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Invited Speaker Abstracts

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Companion Sessions
AIDPATH · Association of Clinical Electron Microscopists
British Association of Cytopathology
British Association of Gynaecological Pathology
British Association of Urological Pathologists
Dutch Irish English (DIE) Cardiac Group · Renal EQA
Renal Transplant EQA · 100,000 Genomes Project

KEY

Ⓟ = Presenter

PRESENTER'S INDEX

To be found at the end of this document, after the abstract listings.

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S1

Interstitial Lung Disease

Ⓟ AG Nicholson

Royal Brompton Hospital, London, UK

In adults with an idiopathic interstitial pneumonia (IIP), an updated classification system was published in 2013. Definitions for the 7 histological patterns remain essentially unchanged, there have been numerous advances in the last decade. For usual interstitial pneumonia (UIP), updated management recommendations were published in 2011 and a pattern of UIP is now being increasingly recognised in biopsied patients who do not have IPF after multidisciplinary review, especially chronic hypersensitivity pneumonitis and connective tissue disease (CTD)-related disease. Idiopathic non-specific interstitial pneumonia is now recognised as a specific clinico-pathological entity, with the majority cases proving to have secondary associations/causes after multidisciplinary review. Respiratory bronchiolitis—interstitial lung disease is now commonly diagnosed without surgical biopsy, and acute exacerbation of IIPs is now well defined. A group of rare entities, including pleuroparenchymal fibroelastosis and rare histologic patterns, is also introduced. There have also been advances in the undertaking of biopsies with most institutions sampling at least two sites, ideally using preoperative targeting. These histological patterns are also recognised in children, although classification is more complex and includes entities specific to a younger age group (e.g. neuroendocrine hyperplasia of infancy, pulmonary interstitial glycogenosis). Surfactant protein gene mutations are also being increasingly identified. In relation to microscopy, for CTDs in particular, it is important to remember that these diseases can affect all compartments of the lung. As an example, rheumatoid disease is not only associated with patterns of IP, but also, rheumatoid nodules, apical fibrosis, airways disease (follicular bronchitis, bronchiectasis, bronchocentric granulomatosis, constrictive obliterative bronchiolitis), pulmonary hypertension, and rarely development of lung malignancies.

S2

The Emerging Spectrum of Non-HPV Related Cervical Adenocarcinomas

Ⓟ W McCluggage

Belfast Health and Social Care Trust, Belfast, UK

Most adenocarcinomas of the cervix are associated with high-risk human papillomavirus (HPV) infection and are referred to as usual-type adenocarcinomas. However, there is an emerging spectrum of non-HPV related cervical adenocarcinomas, the most common of which is so-called gastric-type; this accounts for approximately 10-15% of primary cervical adenocarcinomas and 2–4% of all cervical carcinomas. Cervical gastric-type adenocarcinomas are aggressive neoplasms which have a poor prognosis and often present at high stage with a propensity for ovarian, peritoneal and omental metastases. Adenoma malignum (mucinous variant of minimal deviation adenocarcinoma) represents the well differentiated end of the spectrum of gastric type adenocarcinomas. The precursor lesions of cervical gastric type adenocarcinoma are still being described but include gastric-type adenocarcinoma in situ and atypical lobular endocervical glandular hyperplasia. A variety of benign cervical glandular lesions exhibiting gastric differentiation also occur. Other non-HPV related cervical adenocarcinomas include most clear cell carcinomas and all mesonephric adenocarcinomas; a recent study has shown that the latter are commonly associated with KRAS mutations.

S3

How Do We Assign Primary Site in Extrauterine High Grade Serous Carcinoma

Ⓟ N Singh

Bart's Health NHS Trust, London, UK

Purpose: To present evidence favouring a uniform approach to primary site assignment in extra-uterine high grade serous carcinoma (HGSC)
Methods: Review of literature regarding tubal origin of HGSC, variation in practice and benefits of uniform primary site assignment.
Summary of results: The new unified FIGO staging system (2013) for ovarian, tubal and peritoneal carcinomas requires pathologists to assign a primary site to all cases. There is a wealth of scientific evidence indicating that the majority of HGSC arise in the fallopian tube, however this evidence is not widely known/accepted. In the absence of a uniform protocol there is potential for cases to be assigned different primary sites and even different stages in low-stage cases. A uniform approach will help minimize these discrepancies in an era of optimism over exciting new developments in prevention, early detection and treatment of HGSC that show potential to improve patient outcomes.
Conclusions: There is an urgent need for universal agreement on uniform terminology and staging parameters in HGSC. These have been proposed in international guidelines for reporting ovarian, tubal and peritoneal carcinomas.

S4

The Clinical Significance of Stratifying Vulval Squamous Carcinoma into HPV and Non-HPV Related Variants

Ⓟ CB Gilks

Vancouver General Hospital and University of British Columbia, Vancouver, Canada

Vulval squamous cell carcinoma (VSCC) and its precursor (vulvar intraepithelial neoplasia/VIN) can be subdivided based on HPV status into two molecularly distinct entities. While the HPV-associated precursor of invasive squamous cell carcinoma (HSIL (VIN2/3), as per the proposed LAST terminology) is more common than HPV-independent precursor lesions (differentiated VIN or dVIN), the HPV-independent invasive squamous cell carcinomas are more common than their HPV-associated counterparts. This reflects the different natural histories of dVIN and HSIL (VIN2/3), with the former more likely to progress to invasive squamous cell carcinoma, and over a relatively short time period. In a review of all cases of dVIN (without associated invasive squamous cell carcinoma) seen at our institution, most patients progressed to invasive carcinoma and ultimately died of disease, a significantly worse prognosis than was seen in a control group of patients with HSIL (VIN2/3). Studies on the prognostic significance of HPV status in VSCC have given conflicting results in the past. p16 immunostaining has emerged as a sensitive and specific surrogate for determination of HPV status in VSCC. A retrospective analysis of overall survival (OS), disease-specific survival (DSS), and progression-free survival (PFS) in 217 patients with VSCC from our institution demonstrated that patients with HPV-associated tumours had superior PFS (HR 0.37, 95% CI 0.18-0.70), DSS (HR 0.19, 95% CI 0.08-0.41) and OS (HR 0.35, 95% CI 0.21-0.59). This difference was driven by worse outcomes (PFS, DSS and OS) for patients with HPV-independent tumours compared with those with HPV-associated tumours in patients who underwent surgery after 1995, when treatment consisted of more localized radical surgery through separate vulvar and groin excisions (1996–2005). No differences in outcome were seen between HPV-independent and HPV-associated VSCC for cases from the era of more aggressive en bloc radical dissections (1985–1995).

S5

Fibrosing Organising Pneumonia (FOP) and Pleuroparenchymal Fibroelastosis (PPFE)

Ⓟ DM Rassl

Papworth Hospital NHS Foundation Trust, Cambridge, UK

Organising pneumonia is a non-specific pattern of acute lung injury showing plugs of granulation tissue within alveoli, alveolar ducts and small airways. Most patients respond to corticosteroid therapy; 10–15% experience progressive disease. An important factor appears to be ongoing lung injury. Cases which do not respond are more likely to show interstitial and granulation tissue fibrosis. A proportion of patients have progressive FOP as a primary process. In these cases the normal healing process may be disrupted, with delayed alveolar re-epithelialisation, ongoing pneumocyte apoptosis, an imbalance between coagulation and fibrinolytic cascades, release of profibrotic cytokines and growth factors, and epithelial-mesenchymal transition of type II pneumocytes. Lung injury and inflammation may also be the initial step in the development of PPFE, which affects the nondependent areas of the lungs. Histologically PPFE shows pleural fibrosis, subpleural intra-alveolar fibrosis and prominent elastosis with abrupt transition to unaffected parenchyma and scant patchy lymphoplasmacytic infiltrates. In some cases pleural thickening is not seen. A proportion of cases appear idiopathic, but PPFE has been associated with lung and bone marrow transplantation, chemotherapy, recurrent infections and autoimmunity. Some familial cases have also been reported. As with FOP, the intra-alveolar fibrosis seen in PPFE may be the result of an imbalance in the rate of deposition and clearance of intra-alveolar fibrin and fibroblastic tissue following acute lung injury. This imbalance may have a genetic basis, be due to environmental factors, or both. In certain animal models elastin gene expression is increased following lung injury, and differences in elastosis between PPFE and other fibrosing lung diseases may give insights into the pathogenesis of this condition.

S6

Cystic Lung Disease

Ⓟ A Fabre

St Vincent's University Hospital, Dublin, Ireland

Cystic lung diseases (CLD) represent a diverse group of uncommon disorders that can present a diagnostic challenge and be associated with multi-system diseases. High-resolution computed tomography of the chest helps to define the morphological aspects and distribution of lung cysts seen on pathological samples. The main diseases in this group that are presented include lymphangioleiomyomatosis, pulmonary Langerhans cell histiocytosis, Birt–Hogg–Dubé syndrome and their differential diagnoses, as well as other rare causes of cystic lung disease, including cystic metastatic sarcomas and inflammatory disorders. Recent molecular advances in the diagnosis of CLD will also be discussed.

S7

UIP, NSIP and Their Differential Diagnoses

Ⓟ AG Nicholson

Royal Brompton and Harefield NHS Foundation Trust, London, UK

In adults with an idiopathic interstitial pneumonia (IIP), an updated classification system was published in 2013. Although definitions for the seven histological patterns remain essentially unchanged, there has been substantial progress in our understanding. In relation to usual interstitial pneumonia (UIP), updated management recommendations were published in 2011, with the most significant change recommending varying degrees of confidence in diagnosis. A pattern of UIP is also being increasingly recognised in patients with chronic hypersensitivity pneumonitis, and can also be seen in connective tissue disease (CTD)-associated ILD, especially in patients with rheumatoid arthritis, drug toxicity, familial ILD and pneumoconiosis. Idiopathic non-specific interstitial pneumonia (NSIP) is now defined as a specific clinico-pathological entity, although the majority cases prove to have secondary associations/causes after multidisciplinary review. Indeed, even in cases that are idiopathic at presentation, a pecentage will subsequently present with a CTD . NSIP is also recognised in children, although classification is more complex and includes entities specific to a younger age group (e.g. pulmonary interstitial glycogenosis) in the differential diagnosis. Surfactant protein gene mutations are being increasingly identified in this age group.

S8

Immunomodulatory Therapy in Non-Small Cell Lung Cancer: A Year into Clinical Practice

Ⓟ JR Gosney

Royal Liverpool University Hospital, Liverpool, UK

The approach to the diagnosis, classification and analysis of non-small cell lung cancer (NSCLC) has advanced beyond all recognition in the last decade, a revolution driven by the development of drugs active against particular sub-groups of tumour defined by their genetic pathology or protein expression rather than by their morphology. The most recent of these, the immune modulators (IMs), act by inhibiting the binding of programme death ligand (PDL)-1 on tumour and immune cells to its receptor programmed death (PD)-1 on T lymphocytes. The more PD-L1 is expressed by the tumour, the greater is the inhibition of the immune response, and the more likely is the tumour to respond to drugs targeting the PD-L1/PD-1 interaction and re-exposing it to immune attack. Unfortunately, assessing PD-L1 expression by immunochemistry as an indicator of sensitivity to IMs is not straightforward. Not only is PD-L1 expression a continuum, it changes as the tumour develops and is heterogeneous within it. In addition, each of the currently available IMs was developed with its own companion diagnostic anti-PD-L1 test. These employ different antibodies on different platforms and take different approaches to scoring. Despite these considerable challenges, development of the necessary technical and interpretative expertise and harmonisation of testing protocols has been rapid and the use of PD-L1 expression as a guide to the effective and rational use of IMs is becoming standard practice in the management of patients with NSCLC.

S9

Prognostic Factors in Mesothelioma

Ⓟ RL Attanoos

Cardiff and Vale University Health Board, Cardiff, UK

Diffuse malignant mesothelioma has a poor prognosis although it is recognised that some persons with the disease do have improved survival. Prognostic factors may be classified as: clinical; haematological/serum; imaging; pathological; and molecular. Clinical factors associated with poor prognosis include: old age, male gender, high tumour stage, poor performance status, and weight loss. Adverse haematological factors include: high inflammatory markers (C-reactive protein, neutrophil to lymphocyte ratio, leucocytosis); anaemia; thrombocytosis; raised lactate dehydrogenase and mesothelin-related peptide. Imaging: Clinical staging is an important prognostic factor. CT-PET scan identifies metastatic disease and total glycolytic volume and metabolic activity correlates with shorter median survival. Adverse pathological factors include non-epithelioid subtypes especially desmoplastic variant, high nuclear grade, high mitotic and Ki-67 index, low chronic inflammatory stromal response, and high CD10 expression. Myxoid rich epithelioid subtype is a more favourable variant in both pleura and peritoneum. Molecular prognostic factors include FISH 9p homozygous deletion, a marker of malignancy and poor prognosis. Homozygous p16 deletions are present in including almost all sarcomatoid mesotheliomas although only in a lower percentage of epithelioid tumours. Germline BAP-1 mutations (observed in 1–2% mesotheliomas) appear to confer a favourable prognostic impact on overall survival. Somatic mutations are more common in mesothelioma (~60%) although have no clear prognostic significance. Gene expression profiling has identified a limited array of patterns with potential prognostic utility although this is not routinely established. Overall the most significant improvement in survival has been for young female subjects with diffuse malignant mesothelioma of the peritoneum following cytoreductive surgery and heated intraperitoneal chemotherapy.

S10

Diagnostic Tools That Make You Smart: Defending Pathologists' Attributes in the Age of the Machine

Ⓟ J Molin

Sectra AB, Linköping, Sweden

With the rise of digital pathology, pathologists will start to perform the majority of their diagnostic review using computer workstations instead of microscopes. This talk will take a critical look at the digitization process from a human-centered perspective, and analyze how the routine diagnostic review experience could be improved by designing smart tools. A number of research projects will be presented where the latest visualization and human-computer interaction research has been used to create novel tools that leverage what pathologists' are good at alongside the machine's strengths. This talk will both focus on how the manual digital review process could be improved by the digitization as well as review together with automated image analysis tools.

S11

Deep Learning Based Algorithms Significantly Aid Breast Cancer Histopathology

Ⓟ J van der Laak; B Ehteshami Bejnordi; D Tellez Martin; P Bandi; MCA Balkenhol; P Bult; GJS Litjens

Radboud University Medical Center, Nijmegen, Netherlands

Deep learning is a state-of-the-art pattern recognition technique that has been found extremely powerful for analysis of digitized histopathological slides. In our research we study different applications of this technique for improved diagnostics and prognostics of breast cancer patients. Histopathological assessment of the axillary lymph node status is one of the three components of breast cancer staging. Assessment of the lymph node status is a straightforward yet promising candidate application for deep learning based automation. Our current algorithms for this task perform equally well as trained pathologists, making them suitable for large scale routine validation and implementation. We also developed algorithms for fully automated recognition and counting of mitotic figures, which aids breast cancer grading. As a result of these techniques, routine diagnostics becomes more efficient and reproducible. More advanced automated techniques are developed to identify novel prognostic biomarkers, contributing to the development of personalized medicine. We study the tumor to stroma ratio, the presence of tumor infiltrating lymphocytes and the appearance of the tumor stroma as possible future prognosticators.

S12

The Application Process and Specialty Training in Histopathology

Ⓟ M Moore; J Houghton

Department of Pathology, Royal Victoria Hospital, Belfast Health and Social Care Trust, Belfast, UK

Histopathology is a run-through postgraduate specialty training programme, regional applications for which can be made at the end of foundation training, via an online registration system. Over a minimum of 5 years, which encompass stages A–D, trainees are exposed to surgical pathology, cytopathology and autopsy pathology, in addition to exposure to subspecialty areas such as neuropathology, paediatric pathology and forensic pathology. The curriculum is set by the Royal College of Pathologists, with the purpose of attaining a certificate of completion of training (CCT). Throughout training, continuous assessment is obtained through work-place based assessments, the complexity of which corresponds to increasing grade. There are three formal examinations which assess suitability for specialty and which lead to attainment of Fellowship of the Royal College of Pathologists (FRCPath). Histopathology is a diverse specialty, the focus of which is merging the scientific basis of disease with clinical interpretation in order to provide the referring team with a diagnosis which guides the resultant patient management.

S13

Do You Have the Potential to be a Pattern Recognition Expert?

Ⓟ JP Houghton

Queen's University Belfast, Belfast, UK

One of the most important skills of an expert histopathologist is the ability to visually examine a microscopic image and rapidly extract key information from this image. A widely supported theory explaining how we visually examine images proposes that there are two pathways in visual searching. Firstly, a non-selective pathway which does not require eye movement. This has been described as holistic, Gestalt-like, coup d'oeil, top-down, thin-slicing or subconscious searching and involves a global (at a glance) impression of the image. The second pathway, requiring eye movement, is the selective pathway and involves carefully screening an image for specific findings. In this presentation case based examples will be used to illustrate these processes in histopathology. In addition, a test of visual perception and visual memory will be administered to the audience in this interactive presentation.

S14

Pathological Subtyping of Ovarian and Endometrial Cancers: A Story of Success and Failure

Ⓟ WG McCluggage

Belfast Health Social Care Trust, Belfast, UK

Traditionally there has been significant interobserver variability amongst pathologists in the subtyping of both ovarian and endometrial epithelial malignancies. This resulted in a high incidence of mixed carcinomas and greatly hindered the development of subtype specific management stategies. In recent years, pathologists have become very good at subtyping ovarian carcinomas (SUCCESS) with recent studies using modern diagnostic criteria showing a high degree of interobserver agreement. This has largely been due to the discovery of a robust marker of the serous phenotype WT1 and this has resulted in the recognition that most ovarian neoplasms which were previously reported as high grade endometrioid carcinomas, transitional carcinomas, undifferentiated carcinomas and mixed carcinomas represent high grade serous carcinomas. This, and molecular investigations, have shown that mixed ovarian carcinomas are extremely uncommon, accounting for less than 1% of ovarian carcinomas. The success story regarding the subtyping of ovarian carcinomas has not been replicated with endometrial carcinomas (FAILURE) where there is significant interobserver variability in subtyping, especially of high grade endometrial carcinomas. The Cancer Genome Atlas (TCGA) study identified four molecular types of endometrial carcinoma with prognostic implications (copy number high- poor prognosis; copy number low- intermediate prognosis; microsatellite instability high- intermediate prognosis; POLE ultramutated- good prognosis). Morphology is of some, but limited, value in separating the tumours into these molecular groups. Recent studies have suggested that an approach using MMR and p53 immunohistochemistry and POLE mutation analysis can separate endometrial carcinomas into these four prognostically different molecular groups. Molecular studies also suggest that, similar to the situation in the ovary, mixed endometrial carcinomas are rare.

S15

Omental, Peritoneal and Ovarian Biopsies

Ⓟ CB Gilks

Vancouver General Hospital and University of British Columbia, Vancouver, Canada

Biopsies of omentum, peritoneum and ovary can show a wide range of primary neoplasms of mesothelium or ovary, secondary neoplasms, or tumor-like conditions. Such small biopsies may be taken at the time of surgery for an unrelated condition, when an unsuspected incidental finding is encountered, or they may be small biopsies from patients with more extensive disease, in order to guide treatment. This latter situation has become more common after a randomized clinical trial demonstrated that neoadjuvant treatment for advanced stage tubo-ovarian high-grade serous carcinoma offers equivalent survival with less morbidity, compared to up-front surgery. In these patients it is important to establish a correct diagnosis as neoadjuvant treatment may be ineffective/contraindicated for tumor types other than high-grade serous carcinoma. In this session, a series of cases will be presented, emphasizing the range of pathologies that can be encountered, and the differential diagnosis of these lesions.

S16

Tissue is the Issue: Sample and Practical Challenges in Molecular Pathology Testing

Ⓟ A Oniscu

Royal Infirmary of Edinburgh, Edinburgh, UK

Molecular testing to personalise therapy is an essential part of the investigation of cancer in order to personalise anti-cancer therapy. Availability of sufficient tissue is important and in some settings, for example lung cancer diagnosis is often made on a cytological sample which is also used for molecular phenotyping to allow therapeutic stratification. For cytological specimens residual material remaining after the initial diagnostic slide is made into a cell block. In most pathology laboratories these are prepared by using plasma to form a clot entrapping the cells followed by embedding into paraffin wax. Sections from this allows better morphological assessment and permits immunohistochemsitry. This is the preferred method to prepare cell blocks worldwide. Plasma of course contains cell free DNA. To identify the level of DNA contamination in cell blocks we have analysed DNA extracted from cell free plasma thrombin cell blocks and blank (tissue free) histological paraffin blocks using routine molecular techniques including PCR/Pyrosequencing and a Qiagen Therascreen EGFR RGQ PCR Kit. Plasma is a source of contaminating DNA. As high throughput Next Generation Sequencing platforms make their way into routine diagnostic practice, their superior sensitivity in DNA mutation detection in the presence of any extraneous DNA might generate false positive results and impact on the molecular diagnosis. To overcome this problem and maintain the quality of cell-blocks for histological diagnosis we developed a method to DNase treat plasma. Many of the treated plasma samples did not contain any detectable DNA (BRAF, DIPplex and Qubit analysis) while others contained exceptionally low levels, significantly below the reporting threshold of the assays. The use of treated plasma did not have any detectable impact on the histological assessment of cells or downstream molecular testing. We conclude that treated plasma should be routinely used to prepare cell blocks.

S17

Clinical Implementation of Circulating Tumour DNA Analysis by Digital Droplet PCR for NSCLC

Ⓟ R Butler

University Hospital of Wales, Cardiff, UK

Cancer patients increasingly need to receive personalised medicine (genetic) tests to determine the best course of treatment. However, this requires an invasive biopsy, or sometimes re-biopsy of their tumour. This is not always possible because the patient is too sick, the tumour is not operable, or the patient is simply not willing. Non-invasive sampling through a simple blood test is clearly a preferable alternative, and may now be achieved with circulating tumour DNA technology (ctDNA). ctDNA can be found in the bloodstream of cancer patients and is shed from the tumour, it represents an easily accessible source of tumour DNA without an invasive biopsy. The diagnostic analysis of ctDNA requires novel and highly sensitive molecular techniques to be optimised in association with the development of clinical patient pathways for the handling of these unstable blood samples. Through the use of ctDNA a far greater number of patients will potentially be able to access personalised medicine testing; an estimated 30-40% of lung cancer patients are unable to access personalised medicine treatments because they do not have tissue available for testing. ctDNA is present at only very low levels in a patients blood, and therefore highly sensitive technologies are required for its detection. We have developed and optimised droplet digital PCR (BioRad) for this application. Assays specific for EGFR gene mutations have been validated to detect mutations at an allele frequency of 0.5%, these are now provided clinically for 1st line patinets (to detect patients suitable for EGFR TKIs) and for patients progressing on EGFR TKIs (to detect patients with the resistant mutation EGFR p.T790M).

S18

Microscopic Colitis: A Term in Evolution

Ⓟ MB Loughrey

Royal Victoria Hospital, Belfast, UK

Microscopic colitis is an increasingly recognised cause of chronic watery diarrhoea, typically afflicting elderly females. The term was originally used in a descriptive sense. For several decades now, it has encompassed the distinct entities of collagenous colitis (CC) and lymphocytic colitis (LC), sharing the features of normal, or near normal, endoscopy, normal mucosal architecture histologically and increased lamina propria inflammation, differing essentially in the presence or absence of a sub-epithelial collagen band. Clinicopathological understanding of these conditions has increased in recent years, with rare variants described including pseudomembranous CC and giant cell and cryptal variants of LC. CC and LC both have recognised clinical associations with a range of autoimmune diseases, including coeliac disease (stronger association with LC) and causative drugs, most importantly PPIs (in particular lansoprazole), NSAIDs and SSRIs. Chronology of symptom onset in relation to medication use is the best clue to a drug-related aetiology, supported occasionally by histological evidence of prominent apoptosis and/or eosinophilia. Both diseases typically run a benign course, with excellent response to treatment and refractory cases rare. Optimal endoscopic biopsy approach includes sampling from the right and left colon separately, to maximise the likelihood of a definitive diagnosis and minimise the risk of a false negative diagnosis through inadequate sampling, or of a false positive diagnosis relating to disease mimics. With subtle differences in clinicopathological associations, generally distinct histological features (given adequate sampling) and rare crossover in phenotype on follow-up biopsy, use of a more specific diagnostic term (CC or LC) is preferred to "microscopic colitis", noting a substantial minority of cases with described endoscopic abnormalities.

S19

Ulcerative Colitis Versus Crohn's Disease: Is Biopsy Useful?

Ⓟ RM Feakins

Barts Health NHS Trust, London, UK

The diagnosis of inflammatory bowel disease (IBD) can be challenging. Subsequent classification as ulcerative colitis (UC) or Crohn's disease (CD) may be even more difficult. However, the distinction is important because treatment, prognosis and complications are different. Classification as UC or CD often requires combined assessment of the clinical picture, imaging, endoscopic findings, and histology. Sometimes, the diagnosis is obvious prior to biopsy. For example, the patient might have classical features of Crohn's disease with perianal fistulas, small bowel strictures on imaging, and discontinuous colonic involvement. However, histology can be proportionately more contributory if the clinical picture is less clear-cut. There are several histological features in colorectal biopsies that help discriminate between UC and CD. UC is favoured by: anatomically continuous colorectal involvement; absence of ileal involvement; diffuse mucosal architectural abnormalities; diffuse chronic inflammation; severe mucin depletion; and widespread neutrophil activity. CD is strongly favoured by the presence of granulomas, especially if they are not related to crypt rupture. Unfortunately, granulomas are only found in a minority of CD biopsies. CD is also favoured by: discontinuous involvement; ileal disease; non-diffuse architectural changes; and non-diffuse chronic inflammation. Upper GI biopsies are more likely to be inflamed in CD than UC, although inflammation alone is not discriminatory. Also, there are many other causes of oesophagitis, gastritis and duodenitis. However, upper GI granulomas in the setting of IBD clearly favour CD over UC. "Focally enhanced gastritis" is probably not discriminatory. In many cases, IBD cannot be classified reliably. The pathologist should try to express a preference for UC or CD, as this may assist management. Otherwise, the term "IBD unclassified" (IBDU) can be used, although this is a clinicopathological rather than a pathological term.

S20

Pathology of the Ileoanal Pouch

Ⓟ MR Novelli

UCLH, London, UK

Since its development by Parks and Nicholls in 1978 the ileoanal pouch has transformed many patients' lives. However, its formation may be associated with a number of clinical complications providing a spectrum of pathological changes. An understanding of how a pouch is formed and the normal adaptive changes seen in pouch mucosa is crucial before attempting to assess pouch pathology.

S21

Diagnostic Dilemmas in Barrett's Oesophagus

Ⓟ SL Meijer

Academic Medical Center, Amsterdam, Netherlands

Over the last decades a strong increase in the incidence of oesophageal adenocarcinoma (OAC) is observed and has prompted frequent and strict surveillance endoscopies in patients suffering from Barrett's oesophagus (BO). BO is a known precursor lesion with the potential of developing into OAC through the sequence of inflammation to metaplasia and dysplasia. However, great clinical heterogeneity is observed in the tempo and mode of malignant progression. The reasons underlying this clinical heterogeneity remain unclear. Currently, surveillance and treatment decisions are solely based on conventional histopathological assessment of surveillance biopsies. Although recent research into objective biological markers for progression is promising, clinical implementation of a biomarker panel is far away and histology is the only risk stratification tool available. A histopathological diagnosis of low grade dysplasia (LGD) is considered to be a risk of malignant progression. Risk stratification according to dysplasia grade is nevertheless fraught with uncertainty as data on malignant progression rates for LGD are highly diverging, ranging from 0.6% to 13.4% per patient-year. It has long been recognized that the histologic diagnosis of dysplasia in Barrett's oesophagus is subject to considerable inter- and intra-observer variability and interpretation differences worldwide. The variability between observers relates to the complete spectrum of dysplasia grades, but is especially pronounced in the distinction between regenerative changes and low-grade dysplasia. In this presentation examples of frequently encountered difficulties in the diagnostic work up of Barrett's neoplasia are discussed and several strategies to improve inter- and intra-observer variability for better histopathological risk stratification such as assessment of morphologic features, the use and limitations of ancillary stains and the value of a second opinion of dysplastic cases are explored.

S22

Cutaneous Vascular Tumours: An Update

Ⓟ JE Calonje

St John's Institute of Dermatology, London, UK

The histological diagnosis of vascular tumours is often difficult not only because the morphological spectrum of these neoplasms is very broad but also because classification is complex and distinction between benign and malignant lesions is often difficult. Cutaneous vascular tumours are fairly common and most are benign or low-grade malignant. Tumours in both groups can be confused with angiosarcoma and neoplasms of different lineage may mimic the latter (for example, atypical fibroxanthoma). Immunohistochemistry for vascular markers is very useful as an aid in differential diagnosis and new markers of endothelial cell differentiation continue to be described the most recent being ERG a nuclear transcription factor which is the most specific and sensitive vascular marker introduced to date. In this presentation emphasis will be on selected benign vascular proliferations that are often confused with malignancy including the cutaneous epithelioid angiomatous nodule, the intravascular variant of epithelioid haemangioma and the localized variant of reactive angioedotheliomatosis and a newly delineated tumour of intermediate malignancy that although infrequent, often presents in the skin and displays very few histological features of vascular differentiation and named pseudomyogenic haemangioendothelioma.

S23

Myxoid Tumors of the Skin

Ⓟ SD Billings

Cleveland Clinic, Cleveland, United States

Myxoid soft tissue tumors and myxoid variants of soft tissue tumors are a source of frequent diagnostic difficulty.There is significant histologic overlap in this group of tumors. Myxoid sarcomas are easily mistaken for benign neoplasms, and benign tumors can be mistaken for sarcomas. This presentation will emphasize a practical approach to the diagnosis of cutaneous myxoid tumors. The emphasis will be on key histologic features that aid in the diagnosis. The utility of ancillary diagnostic tests, including potential pitfalls, will also be discussed.

S24

Update on the Clinic-Pathological and Molecular Diagnosis of Melanocytic Lesions

Ⓟ A de la Fouchardiere

Centre Leon Berard, Lyon, France

Melanocytic tumors represent a wide spectrum of entities with various molecular backgrounds. We now have evidence that in most cases there is a progressive accumulation of molecular abnormalities that lead from nevi to melanoma. Melanomas of various subtypes: acral/mucosal melanoma, superficial spreading melanoma, lentigo maligna melanoma should be viewed as different diseases. Modern molecular pathology uses a growing number of tools to identify anomalies. We believe that so far no tool is superior to another but it is more the integrated combination of tools that gives us a more precise vision of what is happening within a single sample. Some recent studies show some strong links between morphological features and genetic anomalies. Clinical features, embryogenesis and morphology are the initial steps of the analysis that screen for the need of other techniques such as immunohistochemistry, gene mutation study, gene fusion search by RNA sequencing or single or multiple studies of gene copy number variations (FISH/aCGH). Each of these more specific techniques can be combined or used to confirm/ precise a result. Above all, the clinical evolution of the patient remains of major interest in the view of the further evaluation of metastatic risk or possibly lethal evolution.

S25

Overview of Next Generation Sequencing Technologies and Bioinformatics in Cancer

Ⓟ JE Hadfield

CRUK Cambridge Institute, Cambridge, UK

Next-generation sequencing (NGS) has had a dramatic impact on the biological sciences particularly in cancer research. It is now possible to sequence a patient's tumour and normal genomes to determine what mutations may be the underlying cause of their disease, this information can also be used for diagnosis/prognosis and to determine specific treatment regimens. However the use of NGS in the clinic is still in its infancy. In this presentation I will give an overview of the basic NGS methods and the major technologies being used. I will introduce the use of genome, exome and amplicome (PCR amplicon) sequencing, and highlight the pros and cos of using either tumour tissue or cell-free circulating tumour DNA in a research setting. Lastly I will discuss the difficulties faced in both the wetlab and bioinformatic methods for NGS. After the presentation you should have a basic understanding of what NGS is and how it might be used, as well as being aware of its major limitations.

S26

Molecular Pathology in Cancer Precision Medicine: The Heidelberg Experience

Ⓟ AS Stenzinger

University Hospital Heidelberg / Institute of Pathology, Heidelberg, Germany

During the last decade high-throughput molecular profiling has charted a genetic landscape of all major cancer types. While e.g. interrogation of RAS genes in colorectal cancer as well as screening for EGFR mutations and gene fusions involving ALK, ROS, and RET in lung adenocarcinoma have already entered routine diagnostics, broad exploitation of this wealth of data is just starting. With an ever increasing number of drugs that will become available in the next decade, scalable detection of clinically relevant genetic underpinnings that enable targeted therapies and the use of agents modulating the immune system will be the key for sucessful implementation of cancer precision medicine. Molecular profiling will also provide insight into the interplay between germline aberrations and the somatic mutational profile of tumors. This data will be particularly important for the understanding of cancer development in younger patients as well as in patients with cancer of unknown primary. Meeting these demands, the National Center for Tumor Diseases and the Center for Molecular Pathology at University Hospital Heidelberg have developed a program that faciliates high-quality targeted sequencing at low turn-around times for broad diagnostic outreach as well as comprehensive molecular profiling of selected patients by whole exome and whole genome sequencing to obtain deep and multi-layered information on tumor biology. This program and complementary approach will be discussed and exemplified using individual case studies.

S27

Genomes for Medicine: 100,000 Genomes Project and CRUK SMP2

Ⓟ MT Ross

Illumina Cambridge, Saffron Walden, UK

There are several points in an individual's lifetime when genomic analysis may be beneficial. Next-generation sequencing (NGS) is widely adopted and its increasing accuracy, speed and throughput, as well as its reducing cost, make it a suitable tool for such use. The precise type of NGS test used will be determined by the nature of the disease and of the actionable information needed. For example, a whole-genome sequence might be the most appropriate choice when diagnostic yield is key or when prognostic information is found among large-scale genomic rearrangements. In other situations a targeted approach may currently be more suitable, for example, when a treatment decision in cancer is based on the presence or absence of specific variants or when a highly sensitive method of detecting minimal residual disease is needed. We are attempting to develop complete, sample-to-answer workflows for the application of NGS in genomic medicine. Our partnerships with Genomics England in the 100,000 Genomes Project and with Cancer Research UK in the Stratified Medicine Programme are essential to our understanding of what is needed. I will discuss the progress of these projects, including an exploration of the challenges we have seen when working with tumour samples and our efforts within both partnerships to surmount these.

S28

Improving Outcomes in Colorectal Cancer: The Importance of Rigorous Pathological Quality Control

Ⓟ NP West

University of Leeds, Leeds, UK

Colorectal cancer is common with around 41,000 new cases diagnosed annually in the UK. Whilst outcomes have improved with advances in multidisciplinary treatment, significant variation remains between centres. Despite the recent focus on rectal cancer, patients with colon and low rectal cancer (LRC) continue to have a poorer outcome. A novel grading system for colon cancer specimens was developed based on the presence and depth of mesocolic defects along with a technique for objective morphological assessment of the amount of tissue resected. Analysis of conventional surgery showed that only 32% of cases were resected intact. These were associated with a 15% greater five year overall survival when compared to cases with major mesocolic defects. Complete mesocolic excision (CME) and Japanese D3 surgery are more radical operations and associated with improved surgical planes, more lymph nodes, extended resection of the mesocolon and better outcomes. Multidisciplinary training programmes have shown that CME training can significantly improve the oncological quality of surgery. A similar analysis of LRC specimens showed that extralevator abdominoperineal excision (ELAPE) resected more tissue around the tumour when compared to conventional surgery, and that this reduced the rate of circumferential resection margin involvement and perforation. ELAPE has been shown to be superior whether carried out in the prone or supine positions, and surgeons using this approach report the best outcomes in the literature. A national UK multidisciplinary LRC training programme has recently focussed on the importance of ELAPE for advanced LRC. These studies have demonstrated that histopathological research can identify the optimum surgical techniques for CRC and be used to inform routine practice. A national CME training programme is urgently required and along with the recent LRC training programme has the potential to save up to 5,000 lives per year in the UK.

S29

Update on Autoimmune Biliary Disease

Ⓟ SG Hubscher

University of Birmingham, Birmingham, UK

This talk will focus on the current role of histological assessments in the diagnosis and management of primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), the two most common autoimmune biliary diseases in adults. For patients with other typical findings, liver biopsy is no longer considered necessary to establish a diagnosis of PBC or PSC. Areas in which histological assessments continue to be relevant include the following: 1. Establishing a diagnosis in cases with atypical features, e.g. anti-mitochondrial antibody negative PBC or small-duct PSC. 2. Identifying subtle features of chronic cholestasis, such as periportal deposition of copper/copper-associated protein (CAP) or expression of keratin 7 in periportal hepatocytes, can sometimes identify cases of early PBC or PSC before other diagnostic investigations have been carried out. 3. The assessment of inflammatory activity (mainly interface hepatitis) is important in the identification of patients who may have a so-called "overlap syndrome" with autoimmune hepatitis. Such cases are relatively uncommon, but may benefit from treatment with immunosuppression. 4. Identifying patients who may have more than one cause of liver disease — e.g. PBC/PSC and fatty liver disease. In cases where a dual pathology is suspected clinically, liver biopsy may help to identify the predominant cause of liver injury. 5. In recent years, there has been increasing interest in the histological staging of PBC and PSC. A system described by Nakanuma et al, which includes semi-quantitative scoring of bile duct loss and CAP deposition in addition to fibrosis, appears to more effective than previously-described staging systems in predicting disease outcomes in both PBC and PSC. Due to the lack of other useful surrogate end-points for determining treatment efficacy, histological staging is likely to be increasingly used to assess outcomes in patients entered into clinical trials investigating new therapeutic agents

S30

Pathology of Non-Neoplastic Pancreatic Diseases

Ⓟ CS Verbeke

Oslo University Hospital, Oslo, Norway

In approximately 5% of all pancreatic resection specimens, the final diagnosis is that of a non-neoplastic lesion. In most instances, the indication for surgery was based on an erroneous preoperative diagnosis of neoplasia. Non-neoplastic disease of the pancreas encompasses a heterogeneous group of cystic and solid lesions. In the latter group, pancreatitis – autoimmune, follicular, "groove" or infectious – is the most common diagnosis. Pseudocysts and retention cysts are not uncommon mimickers of cystic neoplasia, whose morphological diagnosis in the resection specimen is usually straightforward. More difficult can be the diagnosis of rare non-neoplastic cystic lesions such as enterogenous cysts and lymphoepithelial cysts. Diffuse hyperplasia of the endocrine pancreas is a rare disease, which has to be distinguished from the fairly common reactive form of endocrine hyperplasia, which is most often a (multi-)focal finding. The morphology and differential diagnosis of alpha-, beta- and PP-cell hyperplasia will be discussed along with clinical and molecular aspects.

S31

HPV-Associated Head and Neck Cancers: An Update

Ⓟ TR Helliwell

Royal Liverpool University Hospital, Liverpool, UK

Carcinoma of the head and neck region in which human papilloma virus (HPV) are a major driver have shown a rapid increase in incidence in recent years. Although mainly affecting the oropharynx, HPV is associated with a small proportion of carcinoma of the larynx and paranasal sinuses. This presentation will review the diagnostic features of HPV associated carcinoma, emphasising changes in the WHO descriptors and in TNM staging, with an overview of genetic differences between HPV-associated and other carcinomas. The WHO classification now describes HPV positive and negative squamous cell carcinomas of the oropharynx. HPV-associated carcinomas tend to occur at a younger age, arising from the reticulated epithelium of the tonsillar crypts and base of tongue and often have a non-keratinising morphology. Papillary, adenosquamous, basaloid, neuroendocrine spindle cell oropharyngeal carcinomas may also be associated with HPV.All morphological types behave similarly apart from the more aggressive HPV-associated neuroendocrine carcinomas. Over-expression of p16 protein by immunocytochemistry is seen in HPV-associated carcinomas but confirmation of viral DNA should be sought since other genetic mechanisms may result in p16 expression in a few carcinomas. The genetic changes observed in HPV-associated carcinomas are largely due to the HPV E6 and E& proteins inactivating p53 and RB, although other changes relating to modulators of immune regulation are likely also to be of relevance. For TNM staging (UICC 8th edition), the descriptors for T1, T2 and T3 are the same, but T4 is no longer subdivided for HPV-associated carcinomas. Nodal staging for HPV-associated carcinomas is significantly different with N1 describing unilateral metastasis (or metastases) up to 6cm diameter. Extracapsular extension may also be less releavent. The differences in stage grouping reflect the better prognosis for HPV-associated carcinomas and the greater sensitivity to chemoradiotherapy.

S32

Evolving Evidence from Clinical Trials and Personalised Therapy for Patients with Head and Neck Cancer

Ⓟ KJ Harrington

The Institute of Cancer Research, London, UK

In 2016, the US FDA approved two anti-PD1 monoclonal antibodies, nivolumab and pembrolizumab, for the management of relapsed/metastatic head and neck squamous cell cancer (HNSCC) following platin-based therapy. In the phase III CHECKMATE-141 study, the nivolumab treated group had median overall survival 7.5 months versus 5.1 months in the standard arm; estimated rate of OS at 1 year was more than twice that of the standard arm and the overall response rate was 13.3% (95% CI, 9.3 to 18.3) versus 5.8% (95% CI, 2.4 to 11.6) in the standard arm. A separate analysis demonstrated maintenance or improvement of quality of life and/or patient-reported outcomes in patients treated with nivolumab. For pembrolizumab, the data are limited to safety and efficacy results from KEYNOTE-012 and KEYNOTE-055. These data demonstrated a response rate of approximately 18%, with enhanced activity in HPV+ve disease. Data from the KEYNOTE-040 phase III study of pembrolizumab against standard-of-care second-line therapies will be available in 2017. In the first-line relapsed/metastatic setting, phase III clinical trials in which pembrolizumab, alone or in combination with chemotherapy (KEYNOTE-048), and durvalumab plus tremelimumab, as single agent or doublet therapy (KESTREL), have been assessed against standard of care EXTREME chemotherapy (platin, 5-fluorouracil, cetuximab). Both of these studies have completed recruitment. Randomised phase II (CHECKMATE-714) and phase III (CHECKMATE-651) studies of nivolumab plus ipilimumab have also been initiated. In the context of newly-diagnosed locoregionally-advanced disease, a number of clinical trials have commenced or are in start-up (Pembrolizumab – KEYNOTE-412; Nivolumab – RTOG 3504; Avelumab – JAVELIN100). Finally, a number of new immuno-oncology agents (e.g. IDO1 inhibitors, STING agonists, oncolytic virotherapies) are being developed that target other immune checkpoints or related pathways.

S33

Sentinel Nodes in Oral and Head and Neck Cancers: The Surgeon's Perspective

Ⓟ CE Schilling

St Georges Hospital, London, UK

Recent data confirms that elective surgical management of the cN0 neck in early (T1–T2) oral squamous cell carcinoma (OSCC) improves survival compared to watchful wait. However, elective neck dissection (END) in all patients may not be necessary. Sentinel node biopsy (SNB) is recognised as a reliable staging test for the radiologically N0 neck in early OSCC, detecting occult metastasis with a sensitivity of 86–94%. Those with a negative SNB can avoid neck dissection, allowing an individualised treatment strategy that should reduce both treatment related morbidity and cost. Currently the provision of SNB for OSCC in the UK is limited to a small number of centres, but it is likely that this will change significantly in the future as national guidelines recommend the incorporation of SNB into the standard treatment pathway. However, SNB is an operator sensitive technique with a false negative rate of 6–14%. Meticulous technique at all stages of the procedure are required for optimum results. Surgical aspects, pearls and pitfalls will be discussed including new technology and applications in non-oral head and neck cancers.

S34

EBV Quantitation in Health and Disease

Ⓟ SA Feeney; T Curran; AP Watt; C Cox; C McCaughey

Regional Virus Lab, Royal Victoria Hospital, Belfast, UK

Epstein-Barr virus (EBV) is a member of the herpesviridae family, a common virus of global distribution, with up to 95% adults having detectable antibodies indicative of past infection. Most infections are mild and self-limiting. EBV however by its very nature causes persistent latent infection in B-lymphocytes, and lends itself to potential fatal consequences in those with a weakened immune response if reactivation is triggered. The manifestations of primary EBV infection range from asymptomatic infection to infectious mononucleosis (IM) otherwise known as glandular fever, and in rare cases Guillain-Barre syndrome, meningoencephalitis, thrombotic thrombocytopenic purpura/haemolytic-uremic syndrome (TTP/HUS) and disseminated intravascular coagulation (DIC). Complications of primary EBV are rare but may be life threatening. EBV persistence, and potential to reactivate to lytic replication, can on occasion be linked to development of cancers and serious conditions such as Burkitts lymphoma, nasopharyngeal carcinoma, lymphoproliferative disorders including post transplant lymphoproliferative disorders (PTLD) and rare haematological conditions such as hemophagocytic lymphohistiocytosis (HLH). A modern, functional, diagnostic virology laboratory should offer timely serological antibody monitoring together with quantitative PCR assays as supportive and definitive EBV diagnostics. Here we present a number of key cases in which quantitative EBV molecular diagnostics on specimen types blood, serum, CSF and tissue had a direct impact on patient management and outcome. These cases focus on lymphoproliferative disorders and HLH, as in this challenging transplant and biologics era, these conditions are more the differential diagnosis than ever before. Rapid quantitative diagnostics with WHO standardisation enables highly sensitive and reliable detection of EBV DNA in key specimens, and excellent working partnerships with the pathologies ensures rare, complex diagnose.

S35

Cancer Predisposition Syndromes: Lessons for Truly Precision Medicine

Ⓟ DN Church

Oxford Centre for Cancer Gene Research, Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK

Cancer predisposition syndromes are typically uncommon, monogenic, high-penetrance disorders. Despite their rarity, they have proven to be highly clinically relevant in directing cancer prevention strategies. As such, they are similar to an expanding class of low-frequency somatic mutations that are associated with a striking prognostic or predictive effect in the tumours in which they occur. This talk aims to highlight these commonalities, with particular reference to mutations in the proofreading domain of replicative DNA polymerases — the focus of work in my laboratory during the last few years. These mutations may occur as either germline or somatic events, and in the latter case, confer a favourable prognosis and increased likelihood of benefit from immune checkpoint inhibition. My talk will review the potential improvements that incorporation of suchvariants into clinical management algorithms will bring for patient management, and the potential to further improve this by the inclusion of other germline variants, such as those that determine the likelihood of benefit or toxicity from anti-neoplastic therapy. Finally, I will propose that while integrated patient and tumour profiling is essential for the delivery of truly precision medicine for cancer patients, similar to rare germline mutations, we must ensure that we identify and utilize rare somatic mutations with strong predictive and prognostic effects.

S36

The Genetics and Pathology of Mitochondrial Disease

Ⓟ MR Rocha; CL Alston; NZ Lax; DM Turnbull; RW Taylor

Wellcome Trust Centre for Mitochondrial Reseach, Newcastle upon Tyne, UK

Mitochondria are double membrane-bound organelles that are responsible for a variety of fundamental cellular processes including oxidative phosphorylation (OXPHOS), one of the cell's pathways for production of cellular energy in the form of ATP. Its function is under dual genetic control — the 16.6kb mitochondrial genome encoding just 37 genes and the nuclear genes encoding the remaining ~1300 proteins of the mitoproteome — explaining why mitochondrial dysfunction can arise due to defects in either mtDNA or nuclear mitochondrial genes. Mitochondrial disease has an estimated incidence of 1 in 5,000 and can present in childhood or adulthood in association with vast clinical heterogeneity with symptoms affecting a single organ or tissue, or multisystem involvement. There is no cure for mitochondrial disease for the vast majority of mitochondrial patients and a genetic diagnosis is therefore crucial for genetic counselling, recurrence risk calculation and for modulating the clinical management of affected patients. The investigation and diagnosis of mitochondrial disease offers considerable challenge and historically has relied on a combination of techniques (including enzyme histochemistry, biochemical assessment of respiratory chain function) in biopsy tissue to guide molecular genetic studies. Next-generation sequencing strategies are proving pivotal in both the discovery of new mitochondrial disease genes and the molecular diagnosis of clinically-affected patients. Based on our experience of coordinating a national clinical and laboratory diagnostic service with an evolving research programme, my talk will focus on how a newly-developed immunofluorescent assay is helping to both improve the diagnosis and challenge our understanding of disease mechanisms underlying mitochondrial disorders.

S37

Molecular Mechanisms in Atopic Eczema: Insight Gained from Genetic Studies

Ⓟ SJ Brown

Ninewells Hospital and Medical School, Dundee, Dundee, UK

Atopic eczema (synonymous with atopic dermatitis and eczema) is a common heterogeneous phenotype with a wide spectrum of severity from mild transient disease to a severe chronic disorder with atopic and non-atopic co-morbidities. Eczema is a complex trait, resulting from the interaction of multiple genetic and environmental factors. Skin as an organ that can be biopsied easily provides the opportunity for detailed molecular genetic analysis. Strategies applied to the investigation of atopic eczema include candidate gene and genome-wide studies, extreme phenotypes and comparative analysis of inflammatory skin diseases. Genetic studies have identified a central role for skin barrier impairment in eczema predisposition and perpetuation; this has brought about a paradigm shift in understanding atopic disease but specific molecular targets to improve skin barrier function remain elusive. The role of Th2-mediated immune dysfunction is also central to atopic inflammation and has proved to be a powerful target for biological therapy in atopic eczema. This talk will present some of the major advances in understanding eczema pathogenesis which have provided opportunities for patient stratification, primary prevention and therapy development. There remain considerable challenges in the application of this knowledge to optimise benefit for patients with atopic eczema in the era of personalised medicine.

S38

Neoadjuvant Chemotherapy in Breast Cancer: Practical Aspects in Specimen Handling and Recent Advances

Ⓟ E Provenzano

Addenbrookes Hospital, Cambridge, UK

Neoadjuvant therapy is now an accepted management option for high risk early stage breast cancer. Pathological complete response (pCR) shows excellent correlation with individual patient outcome and is a validated endpoint for use in neoadjuvant clinical trials. At present, there is huge variability in the handling and reporting of post neoadjuvant breast cancer specimens. Close correlation with radiology and accurate localisation of the tumour bed, with systematic sampling of areas identified by intelligent mapping of the specimen, is preferable to overly exhaustive sampling in determining the presence of residual disease. Quantification of residual disease is also important prognostically, and there are several systems available for grading of response following neoadjuvant therapy. The lecture will cover practical issues in specimen handling and reporting of neoadjuvant breast specimens, including essential elements to be included in the pathology report and presentation of difficult scenarios. Changes in the 8th edition of the TNM staging will be discussed, particularly as regards the evaluation of nodal disease post chemotherapy.

S39

Macrophage Class Switching and Targeting of Tumour Immunology in Lung Cancer

E Aldujaily[1]; T Kamata[1]; C Pritchard[1];Ⓟ J Le Quesne[2]

[1]University of Leicester, Leicester, UK; [2]MRC Toxicology Unit, Leicester, UK

Purpose of the study: Pulmonary adenocarcinoma represents a major area of unmet need in cancer treatment. Recent advances in immunotherapy which target the PD-L1 immune checkpoint promise great improvements in outcomes for some patients. The immune system offers several other possible targets. One of these is the role of tumour-associated macrophages (TAMs), which are a common feature of lung tumour stroma. Epidemiological data have indicated a possible role of statins in reducing cancer mortality via their anti-inflammatory effects, but the mechanisms underpinning this are not clear We have been investigating the possible roles of pro-tumour vs anti-tumour macrophages in lung adenocarcinomas, and the possibility of influencing this axis with statin drugs.
Methods: 1: Immunohistochemical evaluation and phenotyping of TAMs using multiplex immunohistochemistry in tissue microarray sections of >500 lung adenocarcinomas with matched clinicopathological data. 2: Quantitative digital pathology, using Hamamatsu scanner images and Visiopharm software to count and phenotype TAMs in TMA sections.
Summary of results: Pro-tumourigenic (CD68+CD163+) TAM numbers are elevated in invasive vs in situ tumour regions. Interestingly, statin users have significantly lower pro-tumourigenic macrophage numbers than non-statin users, but only within areas of in situ tumour growth. Tumours in statin users were also of significantly lower histological grade, showing a higher percentage of in situ components than non-statin users.
Conclusions: Automated image analysis methods efficiently count and classify macrophages in tumour tissue. Statin therapy is related to macrophage class, specifically within in situ lesions. These data support a model whereby statins target protumourigenic TAMs in early disease, highlighting their potential as cancer-preventive agents.

S40

Placental Examination for the Generalist

Ⓟ NJ Sebire

GOSH, London, UK

Placental examination is often problematic for general pathologists, in large part due to the emphasis of clinical obstetric knowledge in order to correctly interpret findings. This session will focus on the major areas of placental pathology likely to be encountered in general practice, with discussion of important entities and also difficulties and pitfalls in diagnosis and interpretation. Fetal growth restriction will be used as an example to illustrate these concepts.

S41

Fields of Carcinogenesis in Breast and Oesophagus

Ⓟ JJ Going

Queen Elizabeth Hospital, Glasgow, UK

Slaughter (1944, 1953) identified multifocality of head and neck cancer in space and time with a process he called field cancerisation. Recent debate has questioned whether this concept, sometimes rebranded 'tissue organisation field theory', is compatible with what has become the standard model of carcinogenesis: somatic mutation theory (Boveri 1915). These superficially incompatible formulations can be reconciled completely, but reconciliation requires theories of carcinogenesis simultaneously reductionist (down to the level of cells and molecules) and holistic or integrative. Neither approach is adequate on its own. These issues are discussed in relation to adenocarcinogenesis in Barrett's oesophagus and breast. Specifically, reasons are sought for the failure so far to identify clinically useful simple molecular biomarkers of cancer risk in Barrett's mucosa, in contrast to the effectiveness of dysplasia, which even with its known imperfections, identifies an order-of-magnitude greater risk of neoplastic progression in dysplastic versus non-dysplastic Barrett's mucosa. In breast, the improbabillity (and possible semantic nullity) of the standard view that breast cancer 'originates' from the terminal duct lobular unit is argued. The case for the lobe being the relevant unit of breast tissue organisation in relation to mammary carcinogenesis is presented. Until our present ignorance of normal and abnormal breast lobar anatomy is made good, understanding of mammary carcinogenesis will be deficient in an important aspect. The necessary tools already exist, so all that is required is a recognition of the importance of the task and a willingness to get on with it.

S42

Digital Pathology in the NHS: Experience from a Novel Digital Pathology Training and Validation Study

Ⓟ BJ Williams

St James University Hospital / University of Leeds, Leeds, UK

Histopathologists are faced with an increasing workload, in terms of case number and case complexity, whilst the specialty is in a period of recruitment and retention crisis. Digital pathology offers a flexible platform for new modes of working, and wider transformational service change. It is increasingly apparent that digital pathology does not just represent the replacement of one diagnostic modality with another, but provides the key to the broader transformation of pathology services. It serves as a platform to enable novel and flexible working patterns to attract, retain and optimize use of staff, allows rapid access to second opinion, MDT referral and case collaboration, and brings us a step closer to a paperless NHS. Against this background of emergent need, Leeds Teaching Hospitals NHS Trust, in collaboration with the University of Leeds and Leica Biosystems, has completed a novel training and validation study of digital pathology for the primary diagnosis of breast histopathology specimens. Our innovative protocol incorporates early exposure to live digital reporting with the opportunity to gain experience and competence in specialty specific digital diagnosis in a risk mitigated environment. Our breast pathology team have amassed real world digital reporting experience of over 600 cases, in an NHS diagnostic department which ranks amongst the largest in Europe. As a result of this work, our department is now embarking on a pandepartmental, research led digital pathology deployment, in which we hope to demonstrate the benefits of large scale digital pathology adoption in an NHS setting.

S43

The PEACE Study

Ⓟ M Jamal-Hanjani[1]; C Swanton[2]

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PEACE (Posthumous tissuE donAtion in CancEr) is the first national warm autopsy collection programme, set up as a multi-centre prospective observational study intended to facilitate tissue donation from multiple tumour sites in the post-mortem setting. This study also involves the collection of normal tissue, blood samples for germ line DNA, circulating free DNA (cfDNA) and circulating tumour cells (CTCs). Alongside tissue and blood sampling, clinical data relating to patient medical and treatment history will also collected through the CRUK and UCL Cancer Trials Centre. Establishing this national programme will lead to an unprecedented resource of both fresh frozen tissue and blood in highly clinically annotated patient cohorts from patients recruited to national clinical across different tumour types. This resource will enable future cancer research that would otherwise be restricted to cell line work or archival tissue samples from single sites of disease with associated limitations of tissue sampling and clinical histories. Such research initiatives will include those investigating intratumour heterogeneity, polygenic and convergent mechanisms of resistance to targeted therapies, the tumour immunological landscape and neo-antigen repertoire, the origins and evolution of metastatic subclones, the genetic and phenotypic aberrations and biological pathways involved in the metastatic process, tumour organoid models that efficiently represent the genetic diversity of late stage disease, and the use of cfDNA and CTCs in the context of metastatic cancer and primary brain tumours. Results from the PEACE study may have significant implications for personalised treatment approaches for future patients, including the identification of prognostic and predictive biomarkers and resistance mechanisms to drug therapies. It is important to note that potentially a small number of post-mortem cases in each tumour type may yield clinically meaningful information.
Submitted on behalf of the PEACE Consortium.