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

M Craze[1]; C Joseph[1]; D Soria[1]; C Nolan[1]; A Green[1]; E Rakha[2]; IO Ellis[2];Ⓟ A Mukherjee[2]

[1]University of Nottingham, Nottingham, UK; [2]University of Nottingham and Nottingham University Hospitals NHS Trust, Nottingham, UK

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), FHIT, FOXA1) showed significant positive association with Grade 1 ER positive tumours and 54, significant negative association (e.g. PTEN, GATA3, KAPNA1, p53) (p range = 0.041 — 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 Ki67 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 PathSoc and NIHR.

P2

Stromal Mitotic Count in Fibroadenomas

Ⓟ E Radomski[1]; S Pritchard[2]; M Howe[2]

[1]Bolton Royal Hospital, Bolton, UK; [2]University Hospital of South Manchester, Manchester, UK

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

Ⓟ S Kaptanis[1]; AM Shaaban[2]; I Danial[2]; S Smith[2]; S Bradley[2]; S Fernandez[3]; G Mitsopoulos[3]; D Ryan[4]; Z Winters[5]; LJ Jones[6]

[1]Barts Cancer Institute, Queen Mary, University of London, London, UK; [2]University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; [3]Ealing Hospital, London, UK; [4]Royal London Hospital, London, UK; [5]University of Bristol, Bristol, UK; [6]Barts Cancer Institute, Queen Mary University of London, London, UK

Introduction: Historically, multiple synchronous breast cancers are defined as multifocal (MF) when they are in the same quadrant of the breast, and multicentric (MC) 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 univocalbreast 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).

P4

Cytogenetic Analysis of Recurrent Miscarriages in an Irish Maternity Hospital

Ⓟ C Ryan; P Downey; EE Mooney

National Maternity Hospital, Dublin, Ireland

Chromosomal abnormalities are expected in approximately half of all recognised early pregnancy losses, with trisomies accounting for most genetic abnormalities in the first trimester (1). According to Royal College of Obstetricians and Gynaecologists (RCOG) guidelines for recurrent miscarriages (defined as three or more consecutive miscarriages), cytogenetic analysis of products of conception (POC) is recommended (2). We reviewed the results of cytogenetics tests sent from POC in our institution over three years, from women with recurrent miscarriage. 107 samples (average 9 weeks gestation) were sent from women with mean age of 36.6 years (range 22 to 45 years). Sufficient growth for fetal karyotype was achieved in 81 cases (75%). Maternal tissue only was present in 14/107 cases (13%). Where karyotype analysis was unsuccessful, new molecular techniques yielded a genetic result in another 3/107 cases (2.8%).
Out of 84 miscarriages where a genetic result was available, 25% had a normal karyotype (21/84). The abnormal results included trisomies (64%), polyploidies (11%) and Monosomy X (6%). The most common trisomy was Trisomy 16. More complex abnormalities, including double trisomies and unbalanced translocations, accounted for the remaining abnormal results (19%).
Our results show that the rate of aneuploidy in our population is considerably higher than in other published series. Further investigations are required to ascertain the reasons for this.
(1) Simpson J, Carson S, Glob libr. women's med., (ISSN:1756 - 2228) 2013; DOI 10.3843/GLOWM.10319
(2) Royal College of Obstetricians and Gynaecologists (RCOG). The investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage, London (UK): Royal College of Obstetricians and Gynaecologists (RCOG): 2011 Apr. 18

P5

Audit of the Use of Immunohistochemistry for Ovarian Mucinous Neoplasms

Ⓟ ABA Abdel-Rahman; RH Wei-Shek

University Hospitals of Leicester, Leicester, UK

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 immunophenotyping 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 MCOBM 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

Ⓟ T Balamurugan[1]; F Hussain[2]; V Simanskaite[1]; B Haagsma[1]; I Bagwan[1]

[1]Department of Histopathology, Royal Surrey County Hospital, Guildford, UK; [2]Department of Radiology, Royal Surrey County Hospital, Guildford, UK;

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, 7(7.1%) showed lymph node metastasis. 86% 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

Ⓟ M Ahmed; I Bagwan

Department of Histopathology, Royal Surrey County Hospital, Guildford, UK

Splenic 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

Ⓟ M Ahmed[1]; S Beeslaar[2]; I Bagwan[1]

[1]Department of Histopathology, Royal Surrey County Hospital, Guildford, Surrey, UK; [2]Department of Histopathology, Frimley Park Hospital, Frimley, Surrey, UK

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 macroscopic 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 PDGFRA 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

Ⓟ SW Ghulam[1];Ⓟ AS Azam[2]; U Zanetto[2]

[1]Birmingham University, Birmingham, UK; [2]Sandwell and West Birmingham Hospitals Trust, Birmingham, UK

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's 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 speicmens) 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 where we failed to meet 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.

P10

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

Ⓟ SW Ghulam[1];Ⓟ AS Azam[2]; F Ibison[2]; U Zanetto[2]

[1]Birmingham University, Birmingham, UK; [2]Sandwell and West Birmingham Hospitals Trust, Birmingham, UK

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.

P11

Characterisation of the Oxysterol Pathway in Mismatch Repair Proficient and Deficient Colorectal Cancer

Ⓟ R Swan[1]; AA Alnabulsi[1]; B Cash[2]; A Alnabulsi[2]; GI Murray[1]

[1]University of Aberdeen, Aberdeen, UK; [2]Vertebrate Antibodies, Aberdeen, UK

Colorectal cancer is one of the commonest types of cancer with many patients presenting at an advanced stage. Oxysterols are oxidised derivatives of cholesterol, formed by the enzymatic activity of several cytochrome P450 enzymes and tumour-derived oxysterols have been implicated in tumour growth and survival. The aim of this study was to profile the expression of 7 cholesterol-metabolising enzymes in primary colorectal cancer and assess the association between expression and prognosis. Immunohistochemistry was performed on a colorectal cancer tissue microarray containing 650 primary colorectal cancers using monoclonal antibodies to CYP2R1, CYP7B1, CYP8B1, CYP27A1, CYP39A1, CYP46A1 and CYP51A1, which we have developed. The immunohistochemistry results were assessed by light microscopy using a semi-quantitative scoring system. Unsupervised hierarchical cluster analysis was used to examine the overall relationship of oxysterol metabolising enzyme expression with outcome and based on this identify a protein signature associated with prognosis. Cluster analysis of the whole patient cohort identified a good prognosis group (mean survival=146 months 95% CI 127-165 months) that had a significantly better survival (χ^2=12.984, p<0.001, HR=1.983, 95% CI 1.341-2.799) than the poor prognosis group (mean survival=107 months, 95%CI 98-123 months). For the mismatch repair proficient cohort the good prognosis group had a significantly better survival (χ^2=8.985, p=0.003, HR=1.845, 95% CI 1.227-2.774) than the poor prognosis group. For the mismatch repair deficient group there was a trend towards better survival in the good prognosis group (χ^2=2.518, p=0.113, HR=2.080, 95% CI 0.819-5.279) compared with the poor prognosis group. In conclusion an oxysterol metabolising enzyme expression profile associated with prognosis has been identified in the whole patient cohort and in mismatch repair proficient colorectal cancers. RS was supported by the Jean Shanks Foundation.

P12

Intratumoural Nerve Fibre Detection in Oesophageal Cancer — a Novel Prognostic Feature After Neoadjuvant Therapy

Ⓟ N Verschueren[1]; LC Hewitt[1]; G Fazzi[1]; A Wright[2]; JD Hayden[3]; GG Hutchins[4]; HI Grabsch[1]

[1]Dept of Pathology, Maastricht UMC+, Maastricht, Netherlands; [2]Leeds Institute of Cancer and Pathology,University of Leeds, Leeds, UK; [3]Leeds Teaching Hospitals NHS Trust, Institute of Oncology, Leeds, UK; [4]Leeds Institute of Cancer and Pathology, University of Leeds, Leeds, UK

Purpose of the study: To investigate the clinical importance of intratumoural nerve fibers in patients with oesophageal cancer (OeC) treated with surgery alone (S-group) or neadjuvant chemotherapy (NAC) followed by surgery.
Material and Methods: Tissue microarrays from 257 oesophagectomies were used for immunohistochemistry to detect intratumoural nerve fibers (<5µ in diameter) using PGP 9.5 and neurofilament protein (NF), and CD31 to establish intratumoural microvessel density (MVD). The association between the presence and location of nerve fibers, MVD and clinicopathological characteristics including survival was assessed.
Results: Intratumoural nerve fibers were found in 180 (36%) and 103 (21%) OeC by PGP9.5 or NF, respectively. The median MVD was 13 vessels (range 0-42 vessels). MVD and nerve fibers status were similar in both treatment groups. The nerve fibers status was not related to MVD. The presence of intratumoural NFpos fibers proved to be an independent marker of poor outcome only in patients after NAC (p=0.031). High MVD was related to good prognosis in the surgery alone group (p=0.006).
Conclusions: This is the first study to suggest that intratumoural nerve fibers have a prognostic role for OeC patients after NAC, whereas MVD has prognostic value in the S-group only. This could indicate (a) that the nerve-tumour interaction might be influenced by NAC and thus could represent a potential new druggable target and (b) that the clinical importance of certain components of the tumour microenvironment in OeC might depend strongly on treatment modality. The results of this pilot study warrant validation in a second series.

P13

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

Ⓟ AK Kosierkiewicz; AS Scala; SDP Di Palma

Royal Surrey County Hospital, Guildford, UK

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 ipilmumab 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 is 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

Ⓟ M Evans; LC Tan; S Sah

University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK

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 adjacent to heterologous malignant sarcomatous elements (skeletal muscle, cartilaginous and smooth muscle differentiation). Four out of 66 lymph nodes contained metastatic adenocarcinoma. Immunohistochemically, the carcinomatous element was positive for cytokeratin, focally positive for CK7 and CDX2, 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

Ⓟ HT Morris[1]; L Fort[1]; RA Ridgway[1]; OJ Sansom[1]; FA Carey[2]; LM Machesky[1]

[1]CRUK Beatson Institute, Glasgow, UK; [2]Ninewells Hospital and Medical School, Dundee, UK

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 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 $APC^{fl/fl}$(A) and $APC^{fl/fl}KRas^{+/G12D}$(AK) 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. $APC^{+/fl}$, $APC^{+/fl}NWASP^{fl/fl}$, $APC^{+/fl}KRas^{+/G12D}$and $APC^{+/fl}KRas^{+/G12D}NWASP^{fl/fl}$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 KRas model.
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

M de Wit[1]; L Bishop-Currey[2]; VI Dusseldorp[2]; NCT van Grieken[3]; TV Pham[2]; SR Piersma[2]; RJA Fijneman[4];Ⓟ GA Meijer[4]; CR Jimenez[2]

[1]Netherlands Cancer Institute, Department of Pathology & VU University Medical Center, Amsterdam, Netherlands; [2]VU University Medical Center, Department of Medical Oncology (OncoProteomics Laboratory), Amsterdam, Netherlands; [3]VU University Medical Center, Department of Pathology, Amsterdam, Netherlands; [4]Netherlands Cancer Institute, Department of Pathology, Amsterdam, Netherlands

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 cancer-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 Mesothelioma in the Thyroid

Ⓟ DA Badder[1]; E Youd[2]; R Attanoos[1]

[1]University Hospital of Wales, Cardiff, UK; [2]Royal Glamorgan Hospital, Llantrisant, UK

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.

A 65 year old man collapsed and died and post mortem revealed a right lung tumour with intraventricular, lung, liver and lymph node metastases. The man had a history of both malignant pleural mesothelioma and non-Hodgkin lymphoma, diagnosed following expert regional referrals following pleural biopsy and hemithyroidectomy respectively.

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

Ⓟ DLL Hopkins; F Alchami; R Attanoos

Department of Cellular Pathology, University Hospital of Wales, Cardiff, UK

Introduction: "Pseudomesotheliomata" is the term given to diffuse pleurotropic neoplasms of non-mesothelial histiogenesis. Pseuomesotheliomatous 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 bronichial 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

Glans Penis Metastasis of Pleural Sarcomatoid Malignant Mesothelioma with Heterologous Elements

F Alchami;Ⓟ AR Bamber; RL Attanoos; AR Gibbs

University Hospital of Wales, Cardiff, UK

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 penile mass showed similar morphology and immunophenotype to the pleural tumour; indicating 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

F Alchami; RL Attanoos;Ⓟ AR Bamber; AR Gibbs

University Hospital of Wales, Cardiff, UK

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 classed as high or low grade 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 subtyped 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.

P22

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

F Alchami; RL Attanoos;Ⓟ AR Bamber; RA Gibbs

University Hospital of Wales, Cardiff, UK

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, micropapillary, 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 14.0%, tubulopapillary 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=0.008, median survival 12 months), and pleomorphic forms (p=0.00008, 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.

P23

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

Ⓟ D Krexi; MN Sheppard

CRY Centre of Cardiovascular Pathology, Cardiovascular Sciences Research Centre, St George's University of London, London, UK

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. 29.11% 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 valvular disease (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.

P24

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

Ⓟ PM Ellery; R Khiroya; E Borg

UCL Hospitals NHS Foundation Trust, London, UK

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.

P25

Audit of the Rapid On-Site Evaluation (ROSE) Service for Endobronchial Ultrasound (EBUS) Guided Fine Needle Aspiration Cytology

Ⓟ B Shah[1]; DN Rana[1]; SA Thiryayi[1]; M Holbrook[1]; D Shelton[1]; N Narine[1]

[1]*Central Manchester University Hospitals, NHS Foundation Trust, UK*

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 15(3.4%) lung masses aspirates 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 RCPath guidelines.
Conclusion: The ROSE service plays a vital role in directing our clinicians on how to manage the patients investigated by means of EBUS.

P26

A Case of Methotrexate Associated Lymphoma Masquerading as Pulmonary Granulomatous Disease

Ⓟ MJ Green[1]; N Simmonds[1]; J Pilling[2]; C Thomas[3]

[1]*St Thomas' Hospital, London, UK;* [2]*Guy's Hospital, London, UK;* [3]*Royal Berkshire Hospital, Reading, UK*

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 histiocytes 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.

P27

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

Ⓟ VA Bryant[1]; EK Karaa[1]

[1]*Royal London Hospital, London, UK*

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 21grams (expected 12.9-19.5 grams) and was described as 'dilated with normal constitution'; the lungs were hypoplastic. The placenta weighed 788 grams (>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 haematopoiesis 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 immaturity.

P28

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

Ⓟ M Belasco[1];Ⓟ AS Azam[2]; R Awasthi[2]

[1]*University of Birmingham, Birmingham, UK;* [2]*Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK*

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

Ⓟ JC Hutchinson[1]; OJ Arthurs[1]; IG Haig[2]; NJ Sebire[1]

[1]Great Ormond Street Hospital, London, UK; [2]Nikon Metrology, Tring, UK

Autopsy examination of early miscarriages (<20gw) 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 PM 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

Ⓟ JC Hutchinson; OJ Arthurs; MT Ashworth; NJ Sebire

Great Ormond Street Hospital, London, UK

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 an 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 $4.98x10^{-5}$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 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

Ⓟ JC Hutchinson[1]; M Peltzer[2]; M Darding[2]; H Walczak[2]; NJ Sebire[1]; OJ Arthurs[1]

[1]Great Ormond Street Hospital, London, UK; [2]University College London, London, UK

Retention 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

Ⓟ JC Hutchinson; MT Ashworth; OJ Arthurs; NJ Sebire

Great Ormond Street Hospital, London, UK

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

J Man[1]; Ⓟ JC Hutchinson[2]; MT Ashworth[2]; I Jeffrey[3]; NJ Sebire[2]

[1]University College London, London, UK; [2]Great Ormond Street Hospital, London, UK; [3]St. George's Hospital, London, UK

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 isunclear. We present demographic data from a retrospective cohort autopsy cases from two London centres.

Data was retrospectively collected 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 antepartum (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 midtrimester 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 midtrimester 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

J Man[1];Ⓟ JC Hutchinson[2]; MT Ashworth[2]; L Judge-Kronis[2]; I Jeffrey[3]; NJ Sebire[2]

[1]University College London, London, UK; [2]Great Ormond Street Hospital, London, UK; [3]St. George's Hospital, London, UK

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 SUDI, 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 (68%), 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

J Man[1]; Ⓟ JC Hutchinson[2]; A Heazell[3]; MT Ashworth[2]; I Jeffrey[4]; NJ Sebire[2]

[1]University College London, London, UK; [2]Great Ormond Street Hospital, London, UK; [3]Manchester University, Manchester, UK; [4]St. George's Hospital, London, UK

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 Man[1];Ⓟ JC Hutchinson[2]; MT Ashworth[2]; I Jeffrey[3]; NJ Sebire[2]

[1]University College London, London, UK; [2]Great Ormond Street Hospital, London, UK; [3]St. George's Hospital, London, UK

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 chorioamnionitis. 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 thirdgroup 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 corticomedullary ratios compared with controls ($p=0.02$) but there was no difference between controls and the SGA group.

These findings indicate that whilst in typical IUGR there are histological changes of thymic involution, as evidenced by reduced corticomedullary ratio, there ismarked overlap with non-IUGR cases and subjective assessment of VB grade is not a reliable tool toassess the cause of fetal demise in individual cases.

P37

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

J Man[1];Ⓟ JC Hutchinson[2]; A Heazell[3]; MT Ashworth[2]; I Jeffrey[4]; NJ Sebire[2]

[1]University College London, London, UK; [2]Great Ormond Street Hospital, London, UK; [3]Manchester University, Manchester, UK; [4]St. George's Hospital, London, UK

Despite advances in diagnostic techniques, 15-60% of stillbirths remain unexplained despite postmortem examination. Various classification systems are used to code such deaths, leading to great variation in interpretation of findings and a wide rate of 'unexplained' deaths, with implications for parents and clinicians. The aim of this study was to objectively assign causes and classifications of death based on pre-determined criteria. Postmortem information on 1,064 cases of intrauterine deaths from 2005-2013 from two London tertiary referral centres was retrospectively analysed using pre-defined 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.

P38

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

J Man[1];Ⓟ JC Hutchinson[2]; MT Ashworth[2]; I Jeffrey[3]; NJ Sebire[2]

[1]University College London, London, UK; [2]Great Ormond Street Hospital, London, UK; [3]St. George's Hospital, London, UK

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 normal livebirth weight). This has resulted in studies to reduce stillbirth rates based on improved detection of growth restriction antenatally. The present large study examines effects of changes in fetal weight secondary to intrauterine retention post death and during the post-mortem interval.

A database of 1,064 intrauterine deaths undergoing autopsy at one of two London specialist centres was interrogated to identify cases of stillbirth beyond 23 weeks of gestation (to allow calculation of expected birthweight (BW) based on WHO standards). For each case, the delta BW was derived as the number of standard deviations by which the observed BW differed from expected.

35/674 (5%) stillbirths had a known antenatal diagnosis of IUGR. Of the 533 stillbirths with a recorded birthweight delivered >23 weeks', 192 (36%) had raw birthweight <10th centile (SGA). 308 had documented intrauterine interval (IUI; length of intrauterine retention post-IUD based on ultrasound scans and history). There was a significant relationship between IUI and delta birthweight, indicating that with intrauterine retention fetuses lose weight in utero; average -0.8 SDs at over 3-4 days. In addition, of the 615 cases with both birthweight and bodyweight at autopsy recorded, there was an average 12% further loss of fetal weight during the 6-7 day post-mortem interval.

These findings demonstrate that a significant proportion (around 20%) of the apparent SGA in stillbirths is erroneous and such low body weights are due to changes that occur following death, this effect being even more marked if bodyweight at autopsy is used. The findings have implications for policy regarding stillbirth prevention strategies.

P39

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

M Cummings[1]; G Mappa[1]; R Hutson[2]; N Wilkinson[3];Ⓟ NM Orsi[1]

[1]Section of Pathology and Tumour Biology, Leeds Institute of Cancer and Pathology, University of Leeds, Leeds, UK; [2]Gynaecology Services, St. James's Hospital, Leeds, UK; [3]Dept. Histopathology, St. James's Hospital, Leeds, UK

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 lysates (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. Clinicopathological 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 with Dunn's 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, galectin-3, tissue factor and betacellulin were associated with good prognosis. In addition, while survival analyses confirmed Her2 to be an indicator of poor prognosis, prostasin 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

CJS Kung[1]; C Kiourtis[1]; S Fraser[2]; OJ Sansom[3];Ⓟ T Iwata[1]

[1]University of Glasgow, Glasgow, UK; [2]Queen Elizabeth University Hospital, Glasgow, UK; [3]Beatson Institute for Cancer Research, Glasgow, UK

Purpose of the Study: In the recent years, induction of invasive bladder cancer by carcinogen, N-butyl-N-(4-hydroxybutyl) nitrosamine (OH-BBN), is increasingly used in mice with genetically engineered mutations (GEMs). Resulting histopathology is reported to be similar to that of human bladder cancer. OH-BBN treatment is also known to trigger inflammation, followed by formation of tumours that are highly infiltrated with immune cells. In order to facilitate the evaluation of tumour progression in mice, we generated the "Tumour Progression Scale" and evaluated its usefulness in phenotyping mouse bladder tumours with inflammatory phenotype.

Methods: Mice with FGFR3 mutations, Pten deletion and wild-type were treated with 0.05% OH-BBN in drinking water for 10 weeks and sacrificed at 20 weeks from the treatment start. "Tumour Progression Scale" was drafted in reference to human TNM staging/WHO classification of Bladder tumours 1973/2004 and in consultation with the pathologist, and refined by examining carcinogen-induced mouse bladder cancer samples regardless of genotype (n=98). Scoring was also performed using individual criterion for tumour characteristics and immune cell infiltrations.

Summary of Results: GEM models showed increased tumourigenesis. The model demonstrated a high level of lymphocyte infiltration in tumours and often in the urothelium. Inflammatory infiltrate observed at 20 weeks are likely to be related to tumour progression.

Conclusions: Scoring using Tumour Progression Scale was useful in highlighting overall differences in the level of tumour progression among GEM cohorts. In addition, scoring using individual criterion further differentiated the cohorts' phenotype. It is beneficial to use both Tumour Progression Scale and individual scoring criteria for tumour characteristics and immune infiltrations in assessing carcinogen-induced GEM models of bladder cancer.

CJSK was supported by Pathological Society Bursary for Undergraduate Vacation Studies.

P41

Identification of Inflammasome Expression and Activity in Experimental Autoimmune Encephalomyelitis

Ⓟ S Fleville; M Dittmer; J Falconer; P Bankhead; IV Allen; DC Fitzgerald; Y Dombrowski

Queen's University Belfast, Belfast, UK

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

Ⓟ NB Bowman; S Dojcinov; RL Attanoos

University Hospital of Wales, Cardiff, UK

Epithelioid sarcomas represent a rare and heterogenous group of tumours which are considered to be derived from epithelial stem cells of soft tissue origin. We present a case of a TTF-1 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.
SMARCB1 (INI-1) is a tumour-suppressor gene whose gene product is ubiquitously expressed in nuclei of all normal tissues and its inactivation has been implicated in the pathogenesis of a diverse group of malignant neoplasms that tend to share "rhabdoid" cytomorphology and poor prognosis. Epithelioid sarcoma is favoured over rhabdoid carcinoma when cell cohesion is poor, cytokeratin expression is focal and ERG expression is observed as seen in this case.

P43

Case Report: PEComa of Bone

Ⓟ L Edmunds; MF Amary; R Tirabosco; AM Flanagan

Royal National Orthopaedic Hospital, London, UK

Neoplasms of perivascular epithelioid cell differentiation (PEComas) other than angiomyolipoma, lymphangioleiomyomatosis and clear cell "sugar" tumour of the lung are very rare and PEComas (NOS – not otherwise specified) presenting in bone are extremely unusual. We report the case of a 39 year-old male who, having been previoulsy fit and well, presented with hip pain and was found on imaging to have a pelvic pathological fracture. We discuss the differential diagnoses considered on the needle biopsy histology and the resection specimen findings. We examine our patient's pathology in the light of the radiological studies, and briefly consider the genetics, biological behaviourand prognostic factors of this rare tumour.

P44

Colour Calibration in Digital Pathology: the Clinical Impact of a Novel Test Object

Ⓟ EL Clarke[1]; C Revie[2]; D Brettle[1]; R Wilson[2]; C Mello-Thoms[3]; D Treanor[1]

[1]St James University Hospital, Leeds, UK; [2]FFEI Limited, Hemel Hempstead, UK; [3]University of Sydney, Sydney, Australia

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.

P45

Use of digital teaching sets and its impact on Histopathology trainee education in West Midlands.

Ⓟ AS Azam[1]; N Salmons[2]; R Ganesan[3]

[1]Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK; [2]New Cross Hospital, Wolverhampton, UK; [3]Birmingham Womens Hospital, Birmingham, UK

Background: 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 drifting 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 limitationssuch 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

P46

Concordance Among Pathologists Reviewing Autopsy Clinical Information and External Findings: Implications for Implementation of the Proposed Medical Examiners System

Ⓟ ML Sanders; MR Pugh; AR Bamber; F Alchami; RL Attanoos

University Hospital of Wales, Cardiff, UK

Purpose of the study: Pilot study to evaluate concordance between pathologists assessing post mortem Coronial histories and external examination findings, with a view to informing implementation of the proposed medical examiners system.
Methods: A presentation was prepared comprising 20 consecutive anonymized Coronial histories and associated external findings, covering a variety of natural and unnatural deaths. Ten pathologists ranging from ST1 to consultant were asked to view the presentation and recommend: (1) cause of death, (2) whether the death was natural or unnatural, and (3) autopsy requirements. Opportunity was also provided for free-text comment. The results were analysed to establish patterns of concordance between respondents.
Summary of Results: In 50% of cases there was concordance between cause and classification of death, but in 50% of these cases autopsy requirements varied, and in 50% there was near-complete agreement autopsy was required despite an agreed natural or unnatural cause; suggesting uncertainty regarding autopsy requirements. In 45% of cases the classification and cause of death varied widely; a number of respondents stated improved clinical information may remove the need for autopsy in these cases. There was overall variation in classification of cases (natural vs. unnatural), and in some cases the classification did not correspond to the stated cause of death; possibly representing inexperience of classifying deaths in this way amongst pathologists.
Conclusions: From the perspective of pathologists, implementation of the proposed medical examiners system will require clear guidance on the circumstances in which an autopsy is required, specific training to address determination of natural vs. unnatural deaths, and comprehensive background information in order to minimize the number of unnecessary autopsies. This study should be repeated using larger numbers of cases and respondents, including clinicians other than pathologists.

P47

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

Ⓟ H Helin; C Horsfield; J van der Walt

Guy's and St Thomas' NHS Foundation Trust, London, UK

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 male presented to accident and emergency with generalised aches and pains, fever and hypotension. Gram-negative cocci was 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 only the 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

Ⓟ J Khan; R Morrison; D Penman

Queen Elizabeth University Hospital, Glasgow, UK

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. Our aim was to tabulate contemporary adrenal weight data by age and body weight in a single centre over the past 6 years.
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 ($p = 0.167$). 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

Ⓟ AS Azam; S Muzaffar

Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK

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 unsual case of very long segment of thoraco-abdominal aortic aneurym with large rupture in the thoracic aorta.
Case report: A 95 years old nursing home resident Caucasian women 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

Ⓟ AS Azam[1]; M Belasco[2]; R Awasthi[1]

[1]Sandwell and West Birmingham Hospitals Trust, Birmingham, UK; [2]University of Birmingham, Birmingham, UK

Background: Turnaround times are a measure of laboratory efficiency and performance. The delivery of placental pathology services varies widely between hospitals and is not available to all obstetric units in the UK. Majority of placentas do 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 with 10 calendar days
Objectives: (1) To measure the turnaround times for reporting of placentas. (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 atleast 30 unnecessary placenta referrals were sent every year. Our audit has provided with 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

Ⓟ VN Iyer; K Potter; P Pingle; IN Bagwan

Royal Surrey County Hospital, Guildford, Surrey, UK

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

Ⓟ VN Iyer[1]; A Gavriil[2]; P Pingle[2]; IN Bagwan[2]

[1]Royal Surrey County Hospital, Guildford, UK, UK; [2]Royal Surrey County Hospital, Guildford, Surrey, UK

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. Winpath database was analysed over a period of 5 years (2011-2015).
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.
The presence of microscopic perineural invasion was reported in only 10/21 cases.
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

Ⓟ SMH Rizvi[1]; D Radia[2]; W Ng[2]; A Thomas[3]; S Hill[2]

[1]Barts Health NHS Trust/UCL Partners/London School of Pathology, London, UK; [2]School of Pathology, London, UK; [3]St George's NHS Trust, London, UK

In 2010, the London Deanery funded a whole slide scan based e-learning programme hosted on the world wide web. From a few cases mapped to stage I of the Royal College of Pathologists curriculum, the resource has now developed into a comprehensive resource of histopathology slides that is mapped to stages A through C of the RCPath curriculum, includes sample part two exam sets and specialist collections that support numerous local and national meetings and training days hosted by faculty across London.This includes interactive modules using third party software,online evaluation and assessments built around individual modules and use of different electronic file formats including videos to support learning.This resource is unique and evolutionto this stage has requirednumerous iterations, working with the web based host anduse of e-learning softwares that can be embedded in the website. The usage datahighlights assessment or examinations as the main drivers for increase login/ usage. At other times,the login rates are 5-8% (of all logins supplied to trainees) which would correspond with the enthusiasts on the diffusion of innovation curve. Feedback suggests an open source resource (like Leeds but with a focus on education) would have better uptake. Forthis resource to be more widely used, we should consider the use of digital slidesand photographs inyearly assessments (similar to in-service exam administered in the US), including the ST1end of year evaluation andFRCPath exams with incorporation of adaptive learning. Multiprofessional education is another potential area of future development.

P54

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

Ⓟ SA Kulkarni; SMH Rizvi

Barts Health NHS Trust, London, UK

Diagnostic assessment in cellular pathology is subjective and the process of reporting is a descriptive one and not a 'measurement'. Though, as highlighted in a recent College document some of the steps in preparation of a tissue section may be subject to type B uncertainty evaluation and some measurements may require consideration when applying for accreditation under the ISO 15189:2012 standards. However, this only covers part of the reporting process. The interpretation of findings and their communication in a written or verbal report — a process subject to a range of variables from linguistic ability to diagnostic acumen and experience, is left, more or less, open to random learning paths and interpretation. Besides the datasets for cancers and the guidelines for reporting of inflammatory bowel disease,there is no systematic attempt to include evidence based, structured interpretation and standardised report writing in either the training of future pathologists or in current histopathology reporting practice. Published literature has very limited information on expression of uncertainty (e.g. Galloway and Taiyeb). Only one book (Domizio and Lowe) outlines an approach to standardised reporting. We undertook an audit to study phrases used to express uncertainty in biopsy reporting (detailed results in poster) and compared it with the MDM/clinical outcome. Even though <10% of cases were ambiguous, there was a range of terms to express uncertainty. Given, that standardisation does reduce errors and based on our findings and existing literature, we propose the setting up of minimum datasets for non-malignant biopsy and resection specimens, as a guide for trainees in the first instance.

P55

This abstract has been withdrawn

P56

A Novel Educational Tool for the Assessment of Trainers by Trainees in the Wales Deanery

Ⓟ SL Winstanley[1]; AH Toms[1]; RL Attanoos[1]

[1]University Hospital of Wales, Cardiff, UK

The use of 360 degree / multi-source feedback (MSF) in trainee assessment throughout all specialities, has been commonplace for several years. During histopathology training, trainees will perform three RCPath MSF assessments during ST1, ST3 & ST5. In North America, it is practice for trainees to assess trainers in a similar manner. In the UK, there is often no systematic opportunity to give trainer feedback regarding day-to-day teaching although trainees may provide feedback after formal teaching sessions. We have designed a specific educational tool to assess trainers which may be adopted into annual appraisal. This quality tool allows trainees to acknowledge the strengths and weaknesses of particular trainers teaching styles, thus enabling them to accommodate and improve their teaching accordingly.

Trainer assessment includes one-to-one multi-header slide reading, cut-up and autopsy sessions. The tool includes general components including emotional quotients, ability to inspire and communication skills. Further questions regarding more specific teaching ability are also included such as multi-header microscope teaching as well as the more practical procedures of specimen cut-up and autopsy. Lecturing style and exam preparation training is also assessed. Trainers are individually provided with feedback.

The benefit of our educational tool is that compared to more generic GMC questionnaires, we are able to ask speciality specific questions which in turn is of benefit when providing trainer feedback.

The pilot of our educational tool starts in 2015–2016 academic year. If successful, it is hoped that this could be adapted by other departments within our institution and eventually cascaded across the Wales Deanery.

P57

Reliability of Molecular Methods for High Risk HPV Detection in Benign, Dysplastic and Malignant Lesions

Ⓟ W Anderson;Ⓟ LJ Green; G Baldwin; F Hughes; C Swift; B O'Sullivan; M Smith; P Taniere

University Hospitals Birmingham NHS Trust, Birmingham, UK

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 immunohistochemistry 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, 39, 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, 39, 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 immunohistochemistry 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.

P58

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

Ⓟ O Cain; T Mullis; F Hughes; G Baldwin; C Swift; M Smith; B O'Sullivan; P Taniere

Queen Elizabeth Hospital Birmingham, Birmingham, UK

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 both widely used to test for the ALK translocation, but there remains controversy over the correlation between the two and which should be used in routine clinical practice.
Methods: This series includes over 5000 in house and referral cases tested by our service since 2012. Parallel FISH and IHC was performed for each case using the validated Vysis Abbott break apart FISH probes and the Ventana D5F3 antibody on the Ventana XT platform.
Results: The overall rate of ALK translocation was 3%. Patients with ALK positive tumours were younger than those with ALK negative tumours ($p<0.001$). There was significant discrepancy between FISH and IHC results: 16% of cases were FISH+/IHC- whereas <1% were FISH-/IHC+. The majority of cases were adenocarcinomas. However, the ALK translocation was also found in a subset of squamous cell carcinomas and adenosquamous carcinomas; these tumours had a higher rate of discrepancy between FISH and IHC than that seen in adenocarcinoma.
Conclusions: This large series is from a single institution and includes cases that have been tested using standardised and validated FISH and IHC methodologies. The overall rate of ALK translocation in this series is concordant with previous studies. However the clinical significance of FISH+/IHC- cases needs to be determined before IHC can be introduced as a pre-screening test or as a surrogate for FISH. The ALK translocation in squamoid tumours has not been systematically evaluated, and until its clinical significance is known this data would support ALK testing of all NSCLC cases.

P59

The Spectrum of Mutations in GIST: The Birmingham Experience

Ⓟ OL Cain; B O'Sullivan; F Hughes; C Swift; M Smith; N Deshmukh; P Taniere

Queen Elizabeth Hospital Birmingham, Birmingham, UK

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 sequencingto detectmutations 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 lookfor SDH loss.
Results: Samples were adequate for complete mutation analysis in96% 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 indicate the feasibility of comprehensive mutation testing of a large number ofGISTs in routine clinical practice. SDH loss in wild type GISTs is found in a relativelyhigh number of wild type tumours andrequires dialogue with clinicians to ensure referral of the patient to a geneticist.

P60

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

Ⓟ M Evans; B O'Sullivan; F Hughes; C Swift; T Mullis; R Dessi; M Smith; P Taniere

University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

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).
Conclusions: 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?

Ⓟ L Gilroy; K Walsh; W Wallace; D Harrison; A Oniscu

Royal Infirmary of Edinburgh, Edinburgh, UK

Molecular testing to personalise therapy is an essential part of the investigation of cancer in order to personalise anti-cancer therapy. Availability of sufficient tissue is important. 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 immunohistochemsitry. 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 TKIs and ALK inhibitors.Plasma of course contains cell free DNA.5 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 throughput Next Generation Sequencing platforms make their way into routine diagnostic practice, their superior sensitivity in DNA mutation detection in the presence of any extraneous DNA might generate false positive results and impact on the molecular diagnosis.

P62

The Frequency of EGFR mutations in Lung Adenocarcinoma: The Cardiff Experience

Ⓟ AR Daniels; RL Attanoos; R Butler; H Davies

University Hospital of Wales Cardiff, Cardiff, UK

Lung cancer therapy is tailored by the individual genetic profile of a tumour. The aim of this study was to determine the frequency of one 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 7.5% of cases respectively.
The data suggests that the difference in EGFR expression between NSCC and primary lung adenocarcinoma is not significant, however there appears to be a difference between smaller biopsies and resection specimens which potentially has implications for patient management.

P63

Lymph Node Pathology In a Case of Auto-Immune Lymphoproliferative Syndrome (ALPS)

Ⓟ A Kumar; C Hopper; AD Ramsay

University College Hospital London, London, UK

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 CD5 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.

P64

Chromophobe Renal Carcinomas with no Common Chromosome Loss

Ⓟ M Davie; D Massie; D Stevenson; SR Dundas

Aberdeen Royal Infirmary, Aberdeen, UK

Purpose of Study: Distinguishing between chromophobe renal cell carcinoma and renal oncocytoma is diagnostically important. Chromosome fluorescence in situ hybridisation (FISH) is an emerging diagnostic tool and loss of chromosomes 2, 6, 10 and 17 is reported as a common finding in chromophobe renal cell carcinomas whilst oncocytomas show normal patterning. We investigated whether this pattern of chromosome loss is useful in day-to-day diagnostic practice.
Methods: The morphological diagnoses of a series of renal oncocytomas and chromophobe renal cell carcinomas from our centre were independently reviewed. 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 chromophobe carcinomas and 56 oncocytomas. In the majority of cases the results of chromosome FISH simply confirmed the morphological diagnosis of chromophobe renal cell carcinoma. 6 cases (24%) showed variability in the pattern of chromosome loss. Importantly, 2 cases (8%) with the characteristic morphological and immunophenotypic features (strong and diffusely CK7/ CD117 positive with membranous accentuation) of chromophobe 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 H+E morphology the most robust diagnostic tool in the diagnosis of chromophobe 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 chromophobe carcinomas do not conform to the spectrum of common patterns of chromosome loss.

P65

The Fifth Malignancy in a Patient with Muir Torre Syndrome Associated with MSH2 Microsatellite Instability

Ⓟ VN Iyer; S Di Palma

Royal Surrey County Hospital, Guildford, UK

Sebaceous carcinoma of parotid gland are extremely rare with only 29 cases reported so far. The development of parotid sebaceous carcinoma in association with mutation in the mismatch repair (MMR) gene that causes Muir Torre Syndrome (MTS), a subset of Lynch syndrome, is still unclear. This study describes such a case and reviews the literature to see if an association between parotid sebaceous carcinoma and multiple visceral malignancies as seen in Lynch syndrome has ever been described.
MTS represents a small subset of the Hereditary Non Polyposis Colorectal Carcinoma (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 periocular 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, periampullary, colorectal and multiple cutaneous carcinomas.

P66

Multifocal Intercalated Duct Hyperplasia of the Parotid Gland Coexisting With Salivary Duct Carcinoma and Pleomorphic Adenoma: An Association Not Yet Described

Ⓟ M Ahmed[1]; R Sudderick[2]; S Di Palma[1]

[1]Department of Histopathology, Royal Surrey County Hospital, Guildford, Surrey, UK; [2]Department of Otolaryngology, Royal Surrey County Hospital, Guildford, Surrey, UK

Intercalated duct lesions (IDLs) comprise a group of lesions of the intercalated ducts of the salivary gland ranging from un-encapsulated duct hyperplasia to encapsulated adenoma. The associations of IDLs with salivary gland neoplasms commonly basal cell adenoma, basal cell adenocarcinoma and others. The close proximity of IDLs to those tumours raised the notion that they could represent a potential precursor to neoplasms of the salivary gland.
We present a case of a 44 years female, presented with a mass in the superior part of the right parotid gland. The gland was surgically excised and sent for histopathological assessment. The gross examination showed an irregular multinodular grey white mass located in the superior part of the gland. Histopathological examination revealed an invasive salivary duct carcinoma, with focal component of intra-ductal carcinoma. Interestingly, there was a multifocal intercalated duct hyperplasia, and an adjacent 4 mm focus of pleomorphic adenoma. Those three admixed lesions were located in the superior part of the gland.
The Clinical, histopathological and immunophenotypical features of this case will be described. Interestingly, to the best of our knowledge this is the first case in the literature to describe a combination of salivary duct carcinoma with a hybrid lesion of pleomorphic adenoma and multifocal intercalated duct hyperplasia. This report is shedding the light on the importance of reporting (IDLs) in cases of malignant salivary gland tumours, despite being of ambiguous biological significance; further studies could explore their potential of being a precursor lesion to salivary neoplasia.

P67

Atypical Lipomatous Tumour of Larynx, Closely Simulating Spindle Cell Lipoma: A Case Report

Ⓟ AS Azam; N Momtahan

Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK

Introduction: Atypical lipomatous tumour is defined as neoplasm of mature fat exhibiting at least focal cytological atypia occurring in deep soft tissue, commonly in retroperitoneum. In practice, there is frequent histological overlap between atypical lipomatous tumour and a spindle cell lipoma. In the literature, there are few cases reports of this tumour arising in different locations like salivary glands, oral cavity and gingiva. However, rarely it has been described in the larynx.
Case report: A 58-year-old women presented with difficulty in swallowing. On examination an exophytic tumour was seen involving the supraglottis and piriform fossa bilaterally. Debulking surgery was perfomed and multiple tissue fragments were sent for histological analysis.Histologically, the neoplasm showed features closely resembling spindle cell lipoma, being composed of mature adipose tissue associated with bland spindle cells interspersed within the collagen bundles. No atypical lipoblasts or florette cells were seen. On Immunohistochemistry, the spindle cells stained positive with CD34.
The differential diagnosis included a spindle cell lipoma and atypical lipomatous tumour (well differentiated liposarcoma). Based on the histological features, the former was more favoured. However to further support the diagnosis, FISH analysis was performed for MDM2 amplification. Surprisingly, there was very convincing MDM2 amplification, in keeping with a atypical lipomatous tumour closely simulating a spindle cell lipoma.
Conclusion: Atypical lipomatous tumour is a slow growing, infiltrative, and non-metastasizing neoplasm that is microscopically and diagnostically challenging (2). It rarely arises in larynx and has to be distinguished from a spindle cell lipoma which can closely resemble it morphologically. FISH analysis for MDM2 amplification should be considered in the cases with overlapping features to differentiate atypical lipomatous tumour from a benign spindle cell lipoma.

P68

Diagnostic Yield of Biliary Brushing Cytology: A Single Centre Study

Ⓟ M Wasimi[1]; AS Azam[2]; P Abdullah[2]; S Muzaffar[2]

[1]Royal Shrewsbury Hospital, Shrewsbury, UK; [2]Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK

Introduction: Biliary brushing cytology is a commonly used technique for the diagnosis of extra hepatic biliary and pancreatic malignancy. Despite a high specificity, the sensitivity remains low and variable. British Society of Gastroenterology guidelines recommend cytological analysis of brushing taken from the biliary structure to support diagnosis of malignancy in suspected individuals. We report here a single center experience of diagnostic yield of cytological specimens of biliary brushings.
Objectives: (a) To determine the percentage of biliary brushing cytology cases with positive, negative, false positive and false negative results. (b) To determine the positive and negative predictive value of this test in our centre. (c) To see the correlation between cytological, radiological and clinical findings.
Methodology: This is a retrospective data analysis of all biliary brushing cytology cases reported over three years from Jan 2012 to Jan 2014. The data was obtained from cytology reports and findings were correlated with the radiological diagnosis, outcome from the MDT meetings and subsequent follow up from the clinic letters.
Results: A total of 34 biliary brushing cytology cases were reported between 2012 to 2014. Among them 22 were men and 12 were women. Average age was 69 years (Range 24-92 years). Out of 34, 15 cases (44%) showed presence of malignant cells and all these were true positives with underlying pancreatic and biliary malignancy. Among the remaining 19 cases, 10 cases were true negatives and 9 cases were false negatives. In our cohort, the specificity of biliary brushing cytology was 100% and sensitivity was 63%. The positive predictive value 100% and negative predictive value 53%.
Conclusion: Biliary brushing cytology in conjunction with radiological investigation and serology is a useful technique in patients with suspected pancreato-biliary malignancy. Our results are comparable to studies done in other centres. To be re-audited.

P69

Diagnostic Accuracy of Cytology in Suspected Biliary and Pancreatic Neoplasms

Ⓟ M Evans; P Matthews; S Sah

University Hospital Coventry and Warwickshire NHS Trust, Coventry, UK

Introduction: Bile duct brushing and FNA cytology of pancreatic lesions are increasingly becoming first-line diagnostic tools in the investigation of suspected pancreatobiliary neoplasms.
Objectives: To evaluate the diagnostic efficacy of brushing and FNA cytology and their sensitivity, specificity and predictive values in detecting pancreatobiliary 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

Ⓟ SL Bell[1]; A Ali[2]; L Belkhiri[1]; J McCorriston[1]; R Ferrier[2]; C Nixon[3]; KA Oien[2]; F Duthie[2]

[1]Department of Pathology, Queen Elizabeth University Hospital, Glasgow, UK; [2]Institute of Cancer Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK; [3]Beatson Institute of Cancer Research, Glasgow, UK

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.

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

Ⓟ FM McKay[1]; A Ali[2]; C Orange[3]; J Waller[1]; L Sherry[1]; F Duthie[3]; K Oien[3]; S Bell[4]

[1]OracleBio Limited, Biocity Scotland, Bo'Ness, UK; [2]Beatson Institute of Cancer Research, Glasgow, UK; [3]Institute of Cancer Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK; [4]Department of Pathology, Queen Elizabeth University Hospital, Glasgow, UK

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 HALODIA 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 R^2values 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

A Ali[1];Ⓟ S Bell[2]; A Bilsland[3]; J Slavin[2]; V Lynch[2]; M Elgoweini[2]; M Derakhshan[4]; K Oien[3]; F Duthie[3]

[1]Institute of Basic Medical Sciences, Khyber Medical University, Pakistan; [2]Department of Pathology, Queen Elizabeth University Hospital, Glasgow, UK; [3]Institute of Cancer Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK; [4]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Western Infirmary, Glasgow, UK

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 variablestaining 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 thestrength 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 andp=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.

P73

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

V Primus[1]; A Attygalle[1];Ⓟ JEH Wang[2]

[1]Royal Marsden Hospital NHS Trust, London, UK; [2]St George's University Hospitals NHS Foundation Trust, London, UK

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 marked for HPV infection in skin SCC.