43:** 581-601.

Koido S, Homma S, Okamoto M, Takakura K, Gong J, Sugiyama H, Ohkusa T, Tajiri H. Chemoimmunoltherapy targeting Wilms' tumor 1 (Wt1)-specific cytotoxic T lymphocyte and helper T cell responses for patients with pancreatic cancer. *Oncoimmunology*. 2014; **3:** e958950.