Department of Pathology

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General Summary

The objective of our research in the Department of Pathology is to morphologically investigate the causes of disease and to evaluate morphological changes. We use human tissue samples resected at autopsy and surgery or obtained at biopsy. These samples are examined with such means as light microscopy, electron microscopy, morphological measurement, immunohistochemical staining, and molecular pathological techniques.

Research Activities

Research on the Digestive Tract
1. To clarify predictive factors for metastasis to the lymph nodes and the liver in patients with submucosal cancer invading the stomach, we examined 578 cases of intramucosal cancer or submucosal cancer of the stomach which were endoscopically or surgically resected in our hospital from 2004 through 2015. Of these cases, 230 (39.8%) were submucosal cancers. In patients with submucosal cancer, representative sections were stained with elastica-Van Gieson stain, which is a special stain, and immunohistochemical biomarkers (CD31, D2-40, and MIB-1 antibodies). We regarded the following items as metastatic risk factors to perform a multivariate analysis of extracted data: the presence or absence of ulcer, the presence or absence of elevation or excavation, tumor diameter (< 20 mm, ≥ 20 mm), measured infiltration values (< 500 μm, ≥ 500 μm), histologic types at the invasive site, infiltration patterns, lymphovascular invasion (lymphatic invasion [+/−] and venous invasion [+/−]), the locations and numbers of lymphovascular invasion in the primary lesion, and the form of carcinoma in the lymphovascular vessels (individual tumor cells and tumor cell nest formation).
2. To investigate predictors of lymph-node metastasis in patients with submucosal colorectal cancer, we studied specimens obtained from 124 patients with submucosal colorectal cancer from 2009 through 2015 and stained with hematoxylin and eosin. Representative sections underwent special staining and immunohistochemical staining. Data on the following variables were extracted: the presence or absence of depressions, intramucosal growth patterns (nonpolypoid growth, polypoid growth), the measured depth of invasion (< 1,000 μm, ≥ 1,000 μm), histologic type of the invasion site, the presence or absence of tumor budding (+/−), lymphovascular invasion: lymphatic invasion and venous invasion (+/−), the locations and numbers of lymphovascular invasion sites in the primary lesion, the presence or absence of a mixture of poorly differentiated adeno-

carcinoma and mucinous carcinoma, tumor budding, and types of intravascular carcinomas (sporadic tumors, nested tumors). We are planning to perform multivariate analysis in the future.

3. We studied the histologic characteristics of colorectal neuroendocrine tumors. In particular, we examined the relations of tumor grade based on the 2010 World Health Organization Classification of Gastrointestinal Tumors to vascular invasion and outcomes. Surgically and endoscopically resected colorectal carcinoid tumors were stained with elastica-Van Gieson stain, immunostain (CD31, D2-40, and MIB-1 antibodies), and hematoxylin and eosin. Each lesion was classified according to tumor grade, and the tumor diameter, invasion depth, submucosal invasion distance, number of nuclear division cycles, Ki67 index, and lymphovascular invasion were assessed. The relations of lymphovascular invasion and other risk factors to outcomes were then studied. In our hospital, we are currently analyzing data on 160 cases consisting of 139 endoscopically resected cases and 21 surgically resected cases.

4. Two surgically resected specimens of Crohn's disease of the small intestine were all prepared as tissue specimens., mapped the site of epithelioid granuloma and ulcer, and searched for the distribution of granulomas within the wall and the positional relationship between granulomas and ulcers. Of 385 granulomas, 1.3% were in the mucosa, and 19.8% were in the submucosa. Overall, 97.1% of the granulomas were within 10 mm of ulcers in a horizontal direction. To accurately diagnose Crohn's disease, biopsy specimens, including the submucosa, should be taken from regions within 10 mm of ulcers.

Research on the urogenital system

1. In patients who had prostate cancer with a Gleason score of $3 + 4 = 7$, we examined whether the proportion of Gleason pattern 4 in biopsy specimens and other biopsy variables are useful for predicting outcomes after total prostatectomy. Patients in whom the proportion of Gleason pattern 4 was 5% or higher in biopsy specimens had higher risks of malignancy and biochemical recurrence than did patients with a Gleason score of $3 + 3 = 6$.

2. In 148 patients with urothelial cancer, we examined the relations of the presence or absence of overexpression of human epidermal growth factor receptor 2 (HER2) to the immunohistochemical subtype and clinicopathological factors. Protein overexpression or gene amplification of HER2 was found in 14% of patients. All urothelial cancers were immunohistochemically classified into basal or luminal subtypes. Protein overexpression or gene amplification of HER2 was found in 4% of patients with basal cancers and in 22% of patients with luminal cancers.

Research on the female genital organs

1. To construct a new classification of cervical adenocarcinoma tissue, we participated in an international joint study and obtained the following results.

a. We developed a comprehensive immunohistochemistry algorithm required for the diagnosis of histologic subtypes. The paper was submitted and published in the following journal: Am J Surg Pathol 2018, 42: 989-1000.

b. We demonstrated that invasion patterns can be regarded as predictive factors for

lymph-node metastasis in patients with human papillomavirus (HPV)-related cervical adenocarcinoma but not in patients with HPV-unrelated cervical adenocarcinoma. We submitted a paper to the following journal: Gynecologic Oncology 2018, 150: 56-60.

c. We clarified clinical findings of HPV-related and HPV-unrelated cervical adenocarcinomas and submitted a paper to the following journal: Am J Surg Pathol 2019, 43: 466-474.

d. We examined the histologic, immunohistochemical, and clinical characteristics of cervical squamous-cell adenocarcinoma of a rare histologic type and submitted a paper to the following journal: Modern Pathology 2019, 32: 269-279.

2. We participated in an international joint study of perivascular epithelioid cell tumors (PEComa), which are Uterine tumors of a rare histologic type, to clarify the relation of histologic findings to outcomes and submitted a paper to the following journal: Am J Surg Pathol 2018, 42: 1370-1383.

3. Continuing from last year, we performed a study with the Department of Obstetrics and Gynecology to examine the diagnostic accuracy and outcomes in patients in our hospital with endometrial carcinosarcoma. We found that endometrial carcinosarcoma can occur in young women and contains a mixture of well-differentiated and poorly differentiated components. We are preparing a paper.

Research on the respiratory organs

Depletion and clinical significance of the 3p22 region in the development of lung squamous cell carcinoma: The depletion of the short-arm region of chromosome 3 (3p) might occur most frequently in the earliest stage of development of lung squamous-cell carcinoma, suggesting that tumor suppressor genes exist in the 3p region. However, localized regions of candidate tumor suppressor genes related to carcinogenesis remain unclear, although at least 500 types of known genes exist in this 3p region. Microsatellite instability (MSI) analysis has been recognized as the most powerful method for determining the location of target genes by means of microsatellite makers near chromosomal genes. To determine the 3p region most strongly associated with the occurrence of lung squamous-cell carcinoma, we used a microdissection method to obtain cancerous and noncancerous tissues from surgically resected, unstained, formalin-fixed, paraffin-embedded samples from 81 patients with lung squamous-cell carcinoma. The DNA was extracted from these samples. A comprehensive MSI analysis was conducted with 18 markers in the 3p region. As a result, the MSI frequency of 18 markers in cancer tissues was 6% to 39% compared to non-cancerous tissues. Among 18 markers, MSI was most frequently found in the 3p22 region (39%). Therefore, we conclude that tumor suppressor genes related to the occurrence of lung squamous-cell carcinoma are likely in the 3p22 region.

Other studies

1. To determine age-related changes in the radius of the hepatic lobules, histometric analysis of liver tissue was performed in patients examined at autopsy. The radius (y) of the hepatic lobule increased with age (x). In patients 40 years or older, R2 calculated with the formula y = 0.0032 x + 0.3167 was approximately 0.65, indicating a strong correlation.

2. We have examined autopsy cases of fulminant group A streptococcal infection of the

right lower limb. At the sites of infection, many bacteria were present but inflammation was weak. Previous studies have demonstrated that fulminant group A streptococcal infection is associated with a weak or absent inflammatory response. In the present study, we did not investigate M proteins. However, previous studies have found that the inflammatory response is inhibited by such factors as hyaluronic acid capsules, M proteins, C5a peptidase, and nuclease.

Publications

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