Hong Kong Pathology Forum 2021

30 January, 2021 (Saturday)
Online Zoom

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Department of Pathology
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Welcome from the Forum Chairperson

On behalf of the Department of Pathology of The University of Hong Kong and the Organizing Committee, it is my great pleasure welcoming you to Hong Kong Pathology Forum 2021, which has been delayed by one year on account of the Covid-19 pandemic. In this Forum to be conducted by virtual format, we will share updated pathology knowledge and experience with the medical community. Together with the Pathology profession, we hope this will enhance the community’s understanding of the role of pathologists in Hong Kong.

As in the previous years, this Forum has assembled a very strong program, composed of multiple symposia covering diverse topics in Pathology. This year it includes genetics & genomics, liver pathology as well as artificial intelligence and computational pathology. Each of the symposia aims to provide updated pathological as well as molecular knowledge and clinical management of the disease, that will provide a more comprehensive pathological-clinical interactive picture to enhance understanding.

We are honored to have the contribution of prominent overseas and local experts to this Forum, and grateful to the overseas speakers for overcoming the constraints of time difference and physical distance to join us. In particular, we pleased to have Professor Michael Torbenson of the Mayo Clinic, USA and Dr Cheng-Han Lee from the University of British Columbia, Canada, both giants in their own fields, who will deliver the Hou Pao-Chang Medical Memorial Fund Lecture and the James Gibson Lecture respectively.

In spite of the constraints and the virtual platform, I hope you will find this Forum both rewarding and enjoyable.

Finally, I would like to convey my sincere thanks to the donors of the Hou Pao-Chang Medical Memorial Fund and the James Gibson Fund, as well as our sponsors (Epredia, Gene Company & MSD) for their generous support in contributing to the success of this Forum.

Professor Ui Soon Khoo
Ada MF Chan Professor in Oncological Pathology
Department of Pathology
The University of Hong Kong
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The Hong Kong Pathology Forum (The Forum), organised by the Department of Pathology of The University of Hong Kong, aims to provide updated knowledge in different disciplines of Pathology, through state-of-the-art presentations by renowned local and international speakers in their areas of expertise.

The Forum incorporates two distinguished lectures, the Hou Pao-Chang Medical Memorial Fund Lecture and the James Gibson Lecture. The Hou Pao-Chang Medical Memorial Fund was established by Professor Laurence Hou to commemorate his late father, who was Head of the Department of Pathology at The University of Hong Kong between 1948 and 1960. The James Gibson Lecture, on the other hand, was incorporated into the Forum from 2015. Funded by friends and colleagues of the late Emeritus Professor James Gibson, Chair of Pathology at The University of Hong Kong between 1963 and 1983, to commemorate his retirement after many years of dedicated service to the University and the local community.

The Forum’s target audience includes pathologists, clinicians, physicians, other medical practitioners, as well as allied health professionals. The year’s program continues the tradition of providing cutting-edge, as well as practical knowledge in Pathology pertinent to the different sub-disciplines in clinical practices.
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Department of Pathology
The University of Hong Kong
Professor Hou Pao-Chang was an outstanding teacher, researcher and Head of Department of Pathology of the University of Hong Kong from 1948 - 1960. He had previously been Professor at Cheloo University and West China University and was well-respected within and outside China. His main research area was hepatobiliary disease and the relationship between the liver fluke, Clonorchis sinensis, and the development of bile duct carcinoma. During his tenure at the University of Hong Kong he oversaw the completion of a new Pathology Building in the grounds of Queen Mary Hospital, which was completed in 1958. This new building facilitated the integration of pathology teaching with research and with a clinical pathology service for Queen Mary Hospital.

In 2007, at the 40th anniversary of Professor Hou Pao-Chang’s passing, his son, Professor Laurence Hou initiated the Hou Pao-Chang Medical Memorial Fund in tribute to his late father. The Fund was jointly established by the Hou family, friends, colleagues, students, and the Department of Pathology, The University of Hong Kong, and commemorates Professor Hou Pao-Chang’s life, achievements and contributions to the medical profession. The Fund facilitates visits to the Department of Pathology by distinguished scholars from abroad, and supports teaching and research in Pathology.
Professor James Gibson was the Head of Pathology from 1963 until his retirement in 1983, Dean of Medicine for six years from 1972 to 1978, and Pro-Vice-Chancellor for two separate periods. His contributions to the University as a whole and to the Department of Pathology in particular have been immense, and his influence spread to the future years.

One of Professor Gibson’s achievements was the negotiation of an agreement in 1970 between the University and the Hong Kong government resulting in a grant to run Hospital Pathology Service (HPS). This enabled the Department to provide high quality pathology service to a modern teaching hospital of international standing. It also enabled the University to use its expertise to enhance the quality and scope of clinical laboratory service.

Professor Gibson's other achievements included the setting up of a central electron microscope unit in the University, a new Clinical Pathology Building adjacent to the ‘old' University Pathology Building in 1972, the setting up of a medical laboratory technician training program on a territory-wide basis, the development of cytology service, the setting up of Immunology Section in 1975, and a tissue typing service in 1981. He had approximately sixty publications to his credit and was the principal author of W.H.O. “blue book” on Histological Typing of Tumours of the Liver, Biliary Tract and Pancreas (1978). In 1983, friends and colleagues of Emeritus Professor James Gibson established the James Gibson Fund to mark his retirement after many years of distinguished service to the University and the community. The purpose of the fund is to facilitate visits to the Department of Pathology by distinguished scholars from abroad.
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<td><strong>Symposium I: Liver</strong>&lt;br&gt;&lt;strong&gt;Hou Pao Chang Medical Memorial Lecture&lt;/strong&gt;&lt;br&gt;Well differentiated hepatocellular tumors - a WHO classification update&lt;br&gt;Professor Michael Torbenson&lt;br&gt;Department of Anatomic Pathology, Mayo Clinic, USA&lt;br&gt;&lt;br&gt;Understanding the complexity and heterogeneity of hepatocellular carcinoma&lt;br&gt;Professor Irene Oi-Lin Ng&lt;br&gt;Department of Pathology, The University of Hong Kong&lt;br&gt;&lt;br&gt;Global epidemiology of hepatocellular carcinoma&lt;br&gt;Professor Man-Fung Yuen&lt;br&gt;Department of Medicine, The University of Hong Kong</td>
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<td><strong>State-of-the-Art Lectures</strong>&lt;br&gt;An update on intrahepatic cholangiocarcinoma iCCA and combined HCC-CC&lt;br&gt;Professor Michael Torbenson&lt;br&gt;Department of Anatomic Pathology, Mayo Clinic, USA&lt;br&gt;&lt;br&gt;Personalized oncology requires personalized diagnostics - challenges and opportunities for pathologists&lt;br&gt;Dr Cheng-Han Lee&lt;br&gt;Department of Pathology, University of British Columbia, Canada</td>
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The differential for well differentiated hepatocellular tumors is primarily that of focal nodular hyperplasia, hepatic adenoma, and well differentiated hepatocellular carcinoma. When the liver is cirrhotic, the differential also includes dysplastic nodules. The correct diagnosis of well differentiated tumors is very important for clinical care. This lecture reviews practical, proven methods to classify well differentiated hepatic tumors using the WHO / AFIP classification system. The key morphological and immunostain findings used to diagnose focal nodular hyperplasia are first reviewed. After this, the diagnostic approach to hepatic adenomas is examined in detail, including how to diagnosis the four major molecular subtypes of hepatic adenomas and how to diagnose the three major morphological subtypes of hepatic adenomas. As part of the discussion of hepatic adenomas, the lecture will also review the most important risk factors for malignant transformation of hepatic adenomas. The lecture then concludes by examining the current methods used to diagnose hepatocellular carcinoma.
Understanding the complexity and heterogeneity of hepatocellular carcinoma
Professor Irene Oi Lin Ng
Department of Pathology, The University of Hong Kong

Hepatocellular carcinoma (HCC) is characterized by considerable morphological, molecular and genetic heterogeneity. Discussion in this presentation will focus on all these aspects to address HCC heterogeneity comprehensively. HCC heterogeneity consists of inter-tumoral heterogeneity (including that between patients, found in second primary tumors after curative treatment, and synchronous multifocal tumors of different clonalities) and intra-tumoral heterogeneity (within the same tumors). Morphological classification based on both gross appearance and histology has long been widely used clinically for management and prognostication. The new WHO classification of HCC and the concept of HCC and CC being ends of a disease spectrum will be highlighted in this presentation. Several HCC classification systems using combined histology and molecular findings have been proposed, e.g. a proliferative and non-proliferative phenotype; but they have yet to be incorporated into clinical practice. Comprehensive molecular and genomic analyses using various molecular and next-generation sequencing technology have revealed different degrees of tumor heterogeneity in HCC. It is also to note that inter-tumoral heterogeneity poses severe challenges but also opportunities for the development and administration of systemic molecular targeted therapies. On the other hand, intra-tumoral heterogeneity has emerged as a characteristic of tumors, with cancer cells within a tumor displaying distinct differences in properties including growth rate, metastatic capacity, and response to treatment. Substantial inter-tumoral and intra-tumoral heterogeneity renders biomarker identification challenging when applied to a single tumor biopsy specimen. As a future perspective, studying ctDNA could potentially identify more tumor clones and potentially build up a complete picture of tumor heterogeneity in a longitudinal and dynamic manner. The use of circulating tumor DNA (ctDNA) to evaluate and perhaps overcome overall tumor heterogeneity may be an option to help resolve this problem.
Currently, incidence rate of hepatocellular carcinoma (HCC) is still high worldwide. HCC not only is one of the most common cancers globally, it accounts for substantial morbidity and mortality. Chronic viral infection namely hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection as well as alcoholic liver disease are the three common etiological agents for HCC development while non-alcoholic fatty liver disease (NAFLD) is considered to be a growing contributory entity. Effective screening and management strategies are crucial to reduce the HCC risk and its mortality.

HBV accounting for majority of HCC cases were acquired via perinatal and early horizontal transmission. Universal vaccination of newborns has successfully reduced the HCC incidence in many countries. In addition, antiviral therapies with nucleos(t)ide analogues or pegylated interferon also reduce the incidence of HCC.

The emergence of new direct antiviral agents (DAAs) for HCV has improved infection cure rates of 98 – 100%. All patients with HCV should now be considered for DAAs treatment unless there are strong contraindications.

For NAFLD, the global incidence is increasing rapidly, thus its impact on HCC incidence may be explosive in coming years. Progression to HCC in NAFLD occurs particularly in patients with non-alcoholic steatohepatitis and exacerbated by metabolic syndrome, or PNPLA3 gene polymorphism. Lifestyle changes are essential element of management while effective drug therapy is eagerly awaited.

For management of HCC, early diagnosis via imaging surveillance among persons with HCC risk factors remains the most important strategy to identify early stage disease appropriate for resection or transplantation.
Uterine sarcoma constitutes less than 5% of uterine malignancy but is highly heterogeneous biologically, with varied histology, molecular basis, clinical behavior and treatment options among different tumor types. Driven by improved genomic understanding, the impact on tumor classification is most evident in the categories of endometrial stromal sarcoma, undifferentiated uterine sarcoma and inflammatory myofibroblastic tumor/fibrosarcoma harboring kinase fusions. High-grade endometrial stromal sarcoma is comprised of tumors harboring YWHAE-NUTM2 genetic fusion and tumors harboring BCOR genetic aberrations, which include ZC3H7B-BCOR genetic fusion and BCOR internal tandem duplication (ITD). These tumors are clinically more aggressive than low-grade endometrial stromal sarcomas that harbor genetic fusions such as JAZF1-SUZ12, JAZF1-PHF1 and EPC1-PHF1. Aside from these better-defined genetic fusions, tumors harboring rare genetic fusions such as EPC1-BCOR, JAZF1-BCORL1 and BRD8-PHF1 have also been described, but our experience is limited at this point with regards to its clinical tendency. Rarely, endometrial stromal sarcoma harboring low-grade genetic fusion can transform into tumors showing high-grade histology (dedifferentiated high-grade endometrial stromal sarcoma), though dedifferentiation most frequently occurs in the setting of progressive recurrence of low-grade endometrial stromal sarcoma. Undifferentiated uterine sarcoma remains a diagnosis of exclusion. It is important to exclude high-grade endometrial stromal sarcoma with appropriate molecular analysis, particularly in cases showing monomorphic nuclear features. A subset of tumors showing monomorphic and rhabdoid features can exhibit SMARCA4 (BRG1) deficiency (referred to as SMARCA4-deficient uterine sarcoma), though there can be significant histologic overlap with undifferentiated/dedifferentiated endometrial carcinoma. SMARCA4-deficient uterine sarcoma typically occurs in younger patients (under 40 years of age) and shows intact expression of mismatch repair (MMR) proteins, while the undifferentiated/dedifferentiated endometrial carcinomas occur in older patients and
frequently exhibit deficiency MMR proteins. With regards with uterine (and cervical) mesenchymal tumors that harbor actionable kinase fusion, the majority displays histologic features of inflammatory myofibroblastic tumors that most frequently harbor ALK genetic fusion, while NTRK1/2/3 genetic fusions are present in a subset of predominantly cervix-based spindle cell neoplasm displaying fibrosarcoma-like histologic features. These tumors may mimic smooth muscle tumors (leiomyosarcoma), undifferentiated uterine sarcoma and high-grade endometrial stromal sarcoma with BCOR alterations, and should be discerned from these entities given the potential therapeutic implication of kinase fusion identification.

Genomic analysis coupled with cancer organoid culture technology - building of next generation cancer cell models for therapeutic development

Professor Suet Yi Leung
Department of Pathology, The University of Hong Kong

Recent advances in genomic technology has led to refined delineation of different molecular pathways of cancer development in the gastrointestinal tract. In gastric cancer, the four distinct molecular subtypes (EBV, MSI, Intestinal/CIN, diffuse/GS) each carries distinct combination of driver gene mutations and characteristic epigenetic profiles. In colon cancer, the two major pathways, adenoma to carcinoma sequence and serrated lesion to carcinoma transition are each characterised by perturbation of Wnt downstream or upstream regulators respectively. With recent advances in organoid culture technology, we have been able to generate cell models capturing each of these molecular subtypes, including early lesions at different stages of carcinogenesis. Detailed genomics analysis in these pure epithelial organoid models reveal underlying genetic changes that closely parallel the original tumour. Single cell analysis enables us to capture the dynamic range of cellular differentiation potential. CRISPR-based genome editing can be applied to study driver gene function. Lastly large scale therapeutic screening can be applied to uncover sensitivity to single drug or drug combinations. Overall, these new generation cell models bring exciting new possibilities for the study of cancer cell biology and therapeutic development.
A genomic approach to rare disorders

Dr Ivan Fai Man Lo

Department of Health, Hong Kong SAR Government

Rare disorders are individually rare. However, as there are thousands of rare disorders, they are not so rare collectively, affecting as many as 6-8% of the population. Most of these rare disorders have a genetic origin, and the genetic defects are very heterogeneous in nature, ranging from chromosomal abnormalities to DNA sequence alterations or even epigenetic aberrations. This huge diversity of rare genetic disorders has always been a challenge in diagnosis. The field of medical genetics has transitioned steadily from genetics to genomics over the past 10 years. It was also called a paradigm shift. The adoption of genomic technologies like chromosomal microarray (CMA) and next generation sequencing (NGS) invariably results in increased diagnostic yield, shortened “diagnostic odyssey”, and sometimes sheds light on new treatment options. Nevertheless, the conventional genetic approach is not totally obsolete; the choice between genetic and genomic approaches should depend on the clinical problem, and the availability of clinical and laboratory expertise.
Intrahepatic cholangiocarcinomas show a range of clinical, histological, and molecular associations and they can be subtyped into different types of cholangiocarcinomas. This lecture reviews the current histological approach to classifying cholangiocarcinomas using the WHO / AFIP classification system, which divides cholangiocarcinomas into large duct and small duct types. The small duct cholangiocarcinomas include a subset of cases with unique morphology that are called cholangiolocellular and bile duct plate malformation like cholangiocarcinoma. The lecture examines the morphology and molecular correlates of these subtypes of cholangiocarcinoma, exploring the rationale that provides the basis for this current classification approach. Precursor lesions to cholangiocarcinoma will be briefly considered. The lecture ends by considering combined HCC-CC, with an emphasis on recent advances that provide a robust definition for this rare tumor, a definition that is based on combined HCC-CC having these two features: (1) two distinct morphological components, one that is hepatocellular carcinoma and one that is cholangiocarcinoma, and (2) the hepatocellular carcinoma component staining like hepatocellular and the cholangiocarcinoma component staining like cholangiocarcinoma.
Personalized oncology requires personalized diagnostics – challenges and opportunities for pathologists
Dr Cheng Han Lee
Department of Pathology, University of British Columbia, Canada

The application of high throughput genomics, epigenetics and proteomic analysis has rapidly advanced our understanding of the molecular and genetic basis of cancer. Clinically, these insights have translated into more biologically refined tumor classification and increasing treatment options, with significant impact on the practice of pathology. Diagnostically, pathologists are utilizing more comprehensive ancillary molecular assays to gain additional insights. With regards to treatment, there are also increasing number of companion predictive testing required to inform therapeutics option(s) along increasingly complex treatment algorithms/pathways. Given the convergence of diagnostic and therapeutic needs, pathologists are ideally positioned to combine our histopathology and genetic knowledge with rational integration of molecular diagnostics to guide our clinical colleagues and assist patients in their oncologic journey. This can occur in subspecialty practice settings across most subspecialty areas, where subspecialty pathologists select the most rational ancillary molecular assays in the specific histologic and immunophenotypic context, to enable accurate tumor classification which in turn dictates the most appropriate clinical management. This can be further enabled by developing and instituting site-specific molecular triaging strategy, based on known frequency and mutual exclusivity of actionable/driver genetic alterations to optimize result turn-around time and comprehensiveness of testing. For instance, in lung cancer, this may involve the implementation of a first tier rapid turn-around/low-input focused next generation sequencing (NGS) panel to detect EGFR, MET, ALK, ROS1, KRAS and BRAF alterations, and for cases with wild-type findings, subsequent activation of a second tier comprehensive NGS panel to cover less common alterations of proven or potential therapeutic importance (including clinical trial). Moreover, given the dynamic nature of tumor and the increasing understanding of treatment resistance/escape mechanisms, the need for temporal/longitudinal testing and strategy in addressing heterogeneity of resistance mechanisms will continue to present new challenges and opportunities for pathologists. In the era of increasingly personalized oncologic care, pathologists need to play a central role in personalized diagnostics to achieve best clinical value and outcome.
Digital image analysis and applications in pathology
Dr Rex Kwok Him Au-Yeung
Department of Pathology, The University of Hong Kong

Computational pathology and digital image analysis are hot topics in anatomical pathology. They involve the application of computer vision, machine learning and deep learning techniques in recognizing patterns in digital microscope slides, as well as quantifying objects in the microscope image. This presentation aims to introduce the field of computational pathology to the audience, the hardware and software equipment for histological image analysis, and how these techniques can be applied in pathology diagnostics and research.

Deep Learning for computational pathology
Dr Hao Chen
Insight Medical Technology Co. Ltd

Deep learning represents data with multiple levels of abstraction and has dramatically improved the state-of-the-art in many domains including speech recognition, visual object recognition and natural language processing. Despite its breakthroughs in above domains, its application to large-scale and high-throughput histology image analysis remains under-explored. This talk will share our recent studies on developing state-of-the-art deep learning methods including ScanNet, Fast Scannet, and weakly multi-instance supervised learning for fast and accurate large-scale histology image analysis, with an in-depth dive into several cancer applications. To further unleash the power of deep learning integrated into clinical scenarios, future promises and pitfalls will also be discussed.
Debate: “Can AI replace pathologists?”

There are tremendous advances in digital pathology and artificial intelligence with increased application in various fields of medicine including pathology. It is postulated that artificial intelligence will one day replace doctors, and pathology is one of the specialties that is high on the list of such replacement.

Dr Kam Cheong Lee
Department of Pathology, Princess Margaret Hospital

Dr King Chung Lee
Pathology Department, St. Paul’s Hospital
Enquiry

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