

Department of Pathology

Masahiro Ikegami, *Professor*
 Akihiko Sakata, *Professor*
 Takako Kiyokawa, *Professor*
 Hiroyuki Takahashi, *Associate Professor*
 Yukiko Kanetsuna, *Assistant Professor*
 Tohru Harada, *Assistant Professor*
 Tomoe Lu, *Assistant Professor*

Masaharu Fukunaga, *Professor*
 Masafumi Suzuki, *Professor*
 Satoru Chiba, *Associate Professor*
 Koichi Nomura, *Associate Professor*
 Yasuhiko Endo, *Assistant Professor*
 Shigeharu Hamatani, *Assistant Professor*
 Masakazu Komine, *Assistant Professor*

Research Activities

Liver research

1. Primary biliary cirrhosis was newly classified with Nakanuma's classification, and biochemical data and histopathological findings were compared. Changes in the histopathological findings of hepatitis, cholangitis, bile duct loss, and fibrosis vary among patients, and cases have been found with improvement, no change, or progression of each finding. Bile duct loss and fibrosis represent important histopathological factors in Nakanuma's classification. Various findings of improvement, no change, and progression are also observed in each stage according to Nakanuma's classification. Moreover, because some patients showed improvement of inflammation but progression of bile duct loss, a worse prognosis was feared. The changes in clinical findings do not correspond with changes in histopathological findings. In other words, histopathological findings of inflammation and chronic nonsuppurative destructive cholangitis are sometimes seen even in patients with improved values of alkaline phosphatase and γ -glutamyl transpeptidase. The follow up of patients with primary biliary cirrhosis should, therefore, include both biochemistry laboratory tests and liver biopsy for histopathology.

2. Changes in the liver with aging: Imaging was performed for liver tissue samples from 45 autopsy cases. The size of each hepatocyte was compared with the sizes of the sinusoids and spaces of Disse to investigate changes associated with aging. The sizes of the sinusoids and the spaces of Disse relative to each hepatocyte decreased with aging, and hepatocytes became slightly larger. These findings suggest sinusoid shrinkage and a stromal increase with age.

3. Central necrosis in autoimmune hepatitis was examined in liver biopsy specimens from 72 patients. Forty-eight patients showed centrilobular necrosis and inflammation, 33 had centrilobular necrosis, and 45 had central inflammation. Among the patients with central inflammation, 23 had extension of interface hepatitis and 22 had an opposite expansion of inflammation from the centrilobular areas to the peripheral liver parenchyma. Centrilobular necrosis is not uncommon in autoimmune hepatitis, and a so-called "opposite interface hepatitis," involving the centrifugal spread of inflammation from the centrilobular areas, was a notable finding.

Gastrointestinal research

1. Pathology of colorectal neuroendocrine tumors: Under the World Health Organization

Classification of Tumors of the Digestive System established in 2010, colorectal neuroendocrine tumors have been classified on the basis of the mitotic count and the Ki-67 index into neuroendocrine tumors grades 1 and 2 and neuroendocrine cell carcinoma. With this change, patients previously receiving diagnoses of carcinoid tumors at our hospital were reclassified, and the correlations with vascular invasion and prognosis were examined. A total of 115 patients with colorectal carcinoid tumors were treated at our hospital, with endoscopic resection in 98 patients and surgical resection in 17 patients. Among these 115 patients, 95 (82.6%) had G1 lesions and 20 (17.4%) had G2 lesions. Among the 17 patients undergoing surgical resection, 10 (58.8%) had G1 lesions and 7 (41.2%) had G2 lesions. Seven (41.2%) of the patients undergoing surgical resection had lymph node metastases. Metastases were more common with G2 lesions (5 patients, 71.4%) than with G1 lesions (2 patients, 20%). All patients with metastases showed vascular invasion, suggesting vascular invasion as an important risk factor for metastases.

2. Objective indices for colorectal serrated lesions: We aimed to create objective indices for colorectal serrated lesions (CRSLs) by classify CRSLs with objective indices we have developed and by comparing rates of gene mutation and phenotypic expression. We examined whether the sizes of the nuclei of epithelial cells decreased from the lower part to the surface of serrated gland ducts (an index of cell maturity) and whether gland duct branching (an index of complexity of gland duct structure) was present. On the basis of these 2 objective indices, we morphometrically verified that CRSLs can be classified into 5 types.

3. Clinicopathological features of duodenal epithelial tumors: Duodenal epithelial tumors have not been classified histologically. We therefore classified duodenal epithelial tumors on the basis of the immunohistologic examination of their mucinous characteristics and investigated their clinicopathologic features. We examined 110 duodenal epithelial tumors that were surgically or endoscopically resected at our hospital. Staining with hematoxylin and eosin and various immunostaining tests were performed on the samples to classify the lesions as an intestinal type or gastric type. On the basis of the histologic features, intestinal types were further classified as tubular type or tubulovillous type, and the gastric type was classified as foveolar type or pyloric-gland type. The clinicopathological features of these 4 types were examined.

Duodenal epithelial tumors were commonly found in elderly men and often arose in the proximal duodenum. Most tumors were intestinal type, whereas only about 10% were gastric type. The most frequent intestinal-type tumors were tubular-type lesions that grossly appeared as the flat-elevated type. The tubulovillous, foveolar, and pyloric-gland types were all large and characterized by prominent elevation. Gastric-type tumors tended to have higher atypia. Among the gastric types, the pyloric-gland type often had ectopic fundic glands, suggesting that these were special tumors with differentiation to fundic glands.

Urogenital research

1. Urological pathology in general: Differences in the clinicopathological and molecular biological features of prostate cancer on the basis of its site of origin were investigated. This study included 211 patients with prostate cancer who underwent total prostatectomy

at our hospital. The cancers were classified as anterior/posterior cancer and transition zone/peripheral zone cancer; and factors, such as cancer detection rates on needle biopsy and ERG expression on immunostaining, were compared. ERG expression was significantly lower in anterior/transition-zone cancers than in posterior/peripheral-zone cancers.

2. Evaluation of overexpression of human epidermal growth factor receptor 2 in metastatic urothelial carcinomas: Immunohistochemical testing was performed to investigate whether human epidermal growth factor receptor 2 (HER2) was overexpressed in 116 patients with urothelial carcinoma. The immunohistochemistry score was 3 in 16.4% of cases. On the basis of the site, the score was 3 in 17.9% of urinary bladder cancers, 21.4% of ureteral cancers, and 5.6% of renal pelvic cancers. Overexpression of HER2 in urothelial carcinoma was seen more often in patients with lymph node metastases. Primary lesion and metastatic lesion scores were generally in agreement.

Female reproductive tract research

1. Histopathology in twins with complete mole and similar placentas: Many cases were diagnosed as partial moles, but some were complete moles with mosaicism. None had persistent trophoblastic disease.

2. Atypical polypoid adenomyomas of the endometrium: Clinicopathologic features of atypical polypoid adenomyomas in 71 patients, including our own cases and cases presented at conferences, were examined. The pathologic diagnosis on the basis of endometrial curettage specimens was difficult, and overdiagnosis as endometrioid adenocarcinoma was not uncommon. The clinical presentations were more diverse than previously reported and included cases of invasion into the myometrium and cases of lesions within adenomyosis. Complication by endometrioid adenocarcinoma was seen in 15 patients, but outcomes were good and no patients died. Persistent lesions were seen in all patients who underwent hysterectomy with repeat endometrial curettage or hormonal therapy. Hysterectomy is indicated for treatment, except for patients who strongly wish to preserve their fertility.

Respiratory tract research

1. Prominin 1: We investigated whether the protein prominin 1 was expressed and the significance of prominin 1 expression in 134 patients with surgically resected lung adenocarcinoma and 71 patients with squamous cell carcinoma (SCC). Prominin 1 was expressed in 64 (48%) patients with lung adenocarcinomas, suggesting a weak association between prominin 1 and the development of lung adenocarcinoma. However, prominin 1 was constitutively expressed by normal epithelial cells. This finding suggests that prominin 1 is important in maintaining the structure and function of normal bronchial mucosal epithelial cells. However, prominin 1 was expressed in only 9 (13%) patients with SCC. Therefore, prominin 1 is not a functional protein in cancer stem cells in the development of SCC.

2. The possibility of the microtubule associated tumor suppressor 1 (MTSU1) gene (*MTUS1*), located on the short arm of chromosome 8, as a novel candidate tumor suppressor gene was examined with microsatellite analysis. This subjects included 34 patients with earlier-stage hepatocellular carcinoma (HCC) and 22 patients (64 lesions; 22 pri-

mary lesions, 42 metastatic lesions) with advanced HCC and distant metastases. We investigated the expression of MTUS1 protein in the malignant transformation of hepatocytes using an anti-MTUS1 protein-specific antibody that we developed. The protein MTUS1 disappeared with malignant transformation in 75% of patients with HCC.

Soft tissue tumor research

1. Clinicopathologic features were examined in 8 patients with composite hemangioendotheliomas. The most common combination was retiform hemangioendothelioma and epithelioid hemangioendothelioma. Angiosarcoma was seen in some cases, but as in other patients, the outcomes were good.

Publications

Perry AS, Furusato B, Nagle RB, Ghosh S. Increased aPKC expression correlates with prostatic adenocarcinoma Gleason score and tumor stage in the Japanese population. *Prostate Cancer*. 2014; **2014**: 481697.

Sato R, Joh K, Komatsuda A, Ohtani H, Okuyama S, Togashi M, Omokawa A, Nara M, Nagata D, Kusano E, Sawada K, Wakui H. Validation of the Japanese histologic classification 2013 of immunoglobulin A nephropathy for prediction of long-term prognosis in a Japanese single-center cohort. *Clin Exp Nephrol*. 2015; **19**: 411-8. Epub 2014 Jul 8.

Wakui S, Shirai M¹, Motohashi M¹, Mutou T¹, Oyama N¹, Wempe MF¹, Takahashi H, Inomata T¹, Ikegami M, Endou H¹, Asari M (Azabu Univ). Effects of in utero exposure to di(n-butyl) hthalate for estrogen receptors α , β , and androgen receptor of Leydig cell on rats. *Toxicol Pathol*. 2014; **42**: 877-87.

Ito S, Araya J, Kurita Y, Kobayashi K, Takasaka N, Yoshida M, Hara H, Minagawa S, Wakui H, Fujii S, Kojima J, Shimizu K, Numata T, Kawaishi M, Odaka M, Morikawa T, Harada T, Nishimura SL, Kaneko Y, Nakayama K, Kuwano K. PARK2-mediated mitophagy is involved in regulation of HBEC senescence in COPD pathogenesis. *Autophagy*. 2015; **11**: 547-59.

Mitsuhashi A, Kiyokawa T, Sato Y, Shozu M. Effects of metformin on endometrial cancer cell growth in vivo: a preoperative prospective trial. *Cancer*. 2014; **120**: 2986-95.

Wakui S, Mutou T¹, Takahashi H, Ikegami M, Wanibuchi H¹, Fukushima S (Azabu Univ). Vascular endothelial growth factor mRNA levels as a biomarker for short-term N-butyl-N-(4-hydroxybutyl)nitrosamine-induced rat bladder carcinogenesis bioassay. *J Appl Toxicol*. 2015; **35**: 181-90.

Zlotta AR, Egawa S, Pushkar D, Govorov A, Kimura T, Kido M, Takahashi H, Kuk C, Kovylina M, Aldaoud N, Fleshner N, Finelli A, Klotz L, Lockwood G, Sykes J, Kwast Tv. Prevalence of inflammation and benign prostatic hyperplasia

on autopsy in Asian and caucasian man. *Eur Urol*. 2014; **66**: 619-22.

Koido S, Hommma S, Okamoto M, Takakura K, Mori M, Yoshizaki S, Tsukinaga S, Odahara S, Koyama S, Imazu H, Uchiyama K, Kajihara M, Arakawa H, Misawa T, Toyama Y, Yanagisawa S, Ikegami M, Kan S, Hayashi K, Komita H, Kamata Y, Ito M, Ishidao T, Yusa S, Shimodaira S, Gong J, Sugiyama H, Ohkusa T, Tajiri H. Treatment with chemotherapy and dendritic cells pulsed with multiple Wilms' tumor 1 (WT1)-specific MHC class I/II-restricted epitopes for pancreatic cancer. *Clin Cancer Res*. 2014; **20**: 4228-39.

Yamamoto E, Niimi K, Shinjo K, Yamamoto T, Fukunaga M, Kikkawa F. Identification of causative pregnancy of gestational trophoblastic neoplasia diagnosed during pregnancy by short tandem repeat analysis. *Gynecol Oncol Case Rep*. 2014; **9**: 3-6.

Ikeda Y, Terasawa Y, Yamashita S, Kudo T, Aizawa M, Adachi H, Endo M, Joh K, Ioritani N, Orikasa S. MP54-16 favorable prognosis in end-stage renal disease patients with renal cell carcinoma: A long-term follow-up study in a single institution. *J Urol*. 2014; **191** 4 Suppl: e578.

Dobashi A, Goda K, Hirooka S, Ikegami M, Seino Y, Kato T, Tajiri H. Malignant lymphoma (in Japanese). *I to Cho*. 2014; **49**: 816-7.

Umemori M, Umezawa T, Takahashi J, Horiguchi A, Tsuchiya S, Sawabe M, Takahashi H, Ikegami M. Grocott's stain by BD SurePath™ liquid-based cytology: sputum and bronchoalveolar lavage (in Japanese). *Igaku Kensa*. 2014; **63**: 758-61.

Ide T, Saito S, Inomata H, Ohya T, Tamai N, Aihara H, Kato T, Tajiri H, Ikegami M. Identification of rectal submucosal invasive cancer by using magnifying observation (in Japanese). *I to Cho*. 2014; **49**: 1755-60.

Dobashi A, Goda K, Kobayashi M, Kato M, Sumiyama K, Toyozumi H, Kato T, Hirooka S, Ikegami M, Tahiri H. Tips for use of a newly released second-generation NBI system (in Japa-

nese). *Shokaki Naisikyo*. 2014; **26**: 666-72.
Horiguchi A, Umezawa T, Ashikawa T, Tsuchiya S, Umemori M, Takahashi H, Ikegami M, Yamada K, Okamoto A, Ochiai K. A blood addition test to BD SurePath™ liquid based cytology. *Nihon Rinsho Saibo Gakkai Zasshi*. 2014; **53**: 286-91.

Reviews and Books

Joh K. Renal pathology: SY23-2 a case of a new disease entity: podocytic infolding glomerulopathy. *Pathology*. 2014; **46** Suppl2: S41.

Joh K, Nakamura Y. The diagnosis and therapy of immunotactoid glomerulopathy and fibrillary glomerulonephritis (in Japanese). *Jin to Toseki*. 2014; **77**: 185-91.

Fukunaga M. What is your diagnosis? (in Japanese) *Rinsho Hinyokika*. 2014; **68**: 633-6.

Ashikawa T, Umezawa T, Miura Y, Shiomori Y,

Hiroi T, Fukunaga M. Intraoperative cytology (in Japanese). *Medical technology*. 2015; **43**(1): 48-53.

Fukunaga M. Pathology of cutaneous vascular and myogenic tumor (in Japanese). *Byori to Rinsho*. 2014; **32**: 383-90.

McCluggage WG, Kiyokawa T, Staats PN, Young RH. Sex cord tumorous-pure stomal tumours. In: Kurman RJ, Carcangiu ML, Herrington CS, Young RH, editors. WHO classification of tumours of female reproductive organs. 4th ed. Lyon: International Agency for Research on Cancer; 2014. p.44-9.

Hui P, Gersell D, Baergeu R, Lage JM, Cheung ANY, Ronnott BM, Fukunaga M, Sepire NJ, Wells M. Gestational trophoblastic disease. In: Kurman RJ, Carcangiu ML, Herrington CS, Young RH, editors. WHO classification of tumours of female reproductive organs. 4th ed. Lyon: International Agency for Research on Cancer; 2014. p. 155-67.