Poster Abstracts

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KEY

 Presenter

PRESENTER’S INDEX

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**P1**  
**Molecular Pathology of Low Grade Oestrogen Receptor Positive Breast Cancer: Cues from Immunohistochemistry and Informatics**  
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**Purpose of the study:** Though complex molecular techniques are revolutionising the landscape of pathology, immunohistochemistry (IHC) remains useful in deconstructing molecular portraits. This study aimed to demonstrate the utility of IHC combined with informatics to investigate molecular determinants of low grade (LG) luminal breast cancer (BC).  
**Methods:** Biomarkers (n=214) from a primary BC series (n=1845) were correlated with grade. Pathway enrichment analysis (corrected for false discovery rate) was performed for proteins with significant associations with Grade 1 ER positive cases (n=388) [STRING 10 platform incorporating Gene Ontology (GO) and KEGG]. Computational analysis (C4.5, a decision tree classifier) also identified key determinants of grade within specific protein families (e.g. cdc’s, BUBs, ER related proteins like GATA3).  
**Results:** 28 markers (e.g. Androgen receptor (AR), FHT, FOXA1) showed significant positive association with Grade 1 ER positive tumours and 54, significant negative association (e.g. PTEN, GATA3, KAPNA1, p53) (p range = 0.001 — 0.0001). Enriched pathways for positively associated proteins included intracellular steroid hormone receptor signalling (p=0.003), mammary gland development (p=0.008), AR binding (p=0.01) (GO) while cell proliferation (p=0.0002), radiation response (p=0.0003) T cell differentiation (p=0.004), double-strand break repair (p=0.0004) (GO); HIF1α (p=0.00003), p53 (p=0.0016), ErbB (p=0.002) and JAK-STAT (p=0.01) [KEGG] pathways were enriched in the negative associations. Computational analysis confirmed GATA3, cdc2/cdc42 and BUB3 as predictive of grade in BC (p<0.05) within respective families, with no added value from K667 inclusion.  
**Conclusions:** Biomarkers help identify enriched pathways in LG BC. Existing datasets, notwithstanding selection bias, can mine molecular pathways combining IHC with bioinformatics. This project was supported by a Career Development Fellowship from the Path Soc and NIHR.

**P2**  
**Stromal Mitotic Count in Fibroadenomas**  
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**Purpose of study:** Fibroadenomas are common benign tumours, frequently encountered in clinical practice. Traditionally, stromal mitotic figures are said to be extremely unusual. The aim of the study was to establish if mitoses were present within the stroma of fibroadenomas, and if so, to establish the range of mitotic counts per 10 high power fields, and whether they were associated with any specific features.  
**Methods:** We evaluated the histological features of 76 fibroadenomatous lesions over a one year period (35 core biopsies and 41 excision specimens). We looked at mitotic count, degree of inflammation, stromal cellularity, architecture, tumour border, stromal atypia and stromal overgrowth.  
**Summary of results:** Stromal mitoses were present in 15 lesions (20%) with counts ranging from 1-4/10hpf. The mitotic count did not appear to be associated with any other histological features.  
**Conclusions:** Stromal mitoses within fibroadenomas are present not infrequently and an appreciation of this fact may guide management of these cases.

**P3**  
**Molecular Phenotype and Outcomes of Multifocal and Multicentric Invasive Breast Carcinomas; a UK Multi Institutional Series**  
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**Introduction:** Historically, multiple synchronous breast cancers are defined as multifocal (MF) when they are in the same quadrant of the breast, and multicentric (MC) when they are in different quadrants; a number of authors continue to use this distinction. Multifocality has been reported to be an independent prognostic factor for survival and local recurrence. The molecular implications of MF and MC versus univocal breast cancers remain to be defined.  
**Materials and methods:** Breast cancer excisions reported by three specialist centers between 2005 and 2014 were investigated (n=4409 cases). Data was statistically analyzed and p-values of ≤0.05 were considered significant.  
**Results:** 446 cases (10.12%) were reported as multifocal invasive breast cancer. 71% of multifocal cases were treated by mastectomy, compared to 25% unifocal (p<0.0001). Compared with unifocal breast cancer, patients with multifocal breast cancer were significantly younger (56.6 vs 59 years old, p=0.004) and more likely to have lymph node metastasis on presentation (49% vs 33%, p<0.0001). There were differences, some significant, in the molecular profiles of unifocal cancers vs the largest focus of multifocals (HER2+: negative: 89% vs 76%; p=0.002), Survival, at 70 months median follow-up, was 85% for both multifocal and unifocal cancers (p=0.878).  
**Discussion:** There are important questions unanswered about the molecular classification of multifocal breast cancer. There is a paucity of data on the incidence, degree of intratumor heterogeneity of multifocal breast cancers and its appropriate management. Future genomic testing of those cases may highlight more pronounced differences. The findings form basis of a biomarker driven trial in set up comparing conservative surgery and mastectomy (MIAMI).
P5
Audit of the Use of Immunohistochemistry for Ovarian Mucinous Neoplasms

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The distinction between primary ovarian and metastatic mucinous carcinoma to the ovary is difficult and may be problematic. In a proportion of cases, this dilemma can be resolved by careful pathological examination encompassing both the gross and microscopic findings and taking into account the pattern of distribution of the disease. Immunohistochemistry (IHC) studies have shown a significant degree of immunophenotype overlap between primary ovarian mucinous neoplasms and metastatic mucinous adenocarcinomas to the ovary in particular from the upper gastrointestinal tract. The aim of this study is to audit the use of immunohistochemistry (IHC) in the reporting of Ovarian Mucinous Neoplasms (OMN). This retrospective study documents the interpretation of tumour immunophenotypic in 82 ovarian mucinous neoplasms. All cases were discussed at the local Gynaecological Oncology Multi-Disciplinary Team meeting (MDT). These include Mucinous Cystadenoma Of Borderline Malignancy (MCOBM) and invasive OMN of both intestinal and Mullerian endocervical phenotypes. Advisory comments extracted from the histopathology reports including clinical and/or imaging investigations prompted by the pathologist were documented. All radiology results from post-gynaecological MDT oncology meeting e.g. MRI, CT, CT colonoscopy scans and upper gastro-intestinal endoscopic findings were also documented. Results: 37% of OMN had IHC studies performed and this included 27% of all MCBM cases and 75% of mucinous adenocarcinomas. In 93% of the cases, the pathologist was unable to rule out an extra-ovarian gastro-intestinal, pancreatic or biliary primary. In 30% of the cases, the pathologist had explicitly favoured an extra-ovarian primary. All cases where the pathologist was unable to rule out or had favoured metastasis from an extra-ovarian mucinous adenocarcinoma had imaging and metastasis to the ovary was excluded. We conclude that IHC phenotyping was not helpful in differentiating OMN from metastasis.

P6
An Audit of Pathological and Radiological Correlation of Myometrial Invasion and Histological Features Associated with Lymph Node Metastasis in Endometrial Cancers

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Purpose of the study: The most important prognostic factor of the endometrial cancer is the degree of myometrial invasion. In the absence of deep myometrial invasion, lymph node metastasis is very low.

Methods: The study included total hysterectomy and pelvic lymph node resections performed for biopsy proven endometrial cancers between 01/01/10 and 31/12/2013 at Royal Surrey County Hospital. Histological data regarding the histological type, grade, depth of myometrial invasion, presence/absence of lymphovascular invasion, lymph node metastasis and stage of disease was collected. Correlation was made with depth of invasion and stage documented in radiology reports from the hospital of origin, including Royal Surrey County Hospital.

Summary of results: Of the 98 cases analysed, 717.1% showed lymph node metastasis. 86.6% of the lymph node positive cases were grade 3 carcinomas involving outer half of the myometrium with lymphovascular invasion and at higher stage (III). Of the 40 cases (40.8%) available for radiological correlation, 24 (60%) showed concordance with regards to FIGO stage.

Conclusions: Lower stage (1A) endometrial cancers are unlikely to have lymph node metastasis. Provided lymph nodes are radiologically non-suspicious routine lymph node dissection will be unnecessary. Further detailed evaluation is necessary to improve pathological-radiological concordance.

P7
Epidermoid Cyst of the Spleen: a Case Report of a Rare Entity

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Spicentric cysts are exceedingly rare. They are generally classified into primary and secondary cysts based on the presence or absence of epithelial lining, respectively. Congenital splenic cysts known as epidermoid are very uncommon, accounting for only about 10% of benign non-parasitic cysts. Splenic epidermoid cysts occur predominantly in children and young women. The number of cases reported in the literature increased marginally during the last two decades due to the introduction of more sensitive imaging technologies. We report a case of splenic epidermoid cyst in a 17 years old female patient who presented with a history of left upper quadrant pain and a diagnosis of splenic cyst was diagnosed by imaging. Partial splenectomy was performed, and specimen sent for histopathological evaluation. Grossly, the specimen showed a 75 mm cyst with trabeculated wall and areas of haemorrhage. Microscopically; the cyst was lined by stratified squamous epithelium that appears to be flattened in places with areas of focal epithelial denudation and the diagnosis of epidermoid cyst of spleen was given. We present the clinical, histological, and immunohistochemical findings of this rare case. In addition, we summarize a literature review covering previously reported cases including the reported genetic association encountered in this entity. Lastly, we conclude key points helpful in distinguishing this cyst from other cysts encountered in the spleen.

P8
Gastrointestinal Stromal Tumours Associated with Neurofibromatosis: Report of Two Cases

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Gastrointestinal stromal tumours (GISTs) represent 80% of mesenchymal gastrointestinal (GI) tumours and 0.1 to 3% of all GI malignancies. They always represent as a solitary lesion most commonly in the stomach or small intestine. In the last few years, there are a number of case reports documenting the association of GISTs with Neurofibromatosis (NF). GISTs represent the commonest GI NF associated neoplasms. The clinical and pathological features of GISTs associated with NF are unlike those encountered in sporadic GISTs. Here we document two cases of GISTs in 67 and 68 years old patients who are known to have NF. Both cases had multiple jejunal and mesenteric lesions of variable sizes with variegated cut sections on microscopic examination. The histopathological examination revealed spindle cell tumours with very low mitotic index sparing the mucosa of the small intestine and extensively involving the muscularis propria. Those tumours were immunophenotypically confirmed as GISTs with low risk of progression, and interestingly, with wild type KIT and PDGFRα genes. The clinical, pathological, immunophenotypic and mutation analysis will be presented. We aim to alert the surgeons about GISTs as a potential differential diagnosis in cases of NF presenting with any gastrointestinal symptoms even in elderly patients, which is different from the documented notion of NF patients developing GISTs at younger mean age compared to sporadic patients.
**P9**

**An Audit of Total Mesolectal Excision (TME) in Rectal Cancer Resections**

**Abstract:**

**Background:** Colorectal cancer is the 3rd most common cancer in the UK and 2nd leading cause of cancer deaths. The mesorectum is a fatty tissue directly adjacent to the rectum bound by mesorectal fascia. It contains blood vessels and lymph nodes and the recurrence is often in these lymph nodes. Total excision of mesorectum (TME) in rectal cancer resections is associated with reduced rates of local recurrence, better survival and improved outcome. According to NICE (The National Institute for Health and Care Excellence), TME is the standard treatment for most rectal cancers. The Royal College of Pathologists’ guidelines for colorectal cancer reporting state that “macroscopic assessment of the plane of excision of rectal cancers predicts not only margin positivity but also local recurrence and survival”. So plane of excision (both in AR and APE specimens) should be assessed and documented as one of the three grades, described in the minimum dataset.

**Objective:** To analyse the plane of surgical excision in rectal cancer cases.

**Method:** A retrospective audit which included rectal cancer resections reported from January 2013 to January 2014 at 2 hospitals in UK.

**Results:** Of the 129 cases initially examined, only 25 were rectal cancer cases. Analysis showed that 84% of the 25 cases used TME as the surgical method, in the other 16% of the cases intramesorectal excision was performed to remove the rectal tumour.

**Conclusion:** The practice seemed to meet the guidelines as set out by NICE as most of the rectal tumours were removed by TME. For 16% of the cases, we had to fail the gold standard, multiple reasons such as neo-adjuvant chemotherapy, local perforation, abscess formation and extensive involvement of peri-rectal fat was found. As pathologists we should grade the TME in all cases. We are well aware that failure to perform TME could lead to higher rates of recurrence of the cancer. These results need to be discussed with the surgical team for future planning.

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**P10**

**Are we Meeting the Turnaround Time Target for Colorectal Cancer Reporting?**

**Abstract:**

**Background:** Turnaround times refer to the time taken for the Histopathology department to report, confirm and authorise specimen cases to help make a diagnosis and plan the next step of action for patient care. The turnaround time (TAT) has frequently been used since 1980 to quantify the time for laboratory tests in an objective manner. In the laboratory workflow TAT is an important indicator of performance and is even seen as a “necessary condition for trust between patient and physician”.

**Standard:** The Royal College of Pathologists measure this turnaround time from the date of the procedure to the date of authorisation. The targets set by the College in July 2014 for colorectal cancer turnaround times are: 80% of cases must be completed with 7 calendar days and 90% of cases within 10 calendar days.

**Method:** A retrospective audit of the turnaround times of colorectal cancer histopathology reports over one year (January 2013 to January 2014).

**Results:** When turnaround times were taken from the date of the procedure, 36.5% of the 129 cases were reported within 10 calendar days and 9.3% of the cases were completed within 7 calendar days. The turnaround times were then worked out from the date the resections were received at the department. 39.5% of the cases were reported within 10 calendar days and 13.2% within 7 calendar days.

**Conclusion:** Currently great efforts are made to record and reduce waiting times in cancer care. The targets of 80% and 90% for 7 calendar days and 10 calendar days, respectively, were not met. But on the other end, to our knowledge, those cases which did not meet the target, were not highlighted for any delay in treatment/mortality. From our audit, multiple factors such as adequate fixation, specimen transfer time, weekends/Bank holidays, large block processing etc have been identified, which can influence TAT. Therefore we should endeavour to improve our turnaround times to achieve the target set by Royal College of Pathologists.
P13

Acute Active Colitis after Antibody Blockade of Cytotoxic T-Lymphocyte-Associated Antigen 4

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Purpose of the study: The monoclonal antibody to cytotoxic T-lymphocyte-associated antigen 4, ipilimumab (anti-CTLA-4 antibody), is an approved treatment modality for metastatic melanoma which has improved survival rates. One of the most common side effects associated with ipilimumab is diarrhoea and colitis. The cause of the ipilimumab colitis is believed to be an immune-related adverse event usually controlled by using systemic steroid therapy. Rarely colitis is complicated by perforation and thus requires urgent surgical resection of colon. A review of the literature has revealed numerous cases of ipilimumab-induced colitis, but only in a minority of them is a full description of histological findings included.

Methods: Here we report a case of severe PR bleeding and acute active colitis in a patient treated with ipilimumab for metastatic melanoma. The patient required urgent subtotal colectomy due to the severity of his ipilimumab-induced colitis.

Summary of results: The essential histologic findings assessed on the colectomy specimen showed fissuring ulcers extending through colonic wall, dilated crypts, pseudopolyps and increased inflammatory infiltrate in lamina propria not associated with an increased number of intraepithelial lymphocytes.

Conclusions: This study illustrates that the medical profession needs to become more aware that modern treatments such as humanised monoclonal antibody like ipilimumab are associate with severe toxicity.

P14

Carcinosarcoma of Gastro-oesophageal Junction: a Rare Case Report

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Introduction: Carcinosarcoma of the oesophagus is rare, comprising up to 2.4% oesophageal neoplasms. The majority of these tumours arise in the mid-oesophagus and comprise a squamous cell carcinoma element.

Case Report: A 61 year old man was referred with a seven-month history of progressive dysphagia. Endoscopy revealed a large mass in the distal oesophagus and proximal stomach which was diagnosed on biopsy as a poorly-differentiated adenocarcinoma. He underwent oesophagectomy following neoadjuvant chemotherapy. No recurrence was seen 14 months following resection.

Histology and Immunohistochemistry: Examination of the oesophagectomy specimen revealed a completely-excised carcinosarcoma of the gastro-oesophageal junction (80 mm long, Siewert type 3, ypT3N2Mx). It comprised poorly-differentiated adenocarcinoma. Immunohistochemically, the carcinomatous element was positive for cytokeratin, focally positive for CK7 and CKDX2, and negative for CK20. The sarcomatous element was positive for desmin, focally positive for SMA, and negative for SMMHC, DOG1 and S100.

Discussion: Oesophageal carcinosarcoma is a rare and often unexpected malignancy, with initial biopsies frequently showing only carcinomatous elements. Recognition of this entity is important: there is evidence that more rapid intraluminal growth leads to earlier presentation and better short/medium-term survival than comparable squamous cell carcinomas. Furthermore, there is conflicting evidence for the efficacy of traditional radiotherapy and chemotherapy regimens used for traditional carcinomas.

P15

The Effect of N-WASP Knockout in Murine Models of Intestinal Tumourigenesis

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Purpose of the Study: N-WASP is a protein with multiple functions including regulating assembly of new actin filaments. It is important for cell migration in 3D matrix and is required for the formation of invadopodia in malignant cells. Although increased expression has been reported in a number of cancers, its role in primary colorectal cancer has not been explored. Here we investigate the role of N-WASP in intestinal tumour turnover and tumourigenesis.

Methods: Turnover model: When APC is deleted from the gut, loss of its regulation of Wnt signalling results in a hyperproliferative phenotype, which is enhanced by KRas mutation. Tamoxifen-inducible, gut-specific APC(-/-)A and APC(-/-)RasG12D(+/+) mice were used to investigate the effect of loss of N-WASP (N) on the turnover and organisation of intestinal crypts. Mice were induced with tamoxifen and given bromodeoxyuridine prior to sampling in order to measure proliferation. IHC and special stains were performed to identify cell types of the small intestine and apoptosis.

Tumour Model: Loss of one copy of APC results in formation of adenomas within the small and large intestines; additional mutation of KRas results in a more rapid progression. APC(-/-), APC(-/-)N-WASP(-/-), APC(-/-)RasG12D(+/+) and APC(-/-)RasG12D(+/+)N-WASP(-/-) cohorts were induced with tamoxifen and aged until they developed limiting signs of weight loss and anaemia. Data on survival and tumour burden were collected and samples taken for histology.

Summary of Results: Deletion of N-WASP increased the number of Paneth cells in both the A and Ak models and the number of goblet cells in the A model. There was no effect on the number of enteroendocrine cells, apoptosis or proliferation. In the tumourigenesis model, N-WASP knockout resulted in decreased survival of APC mice. There was no difference in survival in the APC Ak models.

Conclusions: N-WASP may regulate intestinal epithelial differentiation and its loss may promote intestinal tumourigenesis in a murine model.

P16

Protein Biomarker Discovery in Extracellular Vesicles Secreted by Colorectal Cancer

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Background: Colorectal cancer (CRC) is a major health problem. Molecular biomarkers could aid early detection, diagnosis, prognosis, therapy selection, and disease monitoring. Tumour tissue secretomes contain classically secreted proteins and proteins that are secreted via vesicle-mediated transport. These extracellular vesicles (EVs) are cell-secreted membrane vesicles that are released into body fluids, and carry tissue-specific and disease-related molecules; therefore EVs represent a rich source for disease biomarkers. The aim of this study was to identify CRC protein biomarkers in EVs isolated from tumour and matched normal tissue secretomes.

Approach: Secretomes of fresh human CRC (n=17) and colon adenoma (n=4) tissue as well as patient-matched normal colon tissue secretomes were collected. These secretomes where cleared from cells and cell debris by centrifugation and subjected to a peptide-mediated ‘miniprep’ isolation of EVs. The proteins contained by these EVs were analysed by GeLC-MS/MS. Statistical data analysis was based on label-free spectral counting and further data mining on DAVID gene ontology analysis, Secretome/SignalP and STRING.

Results: In total 6390 proteins were identified, of which 471 proteins were significantly 5-fold more present in CRC samples than in normal tissue EVs and 322 proteins 5-fold more present in the adenoma samples than in the normal EVs. Gene ontology analysis revealed enrichment of nuclear proteins involved in DNA damage response, chromosome organization and RNA processing in the CRC EVs. Biomarker selection of 88 candidates was based on consistent over-representation in all matched protein samples when compared to control-secretomes, at a significant 5-fold increase in abundance.

Conclusion: We identified 88 candidate biomarker proteins that have potential to be detected in blood- or stool-based assays to support clinical management of CRC. Further studies are required to validate clinical applicability of these candidate biomarkers.
P17

This abstract has been withdrawn

P18

Expert Referral Panels: a Case of Metastatic Pleomorphic Variant Malignant Mesothelioma in the Thyroid

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The morphological diversity of malignant mesothelioma is well recognised. We present a rare case of pleomorphic variant malignant mesothelioma metastatic to thyroid which was diagnosed as non-Hodgkin lymphoma. The case highlights the diagnostic difficulties and mimicry of mesothelioma with other non-mesothelial neoplasms and also the potential deficiencies of reliance on expert referral panels in an era of subspeciality reporting.

Histological assessment revealed a poorly differentiated anaplastic epithelioid tumour, staining diffusely positive for AE1/AE3, vimentin and D2-40. All other markers were negative. The hemithyroidectomy had been referred to a specialist regional lymphoma panel as suspected non-Hodgkin lymphoma and reported as non-Hodgkin lymphoma, unclassifiable type. Simultaneously, pleural biopsy had been referred to another expert pathologist and diagnosed as epithelioid mesothelioma. On review, the thyroid, lung and pleural tumours were considered morphologically similar. The tumour was designated as disseminated malignant mesothelioma, epithelioid subtype (pleomorphic variant).

This case illustrates the rare presentation of pleomorphic variant epithelioid mesothelioma with thyroid metastasis and its morphological mimicry of high grade non-Hodgkin lymphoma. Expert diagnostic panels play an increasing role in modern day clinical service, although limitations do exist, with such subspecialist reporting not always considering wider differential diagnoses outside their area of expertise. Optimal diagnosis is greatly facilitated by good communication from the primary source pathologist.

P19

Pseudomesotheliomatous Carcinoid Tumour within the Pleura Mimicking Malignant Mesothelioma

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Introduction: “Pseudomesotheliomatoma” is the term given to diffuse pleurotropic neoplasms of non-mesothelial histogenesis. Pseudomesotheliomatous tumours may clinically and radiologically mimic malignant mesothelioma. Such tumours are usually peripheral lung adenocarcinomas, although other primary and secondary carcinomas, sarcomas and metastatic tumours may manifest in this way. An accurate diagnosis of malignant mesothelioma is important with respect to medicolegal compensation claims. This case illustrates the importance of the pathological diagnosis at a time when coronial cases in industrial settings are decreasing.

Case Presentation: We present a case of a seventy year old male, ex-smoker, with a potential history of asbestos exposure via automobile friction products; who presented with a six month history of cough, increasing breathlessness and weight loss. Imaging investigations demonstrated a right sided endobronchial mass, collapsed lower lobe of the lung, pleural effusion and associated malignant appearing, nodular pleural thickening. The patient underwent a vacuum assisted biopsy of the pleural mass to investigate potential malignant mesothelioma. A simultaneous endobronchial biopsy was undertaken of the bronchial mass. Histologically, both samples demonstrated multiple nodules and solid islands of tumour cells which were confirmed by immunohistochemistry to show neuroendocrine differentiation pattern and subsequently diagnosed as typical carcinoid tumour.

Conclusion: This case illustrates the rare presentation of carcinoid tumour as a pseudomesothelioma, mimicking malignant mesothelioma. Carcinoid tumours are not an asbestos related neoplasm and are typically central tumours, rarely involving the pleura. Diffuse pleurotropic growth is exceptional. This case illustrates the importance of accurate pathological assessment in malignant mesothelioma and that caution should always be exercised when relying solely on clinical or imaging appearances in potential asbestos.

P20

Glands Penis Metastasis of Pleural Sarcomatoid Malignant Mesothelioma with Heterologous Elements

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Background: It is well recognized that pleural malignant mesothelioma may involve sites such as pericardium, peritoneum and diaphragm, and rarely metastasise to distant sites. Whilst primary malignant mesotheliomas may arise in the urogenital tract, for example in the tunica vaginalis and ovary, metastatic spread to this region is rare. We present a patient with known pleural sarcomatoid malignant mesothelioma with heterologous elements, who was diagnosed with metastasis to the glans penis at autopsy.

Case Report: A 74-year-old male with a history of extensive asbestos exposure during work as a boiler engineer and a 13 pack-year smoking history presented with chest pain following a fall. Imaging showed opacification of his right hemithorax and video-assisted thoracoscopic surgical biopsy was performed. Histological examination revealed an atypical spindle cell population invading the fat, with prominent cartilage and bone differentiation. The cells were positive for D2-40 and p53, but negative for other mesothelioma and carcinoma markers; he was diagnosed with sarcomatoid malignant mesothelioma with heterologous elements. During treatment he presented with a glans penis mass which was felt clinically to represent a pT3 penile carcinoma. He died before biopsy could be performed. Post mortem histology of the penis revealed metastatic spread to the glans penis.

Conclusions: Pleural malignant mesothelioma may rarely metastasise to unusual distant sites; giving rise to clinical confusion. We present the first reported instance of metastatic spread of pleural sarcomatoid malignant mesothelioma with heterologous elements to the glans penis, which was clinically diagnosed as penile carcinoma despite a known diagnosis of pleural mesothelioma. Metastatic mesothelioma should be considered in the differential diagnosis for all tumours identified in known mesothelioma patients, even at unusual sites.
**P21**

**Pleural Malignant Mesothelioma: Impact of Nuclear Grade on Survival**

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**Purpose of the Study:** To evaluate the impact of nuclear grade on overall survival in pleural malignant mesothelioma.

**Methods:** Cases of pleural malignant mesothelioma epithelioid subtype were retrieved from the archives of the UK Medical Research Council Pneumoconiosis Unit based at University Hospital Llandough. All cases were examined and classified as exhibiting one of the following morphological phenotypes: epithelioid, sarcomatoid, or biphasic type. Nuclear grade was classified as low or high based on published criteria (Kadota et al. Mod Pathol 2012;25(2):260). All cases were confirmed according to standards set by the International Mesothelioma Interest Group (IMIG) and morphological variants confirmed by two IMIG observers. Overall survival was compared amongst patients with each phenotype using Log Rank Test (Mantel-Cox).

**Summary of Results:** 191 cases of pleural malignant mesothelioma were identified. The age range of the group was 30 – 89 years (median age 62). The cases were subclassified as follows: epithelioid 59.7%, sarcomatoid 20.9%, biphasic 19.4%. 51.8% were classified as low nuclear grade, and 48.2% as high nuclear grade. In the epithelioid group, overall survival was significantly different in cases with low nuclear grade when compared with cases with high nuclear grade (p<0.001, median survival 19 months vs. 12 months). There was no significant difference in survival based on nuclear grade for sarcomatoid and biphasic types.

**Conclusions:** Nuclear grade (low vs. high) should be included in pathology reports to convey potential favourable prognostic subgroups of patients with pleural malignant mesothelioma epithelioid type. There is no benefit to routinely reporting nuclear grade in sarcomatoid or biphasic malignant mesotheliomas.

**P23**

**Cardiovascular Causes of Maternal Sudden Death. Sudden Adult Death Syndrome (SADS) is Leading Cause in UK Population.**

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**Purpose of the study:** This study aims to determine the causes of sudden death during pregnancy and in the postpartum period and these patients’ characteristics. Limited knowledge of this topic is available in the literature.

**Methods:** 79 cases of sudden unexpected death due to cardiac causes in relation to pregnancy and postpartum period in a database of 4678 patients were found and examined macroscopically and microscopically.

**Summary of results:** The mean age was 30 years with a range from 16 to 43 years. 29.1% were 35 years old or older. Most deaths occurred during pregnancy (53.16%) followed by postpartum (46.84%). 34 out of 51 (66.67%) were obese or overweight where Body Mass Index data were available. The leading causes of death were Sudden Arrhythmic Death Syndrome (SADS) (53.16%) and cardiomyopathies (12.66%). Other causes include dissection of aorta (5.06%), coronary artery dissection (3.80%), congenital heart disease (2.53%) and vasculardisease (3.8%).

**Conclusions:** This study highlights sudden cardiac deaths in pregnancy or in the postpartum period, particularly due to SADS with possible channelopathies and cardiomyopathy. We wish to raise awareness of these frequently under-recognized entities in maternal deaths and the need of cardiological screening of the family.

**P22**

**Pleural Malignant Mesothelioma Epithelioid Type: Impact of Morphological Phenotype on Survival**

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**Purpose of the Study:** To evaluate the impact of histological pattern on overall survival in pleural malignant mesothelioma epithelioid type.

**Methods:** Cases of pleural malignant mesothelioma epithelioid type were retrieved from the archives of the UK Medical Research Council Pneumoconiosis Unit based at University Hospital Llandough. All cases were examined and classified as exhibiting one of the following morphological phenotypes: myxoid/microcystic, tubulopapillary, solid, microcystic, pleomorphic, or other. All cases were confirmed according to standards set by the International Mesothelioma Interest Group (IMIG) and morphological variants confirmed by two IMIG observers. Overall survival was compared amongst patients with each phenotype using Log Rank Test (Mantel-Cox).

**Summary of Results:** 114 cases of pleural malignant mesothelioma epithelioid type were identified. The age range of the group was 30 – 80 years (median age 62). The cases were subclassified as follows: myxoid/microcystic 42.1%, solid 28.1%, micropapillary 5.3%, pleomorphic 8.8%, other 1.8%. The myxoid/microcystic phenotype was associated with favourable prognosis (median survival 24 months) compared with solid (p=0.040, median survival 14 months), micropapillary (p=0.028, median survival 12 months), and pleomorphic forms (p=0.0008, median survival 8 months). Pleomorphic phenotype had the worst median survival (8 months).

**Conclusions:** Morphological phenotype is an important histological factor that should be included in pathology reports to convey potential favourable prognostic subgroups of patients with pleural malignant mesothelioma epithelioid type.

**P24**

**Metastatic Adenocarcinoma of the Lung with Hepatoid Features: a Case Report and Results of Targeted Next-Generation Sequencing**

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**Purpose of study:** Adenocarcinoma with hepatoid features is an extremely rare histological subtype of primary lung adenocarcinoma. It has a similar morphological appearance to hepatocellular carcinoma (HCC), and the differential diagnosis with metastatic HCC may be challenging. The genetic profile of these tumours has not yet been characterised.

**Case report:** A 75 year-old female ex-smoker presented with neck pain. MRI imaging showed multiple brain lesions, and a 4 cm soft tissue mass in the region of the cervical vertebrae. CT chest/abdomen/pelvis revealed a 1.5 cm spiculated right lower lobe lung mass; no other lesions were seen, and in particular, there was no evidence of hepatic cirrhosis or a mass lesion in the liver.

**Results:** Core biopsy of the neck mass showed a poorly-differentiated adenocarcinoma with hepatoid morphology. Immunohistochemistry was positive for the following markers: CK7, HSA (focal), pCEA, inhibin (focal), CK20, TTF-1 and ALK were negative. Targeted next-generation sequencing using a multi-gene panel detected a KRAS point mutation (p.Gly12Cys) at 63% frequency; this mutation has been associated with decreased responsiveness to EGFR inhibitors in non-small cell lung cancer.

**Conclusions:** Adenocarcinomas with hepatoid features rarely originate from the lung, but this primary site should always be considered in a tumour with hepatoid morphology. Clinical, radiological and immunohistochemical correlation are vital in making the correct diagnosis, and HCC must be excluded. Molecular testing for these tumours may be informative in guiding the use of targeted therapies.
Audit of the Rapid On-Site Evaluation (ROSE) Service for Endobronchial Ultrasound (EBUS) Guided Fine Needle Aspiration Cytology

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Purpose of the study: The aim of this audit was to assess the utility of the rapid on-site evaluation (ROSE) service for endobronchial ultrasound (EBUS) guided fine needle aspiration (FNA) cytology. The main objectives of this audit were to determine ROSE adequacy per lymphnode sampled and per patient and to correlate ROSE diagnosis with final cytology diagnosis. The secondary objectives were to identify type of malignancy, adenocarcinoma cases with epidermal growth factor receptor (EGFR) mutation and determine the turn around time for authorising final cytology report.

Method: Data was collected using Labcentre and analysed using Excel.

Results: 429(96.6%) lymphnodes and 153(3.4%) lung masses aspires from 266 patients were included in the study period from 01-01-13 to 30-06-14. ROSE adequacy per site and per patient was 82.2% and 89.5% respectively. The final adequacy per patient was 96.2%, demonstrating full compliance with the standard of >71%. 87.8% of ROSE diagnoses were concordant with the final cytology diagnoses. The number of adenocarcinoma cases was higher than squamous cell carcinoma and small cell carcinoma. 40.1% of malignant cases were identified to be eligible for EGFR mutation testing with 10% of all cases sent showing the presence of an EGFR mutation. All of the EBUS cases were reported and authorised within the standard of the RCPPath guidelines.

Conclusion: The ROSE service plays a vital role in directing our clinicians on how to manage the patients investigated by means of EBUS.

Unpreviewed Diagnosis of Congenital Dyserythropoietic Anaemia Type 1 in a Stillborn: an Atypical Presentation

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Objective: Congenital dyserythropoietic anaemia type 1(CDA1) is a rare autosomal recessive disorder causing ineffective erythropoiesis and iron overload. It results from mutations in CDAN1. The incidence is unknown and diagnosis is usually made in childhood or adolescence. Rare cases have been detected in utero manifesting as foetal hydrops.

Method: We report a stillborn male born at 36 weeks gestation. There was no consanguinity or significant family history. The antenatal course was complicated by unexplained cardiac enlargement and short femurs. Growth velocity remained normal and there was no haemodynamic compromise at 35/40.

Results: Autopsy examination revealed marked pallor and mild scrotal oedema but no hydrops. The long bones were short for gestational age otherwise there were no external malformations. The heart weighed 21gms (expected 12.9-19.5 gms) and was described as “dilated with normal constitution”; the lungs were hypoplastic. The placenta weighed 788 gms (>97th centile). Histology revealed abundant immature haematopoietic cells within the vasculature of all organs and foetal vessels of the placenta, confirmed to be erythroid precursors. There was extensive haemosiderin deposition and excess extra-medullary haematopoeisis in the liver, involution of the thymus, fatty changes in the adrenal medulla and aspirated squames in the lungs.

Placental maturation was severely delayed. The diagnosis was suggested as anaemia due to haemolytic disease. Maternal Parvovirus B19 and CMV IgM titres were negative. Kleihauer-Betke test was negative. Genetic analysis performed on cord blood found compound heterozygous mutations in the CDAN1 gene and both parents were confirmed to be carriers.

Conclusion: This is an atypical presentation of CDA1; cardiac enlargement without haemodynamic compromise and short long bones provided no clues at antenatal assessment. Intrauterine death may be explained by decompensated anaemia on a background of placental immunity.

Audit of Adherence to Referral Guidelines by Royal College of Pathologists

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Introduction: Methotrexate-associated lymphoproliferative disorders affecting the lung have been reported previously in rheumatoid arthritis patients and rarely in those with psoriasis. Diagnosis can be challenging due to the rarity of the entity and its variable clinical, radiological and pathological features.

Case description: This is a case of Epstein-Barr Virus (EBV) positive large B cell lymphoma with Hodgkin like morphology in a 65 year old woman with psoriatic arthropathy taking regular methotrexate. Multiple bilateral lung nodules and mediastinal lymphadenopathy were found on investigation for chest symptoms. Some lesions reduced markedly in size over time and initial biopsies revealed granulomas and necrosis. The differential diagnosis included mycobacterial disease, sarcoidosis and vasculitis. Ultimately a wedge resection of an enlarging lung nodule revealed lymphoma which exhibited prominent necrosis and histocytes similar to necrotising granulomatous inflammation.

Discussion: Clinicians should be aware of the occurrence of EBV positive lymphomas in patients taking methotrexate and radiologists should be aware that lesions may wax and wane in size. Definitive diagnostic procedures such as excision biopsy may be required. Pathologists should look closely at the cells surrounding apparent necrotising granulomatous inflammation to detect any large lymphoid cells and perform the required immunostaining to rule out lymphoma where necessary. This case had Hodgkin like features which also added a further layer of diagnostic difficulty.

Does every placenta needs histological examination? An Audit of Adherence to Referral Guidelines by Royal College of Pathologists

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Background: Examination of the placenta is effectively a whole organ biopsy that provides a record of pregnancy-related events and changes to the intrauterine environment (3). As the vast majority of pregnancies, newborns and placentas are normal, pathological examination of all placentas is neither required nor feasible for many institutions. Therefore, only a subset of placentas requires submission for histological examination. Royal College of Pathologists has provided guidance on clinical indications for placenta referral. In our unit, an increasing trend was noticed in number of placenta referrals sent for histological examination every year.

Objectives: (1) To assess if all the placentas sent for histological examination meet the referral criteria provided by Royal College of Pathologists, UK. (2) To implement the triage system for placental examination (in agreement with local clinicians and midwifery team).

Methodology: A retrospective audit of placenta referrals sent to the Histopathology department over a period of one year (1/1/14 to 31/12/14).

Results: Total 408 placentas were referred for histological examination over one year. 337 out of 408 (83%) placentas met the referral criteria. Atleast 30 placentas (7%) did not require histological examination according to the guidelines. A significant number 41/408 (10%) could not be classified into either ‘indicated’ or ‘not indicated’ category due to insufficient clinical information provided. Using triage tool, 33 placentas required macroscopic examination only and 56 (14%) storage.

Conclusion: Each placental examination (including cut up, reporting time and tissue processing) costs £99.25 to the trust. From our results, it would essentially mean nearly £3000 to the trust every year. The importance of providing the pathologist with appropriate clinical history cannot be overemphasized. Unnecessary referrals for histology increase the workload, waste resources and possibly cause a delay in delivery of reports.
**P29**

**Novel Clinical Autopsy Performed with Postmortem Micro-CT: First Experience**

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Autopsy examination of early miscarriages (<20g) can be technically challenging and is inherently a destructive process, with the possibility that congenital abnormalities may be missed or misinterpreted. Imaging is increasingly used to guide the autopsy process and post-mortem 1.5T MRI shows excellent correlation with autopsy findings over 18gw / 500g bodyweight, however, its diagnostic accuracy is reduced below these thresholds. High-field MRI can provide the necessary resolutions, but is expensive and scan time is hard to obtain. Micro-CT may be one solution, and has been used in animal imaging and industry for many years. We present a pathological and radiological correlation of the findings from the first clinical use of micro-CT in perinatal autopsy practice. The case was selected prospectively from referrals to our institution; full written consent to research was provided. The clinical history was that of a termination of pregnancy at approximately 14gw for a presumed sacrococcygeal teratoma. A micro-CT scan was acquired using a Nikon XTH225 micro-CT scanner and post-processed using VG Studio MAX. Excellent internal contrast was demonstrated, with views of all organ systems obtained. Micro-CT demonstrated membranes in contact with the fetal skin and multiple deformations. Standard CT was non-diagnostic for every organ system. At subsequent (unblinded) autopsy, no teratoma was identified but a final diagnosis of ADAM complex was reached.

This case report demonstrates the potential of micro-CT for detailed PMI imaging of entire fetuses whilst maintaining tissue integrity, with significant implications for perinatal autopsy practice. In addition, 3D volumes generated by micro-CT provide a permanent record of findings that can be virtually dissected and discussed with the clinical team.

**P30**

**Microcomputed Tomography and Histological Features of Severe Pulmonary Hypertension**

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Microcomputed tomography (Micro-CT) can provide 3D volumes with resolutions equivalent to that of low-power histology. Acquisition times can be shortened by pre-soaking specimens in a solution with high atomic number, such as Lugol’s iodine. We present a patho-radiological correlation of lung biopsy material from a 10 year old with a clinical history of severe idiopathic pulmonary arterial hypertension and explore technical considerations around specimen preparation for micro-CT examination. Three samples of lung weighing approximately 0.5g were selected at random from explanted lung (explanted for pulmonary arterial hypertension). These were randomised to either simple iodination (Lugol’s solution, 2.94X10^-4 mol/ml) or formalin fixation for 48 hours followed by iodination in Lugol’s solution of either 2.94X10^-4 mol/ml or 4.98X10^-4 mol/ml prior to micro-CT examination. Images were acquired using a Nikon XTH225 micro-CT scanner and post-processed using VG Studio MAX. Following micro-CT examination, the tissue samples underwent routine histological preparation. Histological examination demonstrated changes of severe pulmonary arterial hypertension, including plexiform lesions and thickening of the muscular arteries, pulmonary veins and bronchioles. Iodination and fixation did not interfere with tissue processing, embedding or H&E staining of slides (sections from the unfixed iodinated sample showed nuclear smudging and variation in staining). The pre-fixed tissues showed good preservation of cellular detail. Micro-CT volumes demonstrated adequate tissue contrast with diagnostically thickened vessels within the volume renderings. Complex interstitial lesions and dilated pleural lymphatics were also present in the micro-CT data. The findings demonstrate the potential for micro-CT to produce diagnostically relevant datasets but highlight the need for adequate tissue fixation prior to or during iodination.

**P31**

**Non-destructive Imaging of Pathology in Mouse Embryos Using Micro-CT: Implications for Human Fetal Autopsy Practice**

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Retrieval of embryonic tissue for teaching and research has become complex for medico-legal reasons following numerous organ retention issues. In addition, anatomical dissection of very small embryos is technically demanding. Virtual datasets of embryos would allow anatomical diagnosis and are both less controversial and simpler to obtain and store. Virtual datasets of embryos have previously been described using destructive methods such as episcopic fluorescence microscopy and high-resolution episcopic microscopy, however, high-field MRI and micro-CT present methods of obtaining these datasets in a manner that maintains tissue integrity. We present a series of images from phenotypically normal and abnormal mouse embryos (length 4-5 mm) obtained using micro-CT. Mouse embryos were immersed in Lugol’s iodine for 24 hours prior to being rinsed in water and immobilised using non-nutrient agar. Images were acquired using a Nikon XTH225 micro-CT scanner, reconstructed using proprietary software and post-processed using VG Studio MAX. Even in these tiny specimens, excellent internal contrast was demonstrated, with good views of all organ systems obtained. Specific abnormalities identified include a VSD (0.24mm), exencephaly and foreface disruption. Excellent views of normal central nervous system, respiratory system, cardiovascular system, genitourinary and digestive tract systems were also obtained at micrometer resolution. Micro-CT technology is able to non-destructively create datasets of embryos at high resolution, which can then be re-dissected; 3D printed or indefinitely stored and could provide a solution to current issues affecting the use of embryonic tissue for diagnosis, teaching and research.

**P32**

**Ancillary Endoscopic Assisted Examination of Explanted Hearts**

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Cardiac transplantation is an increasingly common procedure, usually undertaken either for cardiomyopathy or complex congenital heart disease. Gross dissection of these specimens is an important step in diagnostic correlation due to complex genotype-phenotype relations. Standard procedure at macroscopic examination may include a single cut placed from apex to base resulting in a simulated 4-chamber view through the atria and ventricles. Surgical procedures, valve harvesting or the presence of a ventricular assist device may make gross assessment of an explant in such a manner more difficult. Furthermore, it is difficult objectively to assess valve function following the use of this technique. We present initial experience with the use of endoscopic assisted evaluation of these explant specimens. Fresh explanted hearts were examined using a straight forward 0 degree 3mm laparoscope as part of a standard Storz laparoscopy stack. The camera was introduced to the right atrium and right ventricle via the caval vein orifices and right ventricular outflow tract to retain structural integrity. Excellent in-situ views of the right atrium, inter-atrial septum, tricuspid valve and right ventricular myocardium were obtained. Examination of the left atrium and ventricle utilised cannulation of the pulmonary vein orifices and aorta, and facilitated views of the coronary artery ostia, mitral valve and interventricular septum. Examination of the specimen under water facilitated recording of simulated valve function. This novel technique as part of examination of explanted cardiac specimens represents an innovative approach for evaluating anatomical features in the intact heart and allows evaluation of valve function. It also has the potential for use in education and training of cardiac pathologists, echo sonographers and paediatric surgeons.
P33
Contemporary Demographic Features of Intrauterine Death: a Review of >1,000 Stillbirths and Intrauterine Deaths in London
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It is estimated that there are at least 3.2 million stillbirths worldwide per year. Reported associations include extremes of parity and maternal age, maternal obesity, maternal ethnicity, gestational diabetes and antenatal vaginal bleeding, however, the strength of many of these associations is unclear. We present demographic data from a retrospective cohort autopsy cases from two London centres. Data was retrospectively defined from 1,064 postmortem reports of intrauterine deaths before 124 weeks and later stillbirths. Objective criteria were defined a priori and applied to cases within the database. Statistical comparisons were made to establish demographic associations. There were 639 were stillbirths and 425 pre 24 week intrauterine deaths (miscarriage). The majority of deaths were ante partum (72%). Women within the study cohort were significantly more likely to be older (p<0.0001) and more obese (p<0.0001) than the matched National distribution of maternities. Women of black ethnicity were over represented within the study, with a particular increased risk of mid trimester miscarriage (p<0.0001). Maternal fibroids (p=0.0002) and antenatal vaginal bleeding (p=0.0004) were significantly associated with miscarriage compared to stillbirth. Any form of maternal diabetes was associated with an increased risk of stillbirth (p=0.02) compared to miscarriage, whilst maternal hypertension was strongly associated with stillbirth (p<0.0001). These data demonstrate that certain demographic features, such as increasing maternal age and obesity, are associated with generalised increased risk of intrauterine death across gestation, whereas other features are more specifically associated with mid trimester loss (black ethnicity, antenatal vaginal bleeding), or later stillbirth (maternal diabetes and hypertension). Such findings provide additional information regarding the aetiologies of fetal demise across the gestational age spectrum.

P34
Utility of Histological Examination of Internal Organs for Determination of Cause of Intrauterine Death: Analysis from >1,000 cases
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The Royal College of Pathologists advises that at least one block of all major thoracic and abdominal organs is taken at autopsy as part of investigation of fetal and perinatal death. These guidelines are based on expert opinion, rather than published data. Stillbirth is more than ten times as common as SUD, with no large scale evaluation of the importance of organ specific histological examination in fetal demise investigation. A postmortem database was used to collate a retrospective cohort of intrauterine deaths from two London tertiary referral centres. Criteria for significant findings on histological examination were defined a priori and applied to every case; specific additional coding was used to categorise cases in which histology was not taken or too autolysed to contribute. Data was analysed using statistical packages, including Stats Direct. Of 1,064 intrauterine deaths, 31 organs across 28 cases (excluding placental examination) demonstrated abnormal histological findings that directly contributed to the cause of death. Of these, the majority were identified on histological examination of lung (66%), kidney (16%), brain (10%), heart (3%) and liver (3%). In no case did histology of the spleen, adrenals, thymus, pancreas or thyroid provide a cause of death. (Cases in whom histological examination was abnormal but without which the cause of death would still have remained the same were not included in this analysis). These data indicate that histological sampling of visceral organs (excluding the placenta) adds little to investigation of intrauterine death in terms of direct determination of the underlying cause of death. Whilst routine histology retains value in specific circumstances and macroscopically abnormal organs, additional alternative postmortem investigations are required to better aid pathologists, clinicians and families to provide definitive causes of death.

P35
Importance of Placental Examination in the Investigation of Intrauterine Death: Evidence from a Cohort of >1,000 Cases
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Histological examination of the placenta forms a critical part of the investigation of intrauterine death, with placental causes of fetal demise reported as second only to unexplained deaths. We sought to establish the utility of placental examination in a large cohort of intrauterine deaths using pre-defined criteria for likely significance. A post-mortem database was used to retrospectively analyse 1,064 cases of stillbirth and second trimester intrauterine death from two tertiary referral centres in London. Cases were divided into broad groups [early miscarriage (<20 weeks), late miscarriage (20-24 weeks) and stillbirth (>24 weeks)]. Criteria for the significance of findings of placental histology were defined a priori to ensure consistent interpretation. In 964 cases, the placenta was submitted for examination. Nearly one third of placentas showed entirely normal histological examination of the umbilical cord, membranes and placental sections. Overall, 303 cases had the cause of death assigned secondary to placental abnormalities, including cases of ascending infection which were mainly associated with fresh second trimester intrauterine deaths. Of the 575 stillbirths with placenta submitted, 347 showed some placental abnormality of which 109 (19%) were the presumed cause of death. These included placental abruption (26; 24%), features of uteroplacental malperfusion (42; 39%) and a range of other rare specific pathologies such as chronic histiocytic intervillositis (3; 3%) and massive perivillous fibrin deposition (6 (5%)). The remaining 240 cases demonstrated mild changes of uncertain clinical significance such as focal villitis or intervillous thrombus. These findings indicate that placental examination is the single most useful component of a stillbirth autopsy and should be mandatory in every case. However, interpretation of the clinical significance of many findings remains uncertain.

P36
Blinded Objective Assessment of Thymic Involution Shows Poor Association With Cause Of Death
J Man1; JC Hutchinson2; MT Ashworth3; I Jeffrey4; NJ Sebire2
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Thymic involution is characterised by the "starry sky" appearance caused by increased turnover of intrathymic lymphocytes and prominent macrophages. It has been suggested as a marker of intrauterine growth restriction (IUGR) and described secondary to other complications such as choioamnionitis. Grading of thymic involution is described using the van Baarlen (VB) grading system. We aimed to assess how well such thymic involution can be quantitatively assessed in routine stillbirth autopsies. Cases were selected from a database of miscarriages and stillbirths from 2005-2013 across two London centres. The control group (20 cases) comprised unexplained intrauterine deaths with normal biometry, placental and autopsy findings. The IUGR group (14 cases) had known antenatal diagnosis of growth restriction, birthweight <10th centile and maternal vascular underperfusion on placental examination. The third group were small for gestational age fetuses (SGA; <10th centile; 12 cases) but with histologically normal placentas (likely constitutionally small). One haematoxylin & eosin slide of thymic tissue from each case was blindly assessed for: Corticomedullary ratio, number of Hassall’s Corpuscles/field, number of tingible body macrophages/field, distance between lobules and VB grade. There was no difference between the groups for the number of Hassall’s corpuscles/field, number of tingible body macrophages/field, average distance between lobules or VB grade. The only statistically significant finding was that true IUGR cases had reduced VB grade. The remaining 240 cases demonstrated mild changes of uncertain clinical significance such as focal villitis or intervillous thrombus. These findings indicate that placental examination is the single most useful component of a stillbirth autopsy and should be mandatory in every case. However, interpretation of the clinical significance of many findings remains uncertain.
P37

The Role of Autopsy in Determining the Cause of Intrauterine Death; Unexplained Rate is Dependent on Interpretation

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It has been reported that around 45% of stillbirths are small for gestational age (SGA) and that a significant proportion (around 20%) of the apparent unexplained deaths are due to changes that can be detected by autopsy. The cause of 18% was mainly identified from review of the clinical history or external examination. A further 18% of cases had a definite placental cause of death, while invasive autopsy with tissue sampling provided the cause of death in only a small minority of cases. Depending on the criteria used, 25-60% of intrauterine deaths may be assigned the category of ‘unexplained’ highlighting an area of potential interpretive bias, which accounts for the variation in ‘unexplained’ rates across previous studies. The findings highlight the need for objective criteria in the classification of intrauterine death and development of novel investigations beyond current autopsy practice to reduce the number of unexplained deaths.

P38

Effects of Intrauterine Retention and Postmortem Interval on Bodyweight of Intrauterine Deaths: Implications for Assessment of Fetal Growth Restriction in Stillbirth

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It has been reported that around 45% of stillbirths are small for gestational age (SGA) or growth restricted, based on weight at birth or autopsy (<10th centile of expected birthweight (BW) based on WHO standards). For each case, the delta BW was derived as the number of standard deviations by gestation (to allow calculation of expected birthweight (BW) based on WHO standards). A database of 1,064 intrauterine deaths undergoing autopsy at one of two London tertiary referral centres was retrospectively analysed using predefined criteria for the classification of cause of death. Statistical comparisons were made using Stats Direct. Based on strict criteria for definite pathological findings, 63% of the study population had an unexplained cause of death despite full autopsy. Unexplained deaths were more frequent with increasing fetal maceration. 27% of intrauterine deaths had no associated clinical, fetal or placental lesions (fully unexplained) while the remainder had no definite cause but had associated risk factors present or findings of uncertain significance at autopsy. The cause of 18% was mainly identified from review of the clinical history or external examination. A further 18% of cases had a definite placental cause of death, while invasive autopsy with tissue sampling provided the cause of death in only a small minority of cases. Depending on the criteria used, 25-60% of intrauterine deaths may be assigned the category of ‘unexplained’ highlighting an area of potential interpretive bias, which accounts for the variation in ‘unexplained’ rates across previous studies. The findings highlight the need for objective criteria in the classification of intrauterine death and development of novel investigations beyond current autopsy practice to reduce the number of unexplained deaths.

P39

Proximity Extension Multiplex Immunoassay of Tissue Lyses Identifies Potential Prognostic Biomarkers in Endometrial Cancer

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Endometrial cancer (EC) is the commonest gynaecological malignancy in the developed world. Type I ECs (75%) are primarily oestrogen-sensitive, arise on a background of hyperplasia and are low grade. Instead, Type II ECs are high grade, frequently oestrogen receptor negative, are thought to arise rapidly from intraepithelial neoplasia and have poorer outcomes. The aims of this study were to relate tumour microenvironmental and signalling marker profiles with both carcinogenesis and prognosis. Endometrial tissue lyses (38 normal, 25 hyperplastic and 97 cancerous; 46 Type I/51 Type II) were profiled for a panel of 92 cancer-associated protein biomarkers by proximity extension assay. Clinical pathological and follow-up (median 43.4 months) data were collected for all cancer cases (n=97). Tissue type associations were determined by Kruskal-Wallis tests post-hoc, while biomarker associations with progression-free survival were determined by Cox proportional hazards regression. The False Discovery Rate was used to correct for multiple comparisons. 23 of the targets showed significant differences between normal and hyperplastic tissues, and 2 between hyperplasia and Type I ECs. Of the 9 proteins which were significantly higher in Type II vs. Type I ECs, kallikrein-6, stem cell factor, midkine and follistatin were associated with poor prognosis. Of the 11 proteins that were significantly lower in Type II vs. Type I ECs, CD40 ligand, gata3, tissue factor and betacellulin were associated with good prognosis. In addition, while survival analyses confirmed Her2 to be an indicator of poor prognosis, prostatin appeared to be a marker of good prognosis in EC. Proximity extension multiplex immunoassay allowed high-throughput identification of protein markers involved at different stages in endometrial carcinogenesis as well as identifying novel prognostic biomarkers in EC.

P40

Establishment of Tumour Progression Scale for Invasive Bladder Cancer Models

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Endometrial cancer (EC) is the commonest gynaecological malignancy in the developed world. Type I ECs (75% cases) are commonly oestrogen-sensitive, arise on a background of hyperplasia and are low grade. Instead, Type II ECs are high grade, frequently oestrogen receptor negative, are thought to arise rapidly from intraepithelial neoplasia and have poorer outcomes. The aims of this study were to relate tumour microenvironmental and signalling marker profiles with both carcinogenesis and prognosis. Endometrial tissue lyses (38 normal, 25 hyperplastic and 97 cancerous; 46 Type I/51 Type II) were profiled for a panel of 92 cancer-associated protein biomarkers by proximity extension assay. Clinical pathological and follow-up (median 43.4 months) data were collected for all cancer cases (n=97). Tissue type associations were determined by Kruskal-Wallis tests post-hoc, while biomarker associations with progression-free survival were determined by Cox proportional hazards regression. The False Discovery Rate was used to correct for multiple comparisons. 23 of the targets showed significant differences between normal and hyperplastic tissues, and 2 between hyperplasia and Type I ECs. Of the 9 proteins which were significantly higher in Type II vs. Type I ECs, kallikrein-6, stem cell factor, midkine and follistatin were associated with poor prognosis. Of the 11 proteins that were significantly lower in Type II vs. Type I ECs, CD40 ligand, gata3, tissue factor and betacellulin were associated with good prognosis. In addition, while survival analyses confirmed Her2 to be an indicator of poor prognosis, prostatin appeared to be a marker of good prognosis in EC. Proximity extension multiplex immunoassay allowed high-throughput identification of protein markers involved at different stages in endometrial carcinogenesis as well as identifying novel prognostic biomarkers in EC.
P41
Identification of Inflammasome Expression and Activity in Experimental Autoimmune Encephalomyelitis

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Background: Experimental Autoimmune Encephalomyelitis (EAE) is an immune-mediated animal model of Multiple Sclerosis (MS). In this model, mice have multiple demyelinated lesions distributed throughout the central nervous system (CNS). Inflammasomes are intracellular, innate immune complexes known to have a pathogenic role in EAE development. In EAE inflammasomes are activated by danger-associated molecular patterns to mature and release pro-inflammatory cytokines, IL-1beta and IL-18.

Objectives: To identify inflammasome activity in different CNS cells of the spinal cord; we aimed to establish immunofluorescent staining of inflammasome components. To assess the effect of IL-1beta on oligodendrocytes.

Methods: To establish immunohistochemistry protocols, spinal cord sections from EAE mice were stained for inflammasome components AIM2, ASC and IL-1beta. To test the effect of IL-1beta on oligodendrocytes, oligodendrocyte lineage cells were derived from frontal cortices of postnatal mice and treated with IL-1beta. Cultures were stained for oligodendrocyte lineage and myelin markers.

Results: We established immunofluorescent staining for AIM2, ASC and IL-1beta, and thus identified inflammasome activity in demyelinated spinal cord lesions. In vitro, exogenous IL-1beta significantly enhanced myelin protein production from oligodendrocytes. IL-1beta did not increase the number of mature oligodendrocytes.

Conclusions: AIM2, ASC and IL-1beta immunohistochemistry demonstrated inflammasome activity in demyelinated spinal cord lesions. Future studies will develop co-staining for CNS markers to determine which cells express inflammasomes in EAE-induced lesions. Our studies show that IL-1beta drives oligodendrocyte maturation and myelin protein production in glial cultures. Future work will assess the effect of the inflammasome product IL-18 on oligodendrocyte cells.

Research was supported by a Pathological Society Undergraduate Bursary.

P42
TTF1 Positive Primary Epithelioid Sarcoma (Proximal Type) of the Lung

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Epithelioid sarcomas represent a rare and heterogeneous group of tumours which are considered to be derived from epithelial stem cells of soft tissue origin. We present a case of a TTF1-positive primary epithelioid sarcoma (proximal type) of the lung/pleura and discuss the diagnosis in context with cases of the new entity INI-1 deficient rhabdoid carcinoma.

A 65 year old lady presented with a chest mass that suggested primary lung cancer or pleural mesothelioma. A biopsy showed poorly cohesive pleomorphic and mitotically active epithelioid cells with a plasmacytoid or rhabdoid morphology. The cells were positive for TTF1, CD34, CD138, CD68 and ERG plus focal AE1/AE3. Mesothelial, epithelial, lymphoid, germ cell and melanoma markers were negative.

An initial diagnosis was of large cell rhabdoid carcinoma based on AE1/AE3 and TTF1. Further tests showed INI-1 to be negative in the tumour cells thus a diagnosis of epithelioid sarcoma of proximal type was made.

TTF-1 is widely used to identify lung and thyroid tumours and in subtyping non-small cell carcinoma. The expression of TTF-1 in epithelioid sarcoma has not been previously reported.

SUMMARY OF RESULTS: Colour calibrated virtual slides were closer in appearance to the glass slides than uncalibrated virtual slides (median 6.00 vs. 5.00, p=0.001).


Purpose of the Study: Virtual slide scanners have been in use for over a decade; yet digital image viewing has yet to be fully integrated into clinical practice. Colour calibration of virtual slides is one aspect that has remained largely un-investigated, but may influence diagnosis. We created a colour calibration test object, and aimed to evaluate its effectiveness in the clinical setting. The objectives were to investigate: 1. Whether colour calibrated virtual slides are closer in appearance to the glass slides as viewed through the microscope, when compared to uncalibrated virtual slides, 2. To determine whether colour calibrated virtual slides are preferred by pathologists and 3. To ascertain whether colour calibration increases confidence in diagnosis.

Methods: Six glass slides of varying tissue types and stains were selected and scanned to produce virtual slides. These virtual slides then underwent colour calibration using a colour profile created with the test object. A colour calibrated, medical-grade monitor was used to view the virtual slides. Twelve consultant pathologists took part in the experiment and were asked to compare the colour calibrated virtual slides with the uncalibrated virtual slides. Subjective responses were recorded on 7-point Likert scales.

Summary of Results: Colour calibrated virtual slides were closer in appearance to the microscope (40 of 72 trials, 56%) and calibrated slides were also preferred by pathologists (46 of 72 trials, 64%). Colour calibration improved diagnostic confidence (median 6.00 vs. 5.00, p=0.001).

Conclusions: Colour calibration of virtual slides may be beneficial to clinicians by increasing confidence in diagnosis. It also affords virtual slide colour standardisation; an unmet need highlighted by the US Food and Drug Administration and the International Colour Consortium. Further research should focus on the effect of calibrated virtual slides on diagnostic accuracy.
Use of digital teaching sets and its impact on histopathology trainee education in West Midlands.

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Purpose of the study: The core aim of a training program is to facilitate & promote trainee education. Training in cellular pathology is based on understanding of various diagnostic patterns. This is acquired through a wide experience in looking at histological material. Traditionally this is obtained by routine reporting and looking through teaching sets, which consist of glass slide archival collections. In the past few years, the technology is shifting away from traditional slides and moving towards digital slides.

Why Trainees Need Digital Slide Sets?: A pathology trainee education benefits to a great extent from teaching archives of glass slides. However, there are certain limitations such as the slides can be reviewed by only one person at a time, a microscope is required, slides can get broken etc.

Using Digital Slides: Digital slides are generated by electronically scanning the glass slides and these are increasingly being used for regional teaching program to facilitate trainee education. Trainees are provided with a link to digital images that can be viewed on any computer. Trainees examine these slides at their ease & attend regional teaching day where these cases are discussed and useful feedback is provided.

Advantages: (1) Trainees can remotely access whole slide images at their convenience. (2) More efficient and time-saving. (3) Wide variety of cases, (4) Valuable histological material can be maintained on host site and preserved for any future studies which may be required, particularly in view of the marked advances in genetic profiling through molecular pathological studies, (5) For cytological specimens, additional teaching sets are often difficult to produce, and so this new technology provides valuable teaching material.

Impact on Education: The availability of digital slides has made teaching preparation rather an easier, risk free and unlimited time experience. This in turn will have a very positive impact on histopathology training in West Midlands.

Bilateral Renal Cortical Necrosis and Waterhouse-Friderichsen Syndrome in Meningococcal Septicaemia.

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We present a case of a patient with meningococcal septicaemia, who died of multiorgan failure, but at post-mortem was found to have bilateral renal cortical necrosis and Waterhouse-Friderichsen syndrome.

A 27-year-old man presented to accident and emergency with generalised aches and pains, fever and hypotension. Gram-negative cocci were cultured from blood but no meningitic features were noted. However, he became acutely unwell with evidence of disseminated intravascular coagulation, multiorgan failure and acute kidney injury. Despite aggressive treatment he died 5 days later.

Autopsy revealed complete bilateral cortical necrosis of the kidneys with histology showing coagulative necrosis of the renal cortex, capillary congestion and extensive fibrin thrombi within the capillaries. In addition, bilateral adrenal haemorrhage was seen with extensive necrosis, fibrin deposition and inflammatory cell infiltrate of the cortex and the medulla confirmed on histology. No macroscopic or microscopic evidence of meningitis and no rash were noted.

Individually both acute haemorrhagic necrosis of the adrenal glands, Waterhouse-Friderichsen syndrome, and bilateral renal cortical necrosis are severe and often fatal but uncommon complications of meningococcal sepsis. Therefore, to our knowledge this is the only second reported case of these occurring in combination in meningococcal septicaemia.

P48
Paediatric Adrenal Weights at Post-Mortem in the West of Scotland Between 2007–2012

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Purpose of the study: Adrenal weight is measured as part of the standard paediatric post-mortem protocol to help identify pathology. Age and body weight independently affect adrenal weight and standard weight tables according to these factors are available in textbooks. Such tables only include the first year of life, are based on dated studies and may not provide information relevant to the population of post-mortems carried out in modern day practice.

Methods: We retrospectively analysed all West of Scotland procurator fiscal-authorised post-mortem reports (2007–2012). Cases with evidence of significant adrenal abnormality were excluded. We created a table of the mean and standard deviation of combined adrenal weight (g) and adrenal weight as a percentage of total body weight (%TBW) at twelve age intervals from 0 to 5 years based on the stages of adrenal gland development.

Summary of results: Of 281 cases during the study period, 205 cases were included. There was no correlation between time to post-mortem and adrenal weight (r = 0.167). Adrenal weights decreased over the first three months of life and then increased with age whilst %TBW decreased continually from birth. Combined adrenal weight showed a weak positive correlation with age (r = 0.148, p = 0.035) but did not correlate with body weight (p = 0.107). %TBW correlated negatively with age (r = -0.468, p<0.001) although appeared to remain stable around 0.03% after 1 year of age.

Conclusions: We tabulated adrenal weights in the first 5 years of life and demonstrated a fluctuation in adrenal weight with age and body weight as expected due to the physiological development of the adrenal gland. Our findings suggest that expressing adrenal weight as a percentage of total body weight may be helpful for easy reference and interpretation, particularly after the first year of life.
P49

An Unexpected Autopsy Finding: Ruptured Thoracic Aneurysm

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Introduction: Ruptured thoracic aneurysm carries an exceedingly high mortality rate (94-100%). Typical symptoms include chest pain which radiates to the back. However, it can present with non-specific symptoms and can lead to sudden death. Most thoracic aortic aneurysms are detected on imaging tests performed for other reasons. However it is not uncommon that the diagnosis is made at the autopsy. We present here an unusual case of very long segment of thoraco-abdominal aortic aneurysm with large rupture in the thoracic aorta.

Case report: A 95 years old nursing home resident Caucasian woman was brought in to A&E due to vomiting, high blood pressure and history of fall a day before. She was known to suffer from dementia, hypertension, chronic kidney disease stage 3 and poor mobility. Clinically, a diagnosis of stroke was suspected. However, later on it was ruled out and no obvious cause was identified to explain her symptoms, which had started to settle within few hours of admission. But she suffered a sudden death and post mortem examination was requested. The post mortem examination revealed severe complicated aortic atheroma with an aneurysm involving thoracic and abdominal aorta extending up to 25cm in length. The aneurysm had a maximum diameter in the thoracic part, which showed a large (10cm) rupture in the wall. This ruptured area communicated with the mediastinum and caused large hemorrhagic pleural effusion (1000ml) on the left side. This severe bleed caused the death of the patient.

Conclusion: Ruptured thoracic aneurysm carries high mortality rate and can be an unexpected finding on post-mortem examination, in cases where it is not suspected clinically.

P50

Analysis of Turnaround Times for Histological Reporting of Placenta

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Background: Turnaround times are a measure of laboratory efficiency and performance. The delivery of placental pathology service varies widely between hospitals and is not available to all obstetric units in the UK. Majority of placenta does not constitute the urgent case workload. Royal College’s minimum dataset for placenta reporting has provided guidance on criteria for audit that includes monitoring of turnaround times for reporting.

Standard: According to Royal College of Pathologists’ key performance indicators (KPI), all cases should be reported and authorized within 10 calendar days after the delivery of the placenta.

Objectives: (1) To measure the turnaround times for reporting of placenta. (2) To investigate the factors affecting TAT in our unit.

Methodology: This is a retrospective audit of all the placental histology cases reported at our hospital from 01/01/2014 to 31/12/2014. The reports were accessed via TELEPATH software and data was collected on an excel sheet.

Results: Over a period of 1 year, total 408 placentas were reported. Nearly 35% (144/408) cases were reported within 10 calendar days and the remaining 65% (264/408) were over 10 days. In our audit, we identified the following factors that possibly affected TAT such as, increased workload and unnecessary referrals where no indication for histological examination was given.

Conclusion: Turnaround times are monitored as one of the laboratory’s performance indicators. The TAT target was met in only 35% of the cases, but various factors have been identified which affect TAT. In a recent departmental audit, it was noticed that at least 30 unnecessary placenta referrals were sent every year. Our audit has provided useful results and it has re-emphasized the importance of being aware of TAT targets to achieve better results.

P51

Radiological and Pathological Comparison of Tumour stage (T) and Nodal Stage (N) for Colorectal Carcinoma in a Cancer Centre

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Introduction: Colorectal cancers are the fourth most common cancer in the UK with more than 16,000 deaths per year.

Methods: * All colorectal carcinomas over a period of two years (2012-2014) in a tertiary cancer centre were assessed using the Winpath software. * The tumours were staged according to the TNM 5th edition. * The radiological data was obtained through the Sommerset cancer database. * Cases which had more than two stage discrepancy were again reviewed by expert pathologists and radiologist.

Results: Out of 118 cases, consistent pathological and radiological correlation was achieved with T3 tumours (38/63) and was 64%, 62.5% and 54.5% in the right, upper rectum and left colon respectively. Of the twelve cases reported as T3 on histology but showed T2 on radiology, seven cases were T3a. Four cases of T4 reported as T2 on radiology were reassessed by experts and were found to be at least T3b. For nodal metastasis consistent pathological and radiological correlation was achieved for N0 tumours (64/77) and was 85%, 83.8% and 80% for upper rectum, right and left colon respectively. Two cases which showed more than two N stage discrepancy were reviewed by experts and were found to be equivocal due to small size of nodes (4mm).

Conclusion: (1) There is a good pathological and radiological correlation for colorectal tumours. (2) Most common causes for mismatch in T stage were due to inflammation, ascites and intussusception and in N stage were due to size of the nodes.

P52

Clinicopathological Assessment of Pancreatic Neuroendocrine Tumours Excisions in a Tertiary Cancer Centre

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Introduction: Neuroendocrine tumours (NET) comprise approximately 2% of pancreatic neoplasms.

Aims: The aim of the audit is to assess the clinicopathological parameters of tumours excised in the Royal Surrey County Hospital between 2011 and 2015.

Materials and methods: The Royal College of Pathologists dataset for neuroendocrine tumours of the gastrointestinal tract was used to determine pathologic parameters.

Results: Total 21 cases were assessed. Metastatic tumours tend to present at a younger age: for N0 tumours the mean of 68.8 years. For N1 tumours the mean age of 57.8 years. Metastatic tumours tend to arise more often at the head of the pancreas (5/8 tumours) while non-metastatic tumours arise more often distally (9/13 tumours). For N0 tumours the size range was 14-120 mm and for N1 tumours it was 25-76 mm. The commonest peptide produced was glucagon (10/21 tumours). All N1 cases manifested lymphovascular invasion, whereas only 2/13 N0 cases showed that feature.

Conclusions: Metastatic neuroendocrine tumours of the pancreas present in younger age group and frequently involve the pancreatic head. The incidence of lymph node metastases is unrelated to tumour grade, but marginally related to tumour size and strongly associated with the presence of lymphovascular invasion.
P53
Five Years of Experience of Developing and Running an e-Learning Resource: Sharing the London Experience

P55
This abstract has been withdrawn

P54
Measurement and Communication of Uncertainty in Histopathology: Less Art, More Science?

P56
A Novel Educational Tool for the Assessment of Trainers by Trainees in the Wales Deanery
P57
Reliability of Molecular Methods for High Risk HPV Detection in Benign, Dysplastic and Malignant Lesions

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Introduction: Human papillomavirus (HPV) is an oncogenic virus associated with a subgroup of oropharyngeal squamous cell carcinomas (OPSCC) which have a favourable prognosis [1]. The incidence of HPV-associated OPSCC is growing significantly, making detection of such cases increasingly important.

Materials and Methods: Cases with high and low probability of HPV presence were identified from the electronic database. Formalin-fixed paraffin-embedded tissue (FFPET) was tested with p16 immunochemistry and high risk HPV ISH as a two-tiered approach and compared with high risk HPV real-time DNA PCR. ISH screened for HPV types including 16, 18, 31, 33, 35, 45, 51, 52, 56, 58, and 66 using the Ventana INFORM HPV III family 16 probe (B). All blocks were checked for adequacy. DNA was extracted with tissue microdissection if required. mpliSens® HPV HCR-Screen kits (InterLabService, Moscow, Russia) were used to detect HPV subtypes 16, 18, 31, 33, 35, 45, 52, 58, 59 and 67. All preparations were examined independently by 3 pathologists and a consensus reached. Sensitivity and specificity were calculated for the complete series and benign and malignant subgroups.

Results: 26 cases were included. The two-tiered system has a sensitivity of 47% and specificity of 100% when compared with HPV PCR. No cases proven negative by PCR were positive by p16 immunochemistry or HPV ISH. Sensitivity is not increased with invasive carcinoma (50%), is slightly higher for dysplastic lesions (75%) and remains low for benign lesions (36%).

Conclusion: Results of our preliminary series show that overall sensitivity is not in keeping with current literature [2, 3]. Sensitivity has been reported between 92% and 97% previously [4]. Immunohistochemistry and ISH are inconsistent for malignant, dysplastic and benign lesions and would not be recommended as stand-alone tests. Our data favours direct screening with PCR; we are currently testing a larger series of tumours for confirmation.

P59
The Spectrum of Mutations in GIST: The Birmingham Experience

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Purpose of the study: Most GISTs carry activating mutations in either KIT or PDGFRA; the type of mutation has prognostic significance and may indicate the likelihood of the tumour responding to tyrosine kinase inhibitors. Some wild type GISTs show loss of succinate dehydrogenase (SDH), raising the possibility of the inherited Carney-Stratakis syndrome. The type of mutation is therefore of clinical significance and molecular testing of all GISTs is now recommended.

Methods: As part of our Diagnostic Molecular Pathology Service we have tested 1249 in house and referral cases over the last decade, comprising resection, biopsy and fine needle aspiration cytology specimens. We have used Sanger sequencing to detect mutations in exons 11, 9, 13 and 17 of KIT and exons 18, 12 and 14 of PDGFRA. We have recently introduced real time PCR for the Braf V600E mutation and immunohistochemistry to look for SDH loss.

Results: Samples were adequate for complete mutation analysis in 96% of cases (n=1200); A mutation in either KIT or PDGFRA was found in 85% of cases. Exon 11 KIT deletion and missense mutations were the most common mutations (60% of all cases) and the exon 11 D842V mutation was the third most common mutation (7% of all cases). SDH loss was found in 14% of the wild type tumours tested. A single wild type tumour was found to have the Braf V600E mutation.

Conclusion: Our results meet the threshold of a comprehensive mutation testing of a large number of GISTs in routine clinical practice. SDH loss in wild type GISTs is found in a relatively high number of wild type tumours and andrequisites dialogue with clinicians to ensure referral of the patient to a geneticist.

P58
Parallel FISH and IHC for ALK Testing in Non Small Cell Lung Cancer: The Birmingham Experience of 5000 Cases

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Purpose of the study: Some patients with non small cell lung cancer (NSCLC) and rearrangement of the ALK gene gain dramatic benefit from crizotinib treatment. FISH and IHC are inconsistent for malignant, dysplastic and adenocarcinoma; these tumours had a higher rate of discrepancy between FISH and IHC than that seen in adenocarcinoma.

Results: 97% previously [4]. Immunohistochemistry and ISH are inconsistent for malignant, dysplastic and adenocarcinoma (50%), is slightly higher for dysplastic lesions (75%) and remains low for benign lesions (36%).

Conclusion: Results of our preliminary series show that overall sensitivity is not in keeping with current literature [2, 3]. Sensitivity has been reported between 92% and 97% previously [4]. Immunohistochemistry and ISH are inconsistent for malignant, dysplastic and benign lesions and would not be recommended as stand-alone tests. Our data favours direct screening with PCR; we are currently testing a larger series of tumours for confirmation.

P60
The Spectrum of EGFR Mutations in Non-Small Cell Carcinoma of the Lung

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Introduction and objectives: The availability of tyrosine kinase inhibitors targeting EGFR mutations have revolutionised the management of non-small cell carcinoma (NSCC) of lung. Increasingly, however, attention has shifted to the prognostic and treatment significance of individual mutations within the EGFR gene. We aimed to examine how the spectrum of EGFR mutations varies by patient age and sex.

Methods: 15,068 lung NSCC EGFR mutation reports issued between 10/05/2009 and 02/09/2015 were retrospectively reviewed. Of these, 1,905 reports were excluded because they included repeat results (759) no valid result (138), failed tests (738) and equivocal results (270). For the remaining 14,310 reports, information was collected about patient sex, patient age and the mutation type.

Results: 1,383 (10.5%) specimens tested harboured an EGFR mutation. 6.7% of males and 14.1% of females bore a mutation. Mutations were significantly more common in patients aged 41-50 years (14.3%, ± 2.7%) and 81-90 years (13.6%, ± 1.8%) than in patients aged 61-70 years (9.2%, ± 0.8%). The most common mutation was deletion of exon 19 (45.5% of all mutations) followed by L858R (33.3%). No significant difference was found in the incidence of any of the individual mutations between male and female patients. Del19 was the most common mutation in patients younger than 70 years (47.5% of all mutations, ± 2.8%), with its incidence falling with increasing age. Conversely, the incidence of L858R increases with age, to become approximately as common as Del19 in patients older than 70 years (40.7 ± 6.7% and 32.8 ± 6.4% of all mutations, respectively).

Conclusion: We found that EGFR mutations in this population are substantially more common than in previously-published series, which may reflect the high level of ethnic diversity in the local patient population. In addition, we identified a striking predominance of Del19 mutations in younger patients, with the incidence of L858R increasing with age.
P61

Do We Know What is in Our Samples?
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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. For cytological specimens residual material remaining after the initial diagnostic slide can be 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 of the malignant cell population and permits immunohistochemistry. This is the preferred method to prepare cell blocks world-wide. Current molecular pathology guidelines from the College of the American Pathologists, International Association for the Study of Lung Cancer and the Association for Molecular Pathology recommend the use of cell blocks for molecular testing and therapy selection criteria for EGFR TKS and ALK inhibitors. Plasma of course contains cell free DNA. Plasma sources vary between labs as does the volume of plasma used to form cell blocks. 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 PCR Kit. DNA product was detected in the elute extracted from the empty cell blocks; however, no DNA was detected in the control paraffin blocks. We conclude that plasma is a source of contaminating DNA. Fortunately, a review of our molecular assays performed on cell blocks found no evidence of false positive or negative results. As high throughputs 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.

P62

The Frequency of EGFR mutations in Lung Adenocarcinoma: The Cardiff Experience
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Lung cancer therapy is tailored by the individual genetic profile of a tumour. The aim of this study was to determine the frequency of on such profile - the EGFR mutations - and how histopathological diagnosis and specimen type influence its frequency. Within a 58 month period (2010-2014) a total of 350 specimen requests were generated from Cardiff and Vale University Health Board. The outcome measure included the frequency of activating EGFR mutations on exons 18, 19 and 21. The overall positivity rate was 11.17%, 13.8% for females compared with 7.1% for males. An EGFR mutation was detected in 21.4% of non-smokers compared with 9.2% of current or ex-smokers. Specimens with a diagnosis of non small cell carcinoma and primary lung adenocarcinoma demonstrated a 10.91% and 12.45% positivity respectively. No mutations were detected in patients with an adenocarcinoma originating outside the lung or in patients diagnosed with squamous or neuroendocrine lung cancers (12 patients). The positivity rate for endobronchial ultrasound-guided transbronchial needle aspiration (EBUS) and cytology specimens showed a 13.5% and 13.2% positivity. The surgical resection specimens had a higher positivity rate at 18.3% whilst the lung and bronchial biopsies were positive in 12% and 9.2% of current or ex-smokers. Specimens with a diagnosis of non small cell lung cancer showed no loss of chromosomes 2, 6, 10 or 17 despite repeated testing. This included both retrospective and prospective cases. The results of CK7 and CD117 immunostaining were then considered. Finally, the results of chromosome FISH performed on paraffin-embedded tumour sections with probes for chromosomes 2, 6, 10 and 17 were assessed.

Summary of Results: 81 tumours were studied: 25 chromosome carcinomas and 56 oncocytomas. In the majority of cases the results of chromosome FISH simply confirmed the morphological diagnosis of chromosome renal cell carcinoma. 6 cases (24%) showed variability in the pattern of chromosome loss. Importantly, 2 cases (8%) with the characteristic morphological and immunohistochemical features (strong and diffusely CK7/CD117 positive with membranous accentuation) of chromosome renal cell carcinoma showed no loss of chromosomes 2, 6, 10 or 17 despite repeated testing. None of the oncocytomas showed loss of chromosomes 2, 6, 10 or 17.

Conclusions: We found HvE morphology the most robust diagnostic tool in the diagnosis of chromosome renal cell carcinoma. An immunocytochemical panel and chromosome FISH can be useful adjuncts particularly in the context of needle biopsy samples. It is very important to recognise that occasional chromosome carcinomas do not conform to the spectrum of common patterns of chromosome loss.

P63

Lymph Node Pathology In a Case of Auto-Immune Lymphoproliferative Syndrome (ALPS)
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The Case: We present the case of a 19 year old female who presented with a tender enlarged submental lymph node measuring 2.5 cm in diameter. There was a past medical history of autoimmune haemolytic anaemia, autoimmune thrombocytopenia and splenectomy, and genetic studies had previously confirmed a homozygous Fas mutation. The lymph node was excised and histological examination showed small germinal centres separated by markedly expanded paracortex which contained a mixture of small mature lymphocytes and prominent medium-sized to large cells with prominent eosinophilic nucleoli. Numerous mitotic figures and apoptotic bodies were observed in this population.

Immunohistochemistry: The expanded paracortex consisted almost exclusively of T cells; the medium-sized and large cells were positive with CD3 and CDS and were negative with both CD4 and CD8. Cytotoxic markers (perforin, granzyme B) were expressed and MIB1 showed a high proliferation fraction (90%). CD20 and TdT were negative; EBER staining showed scattered positive small cells indicating previous EBV infection.

Conclusion: The enlarged lymph node showed the morphological and phenotypic features of the Auto-immune Lymphoproliferative Syndrome (ALPS). The T cell proliferation relates to defective lymphocyte apoptosis secondary in this case to an inherited homozygous Fas mutation. Most cases of ALPS present in childhood and there is a frequent association with autoimmune disorders. Pathologists should be aware of this entity as the proliferating T cells can be incorrectly diagnosed as leukaemia or lymphoma.
Introducing the significance of reporting (IDLs) in cases of malignant salivary gland neoplasms of the parotid gland, pleomorphic adenoma and multifocal intercalated duct hyperplasia. This report is to be described. Interestingly, to the best of our knowledge this is the first case in the literature to see if an association between parotid sebaceous carcinoma and multiple visceral malignancies as seen in Lynch syndrome has ever been described.

As mentioned, MTS represents a small subset of the Hereditary Non Polypsis Colon Cancer (HNPCC) family, thought to be a subtype of Lynch syndrome, where patients are prone to develop multiple visceral cancers involving gastrointestinal and genitourinary tract along with sebaceous and non-sebaceous tumours of the skin. MTS is a rare hereditary, autosomal dominant cancer syndrome caused by Microsatellite Instability (MSI) and defect in DNA mismatch repair protein. The germline mutation involves mostly hMSH2 and hMLH1 genes. In MTS the skin of the head neck area with the perioncular region in particular, is affected but sebaceous carcinomas of the parotid gland associated with visceral malignancies has not yet been reported in literature. Here we report an index case of sebaceous carcinoma of parotid in a patient with Muir Torre Syndrome who has a history of gastric, perianpillary, colorectal and multiple cutaneous carcinomas.
P69 Diagnostic Accuracy of Cytology in Suspected Biliary and Pancreatic Neoplasms

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Introduction: Bile duct brushing and FNA cytology of pancreatic lesions are increasingly becoming first-line diagnostic tools in the investigation of suspected pancreatic neoplasms.

Objectives: To evaluate the diagnostic efficacy of brushing and FNA cytology and their sensitivity, specificity and predictive values in detecting pancreatic neoplasms.

Methods: 389 pancreatobiliary cytology reports issued between 01/01/2012 and 01/04/2015 were retrospectively reviewed. 42 cases (31 inadequate and 11 with unknown outcome) were excluded. For 347 cases, a final diagnosis had been given on cytology as no malignant cells seen (NMCs), atypical cells present, suspicious of malignancy or malignant. All the cases were discussed at the hepatobiliary MDM with biopsy results (62 pancreatic cases, 29%, 19 biliary cases, 15% and radiology, and a final diagnosis was reached. The NMCs and malignant reports were compared to the final diagnoses and sensitivity, specificity and predictive values were calculated.

Results: 2 (1.5%) biliary brushings were inadequate, compared to 29 (11.8%) pancreatic FNA (p = 0.0005). For biliary brushing, sensitivity, specificity, positive predictive value and negative predictive value were 63.3%, 96.8%, 97.4% and 57.7%, respectively. The same values for pancreatic FNA were 87.6%, 97.9%, 97.5% and 89.5%, respectively. These results are similar to those in published studies.

Conclusion: Both pancreatic FNA and biliary brushing cytology have high rates of adequacy. Pancreatic cytology has very low rates of false positive results, and low rates of false negatives. Biliary cytology has similarly low rates of false positive results, but is prone to giving false negative results. Pancreatobiliary cytology is, therefore, best employed in confirming malignancy in a clinically suspicious lesion and is less accurate in ruling out malignancy; a negative result on biliary brushing should prompt further investigation before a lesion is considered benign.

P70 Generation of a Unique Pancreatic Cytology Resource from Fresh Whipple Resection Specimens – a Pilot Study

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Purpose of the study: Fine needle aspiration, a common diagnostic test, may be the only source of tissue for inoperable diseases (e.g. pancreatic cancer). Archived samples are a precious resource and often underutilised in research due to their limited availability and the need for cytology-specific optimisation of any novel biomarker. We aimed to create a bank of cytology samples from fresh Whipple resections for biomarker optimisation and for future research and development.

Methods: Cytology samples of normal pancreas, normal duodenum and tumour, collected prospectively from fresh Whipple resections between October 2013 and March 2014, were processed into paraffin embedded cell blocks. Sections were stained with H&E and biomarkers (KOC, Maspin and Mesothelin) which had been previously optimised for histology. Sections were reviewed by two pathologists and biomarker staining compared to the corresponding resection specimens.

Summary of results: Ten Whipple resections for tumour were sampled generating 27 cytology samples, all of which were of adequate cellularity. 15 samples (5 normal duodenum, 5 normal pancreas and 5 tumour) were selected for biomarker optimisation. Optimisation of the 3 biomarkers required an increase in pH for antigen retrieval for both KOC and Mesothelin and dilution of the primary antibody for Maspin compared to the protocol used for histological sections. Following optimisation, staining was identical to the corresponding resection specimens.

Conclusions: We have created a unique resource for cytology-specific optimisation of biomarkers, prior to use on the limited material from archived diagnostic cytology specimens. Such a resource could be expanded for use in future research projects.

P71 Use of Digital Analysis Software Versus Manual Histoscore for Biomarker Quantification in Pancreatic Adenocarcinoma

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Purpose of the study: Assessment of biomarker staining in tumours is important for diagnosis, prognostication and prediction of treatment benefit in research and clinical tissue samples. Manual scoring is complex and time-consuming. Automated digital image analysis (DIA) software may accelerate this process. Pancreatic Ductal Adenocarcinomas (PDAC) are particularly difficult to diagnose due to their complex architecture. We aimed to train and test an automated system and compare its analysis of tissue samples with manually scored data.

Methods: Two sample sets of images from tissue microarrays (TMAs) were used: first, relatively homogeneous, pre-clinical patient-derived xenograft (PDX) tumour tissues stained for HER-2; second, more heterogeneous PDAC clinical samples stained for KOC, S100P, Maspin and Mesothelin. Indica Labs HAILODIA software was used to create tissue-specific classifiers to identify tumour areas for assessment and applied to modifiable analysis algorithms to quantify staining. A Histoscore method was used for comparison.

Summary of results: DIA software provided quantification of HER-2 staining in the pre-clinical PDX models: there was a range of HER-2 staining and models with high expression were easily identified. The classifier created for clinical tissues highlighted both stained and non-stained tumour, successfully separating these from areas of stroma, and provided quantitative scores. The automated system and manual scoring produced similar Histoscores with P-values of 0.94 for KOC, 0.83 for S100P and 0.74 for Maspin.

Conclusions: Automated image analysis for quantifying tissue biomarkers appears to provide results of at least similar quantity to manual scoring, potentially even in complex tumours, and may accelerate biomarker development and analysis.

P72 Investigating Various Thresholds as Immunohistochemistry Cut-Offs for Observer Agreement

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Purpose of the study: Clinical translation of immunohistochemistry (IHC) biomarkers requires a reliable and reproducible cut-off for interpretation of immunostaining. Most of the IHC biomarker research focuses on the clinical relevance of cut-offs with less emphasis on observer agreement using these cut-offs. We identified three cut-offs from our diagnostic IHC work: 10% and 20% positive epithelial cells and moderate (+2) to strong (+3) staining intensity for investigating observer agreement. The aim was to establish consensus based cut-off(s) that could potentially be used by pathologists.

Methods: A series of 36 IHC images of microarray cores for four IHC biomarkers with variable staining intensity and percentage of positive cells was used for investigating inter and intraobserver agreement. Seven pathologists participated in the study and they scored the immunostaining of each image for the three cut-offs. Kappa statistic was used to assess the strength of agreement for each cut-off.

Summary of results: The inter-observer agreement between all seven pathologists using the three cut-offs was reasonably good. A good agreement was observed for experienced pathologists using 10% cut-offs and the agreement was statistically higher than junior pathologists (p=0.02). In addition, the mean intra-observer agreement for all seven pathologists using the three cut-offs was reasonably good. For all three cut-offs a positive correlation was observed with perceived ease of interpretations (p<0.0001 for 10% cut-off, p=0.001 for +2/+3 cut-off and p=0.004 for 20% cut-off). Finally, cytoplasmic only staining achieved higher agreement using all three cut-offs than cytoplasmic/nuclear staining and cytoplasmic/membranous staining.

Conclusions: All three cut-offs achieve reasonable strength of agreement modestly decreasing inter- and intra-observer variability in IHC interpretation, but 10% is slightly better than 20% and +2/+3 cut-offs and is reproducible between pathologists.
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The Incidence of High Risk Human Papillomavirus in Cutaneous Squamous Cell Carcinoma: Evaluation of HPV Detection by In-Situ Hybridisation in Comparison with p16 Immunohistochemistry

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Purpose of the study: Squamous cell carcinoma (SCC) is one of the commonest cancers of the skin, as well as being common in the head and neck (H&N) region and cervix of the uterus. In the H&N and cervix, the majority of SCC is caused by specific strains of Human Papilloma Virus (HPV). In these sites, a surrogate marker for HPV infection is p16 expression by immunohistochemistry. The aim of this project is to determine the prevalence of HPV infection in cutaneous SCC and precursor lesions using In-situ Hybridisation, in comparison with p16 positivity by immunohistochemistry.

Methods: A total of 45 cases of SCC, Bowen’s disease, actinic keratosis and viral warts were analysed. These were tested for the presence of HPV by Chromogenic in-situ Hybridisation (CISH) using the Ventana Inform HPV III family probe, as well as p16 protein expression by immunohistochemistry. The sensitivities and specificities of immunohistochemistry with anti-p16 antibodies, as compared with CISH using the HPV probe were then performed.

Summary of results: In total, 29 specimens were found to be positive for p16. In contrast, only 8 cases were positive for HPV. All 8 cases which were positive for HPV were also positive for p16. Conversely, all cases which were negative for p16 were also negative for HPV. However, in 21 cases, the tumours were positive for p16 but negative for HPV. Overall, the sensitivity of p16 testing (compared with HPV) was 100%, with 100% negative predictive value. However, the specificity of p16 was only 43%, with a 28% positive predictive value.

Conclusions: We found that the majority of cutaneous SCC and their precursor conditions are not caused by HPV infection. We propose that the aetiology of skin SCC are more frequently physical (sunlight) or chemical in nature. The high frequency of p16 positivity indicates that p16 expression as detected by immunohistochemistry is not a specific surrogate marker for HPV infection in skin SCC.
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