

Pathologic aspects of tumors of gastrointestinal tract in the era of personalized medicine

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The gastrointestinal (GI) tract is an anatomic term used to denote the tubular digestive system and its accessory organs. It is often divided into the upper GI tract, lower GI tract, and accessory organs for purposes of discussing its diseases. The upper GI tract consists of the esophagus, stomach, and duodenum, whereas the lower GI tract comprises the remainder of the small intestine, the colon, and the anus. The accessory organs include the liver, gallbladder, pancreas, and the hepatobiliary and pancreatic ducts.

Although any portion of the GI tract may develop malignancy, the esophagus, stomach, and colon (including rectum) are the most common. In fact, esophagogastric and colorectal carcinomas are among the most frequently occurring deadly diseases in humans worldwide. Other commonly encountered GI primary tumors include lymphoproliferative disorders, hepatocellular carcinoma, and neuroendocrine and mesenchymal tumors (including GI stromal tumors). The pathogenesis and etiology of GI tumors is typically multi-factorial, varies with the specific tumor type, and may involve environmental factors (dietary, low socioeconomic status, cigarette smoking, alcohol use, nutritional deficiencies), host factors (certain precancerous conditions), infection (human papillomavirus, helicobacter pylori), and underlying genetic susceptibility.

In the emerging era of personalized medicine, the pathologist's role in the management of patients with GI malignancies has been greatly expanded from that of simply a traditional histomorphologist, to an active clinical consultant for gastroenterologists, surgeons, oncologists and medical geneticists, as well as patients. Today, the pathologist not only needs to provide an accurate histopathologic diagnosis, but is also responsible for accurately defining pathologic stage, evaluating surgical margins, assessing the efficacy of various neoadjuvant therapeutic modalities, and identifying the presence or absence of various relevant prognostic parameters and

therapeutic targets. Pathologists also play a key role in analyzing the histologic features of various tumors with potential genetic and/or molecular abnormalities, selecting appropriate tissue for testing for mutation and other genetic testing, and interpreting the results of these important therapeutic and prognostic tests.

This issue is dedicated to the pathologic aspects of commonly encountered GI tumors. Experts in the field offer their perspectives about the histopathology, cytopathology, precursor lesions, and recent advances in molecular pathology, and also provide up-to-date guidance in the application of immunohistochemical and molecular/genetic testing of commonly encountered GI, liver, and pancreatic tumors, with emphasis on their clinical relevance.

In the first article, authors from UCLA review the histopathology and current molecular pathology of colorectal carcinoma and its precursor lesions, with emphasis on their clinical relevance (1). Next, investigators from Harbor-UCLA Medical Center discuss the role played by cell cycle arrest, TLR signaling macrophages and stem cell transformation to form cancer stem cells, and the significance of ballooned hepatocytes that form Mallory-Denk bodies as progenitor pre-cancer cells in the pathogenesis of the transformation of alcohol liver disease to hepatocellular carcinoma (ALD/HCC) (2). Chen and colleagues, from UC Davis, bring us up to date on the current classification of pancreatic neuroendocrine tumors (PNTs), with insight into genetic and molecular changes related to PNT subtypes and their clinical relevance (3). Zhao (UC Irvine) and Yue (LabCorp) update us on gastrointestinal stromal tumors (GIST), including their epidemiology, pathogenesis and genetics, diagnosis, role of molecular analysis, prognostic factors, and management strategies (4).

Next, groups from Loma Linda University and UC Davis provide us with an update on primary gastrointestinal lymphomas and related neoplasms with respect to their

pathogenesis, morphology, immunophenotype, molecular and genetic features, and prognostic factors (5). Following are reviews by teams from Guangdong General Hospital, China, and Loma Linda University, USA, discussing the association between obesity and esophageal cancer (6), and providing an update on Barrett's esophagus, including current diagnostic criteria, clinical surveillance and promising endoscopic techniques for identifying patients at risk for malignancy (7).

The next two articles, by teams from UC Davis and Loma Linda University and AmeriPath General Florida and Memorial Hospital of Jacksonville, Florida, educate us on the current classification of gastric cancer, including histologic features and genetic and molecular phenotypes; they clarify the characteristics of each subtype and highlight the potential for improving early diagnosis, prevention, and treatment (8,9). Advances in current understanding of molecular tumorigenesis and related targeted neoadjuvant therapeutic markers are also discussed, along with the application of immunohistochemical and molecular studies.

The final two articles apply to GI tumors generally. Authors from the City of Hope National Medical Center review the immunohistochemical profiles of various GI tumors and discuss the application of immunohistochemistry in primary and differential diagnoses (10). Investigators from Loma Linda University discuss the role of cytopathology in the diagnosis and management of common GI tumors, including differential diagnoses and pitfalls, along with the advantages and limitations of different collection techniques (11).

In summary, tumors of the GI tract include a wide variety of tumor types and are among the most common malignancies in clinical practice. New classification systems for some GI malignancies based on a combination of histologic features, immunophenotypes, and molecular/genetic abnormalities help us to better understand the characteristics of each subtype and offer a promise for improving early diagnosis, prevention, and treatment of these tumors. Recent advances in the understanding of the molecular pathways of GI tumorigenesis, including abnormalities in cell growth, the cell cycle, apoptosis, angiogenesis, invasion, and metastasis, have increasingly compartmentalized cancer into individual diseases, each with its own phenotype, each with its own set of biomarkers, and each with its own portfolio of targets for therapy. These factors allow the physician to tailored therapeutic

approaches rationally to individual patients, with the potential for improving long-term survival and lowering the mortality of these often lethal tumors.

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