Department of Pathology

Hiroshi Hano, Professor Masaharu Fukunaga, Professor Masafumi Suzuki, Associate Professor Satoru Chiba, Assistant Professor Takako Kiyokawa, Assistant Professor Hiroyuki Takahashi, Assistant Professor Yukiko Kanetsuna, Assistant Professor Yutaka Yamaguchi, Professor Akihiko Sakata, Associate Professor Masahiro Ikegami, Associate Professor Yasushi Kikuchi, Assistant Professor Takashi Nikaido, Assistant Professor Koichi Nomura, Assistant Professor Tohru Harada, Assistant Professor

General Summary

The research projects of our department have focused on studies of the pathogenesis, histogenesis, morphogenesis, and clinical pathology of nonneoplastic and neoplastic human disease by means of light and electron microscopy, morphometry, immunohistochemistry, gene analysis, and other techniques.

Hepatology

On the basis of our previous studies, we have speculated that the restructuring process of the liver lobule from chronic hepatitis to liver cirrhosis represents a change from structural instability to structural stability. In other words, liver cirrhosis might represent self-organization of the liver according to the nonequilibrial thermodynamics of living systems.

Alcoholic liver cirrhosis was studied morphologically by means of the reconstruction of histologic serial sections. Changes in the arteries and lymphatic vessels were significant for the development of morphologic changes of this disease.

Morphologic changes of the liver with aging were studied by means of morphometrical analysis. The results show that the number of bile ducts decreases with aging.

Nephrology

We examined 287 cases of IgA nephropathy collected from hospitals nationwide. On the basis of the results of a statistical analysis of data with histologic variables, a new scale was established for grading the histologic severity of histopathological IgA nephropathy.

Histologic specimens of IgA nephropathy collected worldwide were examined by 18 nephropathologists belonging to the international committee of histological classification of IgA nephropathy. The aim was to establish a new histologic classification for IgA nephropathy.

Nineteen renal specimens obtained from pregnant women with hypertension were examined. The presence of thrombotic microangiopathy, focal glomerulosclerosis, and medullary ray damage indicated a close relation to renal vascular hypertension.

A study of transplanted kidneys revealed that medullary ray damage was caused mainly by urinary tract disorders and immunosuppressants. Renal tissue with chronic rejection showed peritubular capillaritis and basement-membrane thickening. In addition, the number of endothelial cells positive for cavelion-1 increased. These findings showed a close relation to the severity of chronic rejection.

We continued to histologically re-evaluate specimens of renal cell carcinoma collected in the department using revised general rules for clinical and pathological studies of renal cell carcinoma.

A total of 150 cases of hyperplasia, dysplasia, and adenoma of the renal tubules collected in the department were studied clinicopathologically.

Inflammatory pseudotumor of the kidney was examined. The pseudotumor was composed of granulomas with multinucleated giant cells and inflammatory granulation tissue with plasma cells, many of which showed immunoreactivity for IgG4. Fungi and anti-acid bacilli were also detected with special stains.

Gastrointestinal pathology

Risk factors for lymph node metastasis were examined in surgically resected specimens of superficial esophageal cancer. Specimens were immunohistochemically stained with D2-40. Lymphatic channels were identified. Multivariate statistical analysis showed that lymphatic invasion was closely related to lymph node metastasis.

Gynecological pathology

We performed a morphological study of ovarian aging involving histological investigation and microscopic measurement of 96 specimens of the ovary obtained at autopsy. The results showed that atrophy of the ovary begins at about age 30 years and progresses, especially after menopause. Atrophy of the ovary was caused mainly by volume reduction of the ovarian medulla.

A relation between ovarian atypical endometriosis and malignant ovarian tumor was examined, and cotyledenoid dissecting leiomyoma was studied clinicopathologically.

Urogenital pathology

We comprehensively reinvestigated the results of studies of prostatic carcinoma and published a review.

Lung pathology

Pathologic data obtained from 787 cases of primary lung cancer at autopsy were analyzed to examine the prevalence of lymph-node metastasis.

We are preparing to examine the epidermal growth factor receptor gene in specimens of lung cancer.

Other

Histologic evaluation was performed of specimens of various organs obtained from experimental animals to verify the safety of ultrasonography with phase-change nanodroplets. Four histologic stages were established according to the severity of injury induced by ultrasound.

Oncology

Loss of heterozygosity was studied in prostatic cancers of minimal size, of advanced

stage, and with metastasis.

Loss of heterogeneity was studied in liver cancer cells to detect candidate susceptibility inhibitor genes that play an important role in carcinogenesis, progression, and metastasis.

Publications

Nagatsuma K, Hayashi Y (Kochi Univ), Hano H, Sagara H (Tokyo Univ), Murakami K (Tohoku Welfare Pension Hosp), Saito M (Natl Inst Infect Dis), Masaki T, Lu T, Tanaka M, Enzan H (Chikamori Hosp), Aizawa Y, Tajiri H, Matsuura T. Lecithin: retinol acyltransferase protein is distributed in both hepatic stellate cell and endothelial cells of normal rodent and human liver. Liver Int 2009; 29: 47-54.

Wakui S¹, Muto T¹, Kobayashi Y¹, Ishida K¹, Nakano M, Takahashi H, Suzuki Y¹ ('Azabu Univ), Furusato M, Hano H. Sertoli-Leydig cell tumor of the testis in a sprague-dawley rat. J Am Assoc Lab Anim 2008; **47**: 67-70.

Omi H, Okamoto A, Nikaido T, Urashima M, Kawaguchi R, Umehara N, Sugiura K, Saito M, Kiyono T, Tanaka T. Establishment of an immortalized human extravillous trophoblast cell line by retroviral infection of E6/E7 hTERT and its transcriptional profile during hypoxia and reoxygenation. Int J Mol Med 2009; **23**: 229–36.

Hamada T, Kiyokawa T, Nomura K, Hano H. Immunohistochemical analysis of reserve celllink cells of ovarian mullerian mucinous/mixed epithelial borderline tumor. Int J Gynecol Pathol 2008; 27: 199-206.

Kanetsuna Y, Horita S¹, Tanabe K¹, Teraoka S¹, Hattori M¹, Toki D¹ (¹Tokyo Women's Med Univ), Yamaguchi Y. Is patchy tubular injury a histopathological marker of acute rejection? *Clin Transplant* 2008; **22(Suppl 19):** 13–8.

Kamoi S¹, *Ohaki* Y¹, *Mori* O¹, *Kurose* K¹, *Fu-kunaga M, Takeshita* T¹ (*Nippon Med Univ*). Serial histologic observation of endometrial adenocarcinoma treated with high-dose progestin until complete disappearance of carcinomatous foci-review of more than 25 biopsies from five patients. *Int J Gynecol Cancer* 2008; **18**: 1305-14.

Isonishi S, Nishii H, Saitou M, Yasuda M, Kiyokawa T, Fukunaga M, Ishikawa H, Tanaka T. Small cell carcinoma of the ovary: clinical and biological study. Int J Clin Oncol 2008; **13**: 161-5.

Kushima M¹, Akita H¹, Ota H¹, Masuda S¹ ('Showa Univ), Fukunaga M. Benign transitional epithelial(urothelial) cyst of the ovary: proposal of a new entity in the sub-classification of ovarian transitional cell tumor. Showa Univ Med Sci 2008; **20**: 179-85.

Ishida H¹, Omoto K¹, Shimizu T¹, Shirakawa H¹, Nishida H¹, Li X¹, Yamaguchi Y, Tanabe K¹ (¹Tokyo Women's Med Univ). Usefulness of splenectomy for chronic active antibodymediated rejection after renal transplantation. *Transpl Int* 2008; **21:** 602-4.

Li X¹, Ishida H¹, Yamaguchi Y, Tanabe K¹ (¹Tokyo Women's Med Univ). Poor graft outcome in recipients with *de novo* donor-specific anti-HLA antibodies after living related kidney transplantation. *Transpl Int* 2008; **21**: 1145–52. Yamamoto I, Horita S¹, Takahashi T (Vanderbilt Univ), Kobayashi A, Toki D¹, Tanabe K¹, Hattori M¹, Teraoka S¹ (¹Tokyo Women's Med Univ), Aita K², Nagata M² (²Tsukuba Univ), Yamaguchi Y.

Caveolin-1 expression is a distinct feature of chronic rejection-induced transplant capillar-opathy. *Am J Transplant* 2008; **8:** 2627–35.

Saitou M, Isonishi S, Hamada T, Kiyokawa T, Tachibana T, Ishikawa H, Yasuda M. Mitochondrial ultrastructure-associated chemotherapy response in ovarian cancer. Oncol Rep 2009; 21: 199-204.

Taneda S¹, Honda K¹, Horita S¹, Koyama I¹, Teraoka S¹, Oda H¹ (¹Tokyo Women's Med Univ), Yamaguchi Y. Light chain deposition disease after renal transplantation. Am J Kidney Dis 2008; **52:** 621–5.

Shimizu T¹, Ishida H¹, Shirakawa H¹, Omoto K¹, Tanabe K¹ (¹Tokyo Women's Med Univ), Yamaguchi Y. Clinical and histological analysis of chronic tacrolimus nephrotoxicity in renal allografts. *Transpl Proc* 2008; **40:** 2370-2.

Toki D¹, Ishida H¹, Setoguchi K¹, Shimizu T¹, Omoto K¹, Shirakawa H¹, Iida S¹, Horita S¹, Furusawa M¹, Ishizuka T¹, Yamaguchi Y, Tanabe K¹ (¹Tokyo Women's Med Univ). Acute antibody-mediated rejection in living ABOincompatible kidney transplantation: Long-term impact and risk factors. Am J Transplant 2009; **9**: 567-77.

Aihara H, Sumiyama K, Saito S, Tajiri H, Ikegami M. Numerical analysis of the autofluorescence intensity of neoplastic and non-neoplastic color-ectal lesions by using a novel videoendoscopy system. Gastrointest Endosc 2009; 69: 726-33.

Hayashi T, Kawahara H, Yoshimoto K, Kashiwagi H, Yanaga K, Komine K. Early cystoadenocarcinoma of vermiform appendix simulating submucosal tumor of the cecum. *Int J Surg* 2008; 6: e15–7.

Kinoshita S, Hirano A, Komine K, Kobayashi S, Takeyama H, Uchida K, Morikawa T, Nagase J (Nagase Surg), Sakamoto G (Sakamoto Clin). Primary small-cell neuroendocrine carcinoma of the breast: report of a case. Surg Today 2008; 38: 734-8. Nogi H, Kobayashi T, Suzuki M, Tabei I, Kawase K, Toriumi Y, Fukushima H, Uchida K. EGFR as paradoxical predictor of chemosesitivity and outcome among triple-negative breast cancer. Oncol Rep 2009; 21: 413-7.

Nogi H, Kabayashi T, Tabei I, Kawase K, Toriumi Y, Suzuki M, Morikawa T, Uchida K. The predictive value of PgR and HER-2 for response to primary systemic chemotherapy in inflammatory breast cancer. Int J Clin Oncol 2008; **13:** 340-4.

Lu T, Hano H. Deletion at chromosome arms 6q 16-22 and 10q22.3-23.1 associated with initiation of prostate cancer. *Prostate Cancer Prostatic Dis* 2008; **11:** 357–61.

Mikami Y (Kyoto Univ), Kiyokawa T, Sasajima Y (Natl Cancer Cent), Teramoto N (Shikoku Cancer Cent), Wakasa T (Osaka Red Cross Hosp), Wakasa K (Osaka City Univ), Hata S (Kawasaki Univ). Reappraisal of synchronous and multifocal mucinous lesions of the female genital tract: a close association with gastric metaplasia. *Histopathology* 2009; **54**: 184–91.

Sasajima Y¹, Mikami Y (Kyoto Univ), Kaku T¹, Kiyokawa T, Ohishi Y (Kyushu Univ), Hamada T, Sasaki T², Fujita H² (²Hokkaido Cancer Soc), Moriya T (Kawasaki Med Univ), Kasamatsu T¹ (¹National Cancer Cent Hosp), Tsuda H (Natl Med Coll). Gross features of lobular endocervical glandular hyperplasia in comparison with minimal-deviation adenocarcinoma and stage lb endocervical-type mucinous adenocarcinoma of the uterine cervix. *Histopathology* 2008; **53**: 487-90. Nakano M, Takahashi H, Shiraishi T (Mie Univ), Lu T, Furusato M, Wakui S, Hano H. Prediction of clinically insignificant prostate cancer by detection of allelic imbalance at 6q, 8p and 13q. Pathol Int 2008; 58: 415-20.

Nikami T, Saito S, Tajiri H, Ikegami M. The evaluation of histological atypia and depth of invasion of colorectal lesopns using magnified endoscopy with Narrow-band imaging. *Gastroenterol Endosc* 2009; **51:** 10–9.

Reviews and Books

Fukunaga M, Takahashi H, Yasuda M. Mesonephric adenocarcinoma of the uterine cervix: a case report with immunohistochemical and ultrastructural studies. *Pathol Res Pract* 2008; **204:** 671-6.

Kanetsuna Y, Yamaguchi Y. Renal allograft pathology, according to Banff classification. *Jintotohseki* 2008; **65:** 382–8.

Takahashi H. Histological chage s of the benign and malignant prostate following treatments. *Byouritorin* 2008; 26: 473-81.

Kiyokawa T, Hamada T. Ovary. *Byouritorin* 2008; **26(Suppl):** 310-4.

Ikegami M, Mitobe J, Koike Y, Saito S, Tamegai Y (Int Med Center). Development and progression of colorectal cancer studied by growth pattern analysis ofsubmucosal invasive cancers (PG and NPG). *Itotyou* 2008; **43**: 1947-55.

Kiyokawa T. Histopathologic grading of ovarian carcinoma. *Byouritorin* 2008; **26:** 520-1.