THE UNIVERSITY of EDINBURGH

Pathological Society
Understanding Disease

Edinburgh Pathology 2013

7th Joint Meeting of the British Division of the International Academy of Pathology and the Pathological Society of Great Britain & Ireland

18 – 21 June 2013

Hosted by
The Division of Pathology, University of Edinburgh, Scotland

Venue
Edinburgh International Conference Centre
The Exchange, Edinburgh EH3 8EE

Companion Sessions
Association of Clinical Electron Microscopists
UK Renal Pathology Group

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Programme acknowledgements

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EDINBURGH
INSPIRING CAPITAL

08.00 [Reception]
Registration and Coffee

08.45–18.00 [Ochil 3 – Level 1]
Slide Seminar Case Competition Viewing: ***Inflammatory Skin Pathology***

08.55–09.00 [Fintry – Level 3]
Welcome Address
Prof D Salter, University of Edinburgh

09.00–12.35 [Fintry – Level 3]
Symposium: ***Future of Translational Research and Molecular Pathology***

10.45–11.15 [Lomond Suite – Level 0]
Refreshment Break

12.35–14.00 [Lomond Suite – Level 0]
Lunch
Poster Viewing and Trade Exhibition

14.00–16.30 [Fintry – Level 3]
Symposium: ***Upper GI Pathology***

15.00–15.30 [Lomond Suite – Level 0]
Refreshment Break

14.00–17.00 [Harris – Level 1]
Trainees Symposium: ***The Part 2 Histopathology Exam and New RCPath Curriculum – What They Mean to You***

15.00–15.30 [Lomond Suite – Level 0]
Refreshment Break

14.00–17.00 [Ochil 1 and 2 – Level 1]
Undergraduate Forum
Facilitator – Dr RJ Byers, Manchester

Details to be announced.

17.00–17.50 [Fintry – Level 3]
Pathological Society's 10th Doniach Lecture: ***Simplicity and Complexity – Improving Outcomes in Bowel Cancer***
Prof P Quirke, Leeds

18.30–20.30 [Dynamic Earth]
Welcome Reception
Buses depart at 18.00.

07.45 [Reception]
Registration and Coffee

08.45–18.00 [Ochil 3 – Level 1]
Slide Seminar Case Competition Viewing: ***Inflammatory Skin Pathology***

09.00–12.00 [Fintry – Level 3]
Symposium: ***Gynae-Endometrial Pathology***
Sponsored by Gedeon Richter (UK) Ltd Women's Health Division

09.00–12.00 [Harris 1 and 2 – Level 1]
Renal Pathology Mini-Symposium: ***New Insights into the Pathogenesis of Glomerular Diseases***

08.00–09.00 [Carrick – Level 1]
Trainees Breakfast Session – Meet The Experts: ***Post-Mortem Histology***
Prof SB Lucas, London
Light breakfast will be provided. Slides will be available on the website in advance of the meeting.

09.00–12.00
[Carrick – Level 1] and [Ochil 1 and 2 – Level 1]
Oral Presentations

10.20–10.50 [Lomond Suite – Level 0]
Refreshment Break

11.00–11.20 [Lomond Suite – Level 0]
Refreshment Break

10.30–11.00 [Lomond Suite – Level 0]
Refreshment Break

12.00–13.00 [Fintry – Level 3]
Pathological Society's 31st CL Oakley Lecture: ***Post-Genomic and Post-Transcripitonal Mechanisms in Breast Cancer***
Dr JPC Le Quesne, Cambridge

12.30–14.00 [Lomond Suite – Level 0]
Lunch
Poster Viewing and Trade Exhibition

13.30–17.00 [Fintry – Level 3]
Symposium: ***Pancreatobiliary Pathology***

13.30–17.15 [Harris 1 and 2 – Level 1]
Renal Pathology *— continued*

13.30–16.30
[Carrick – Level 1] and [Ochil 1 and 2 – Level 1]
Oral Presentations

14.50–15.15 [Lomond Suite – Level 0]
Refreshment Break

15.00–15.20 [Lomond Suite – Level 0]
Refreshment Break

15.00–15.30 [Lomond Suite – Level 0]
Refreshment Break

17.30–19.30 [Lomond Suite – Level 0]
Poster Rounds and Drinks Reception

08.00 [Reception]
Registration and Coffee

08.45–18.00 [Ochil 3 – Level 1]
Slide Seminar Case Competition Viewing: *Inflammatory Skin Pathology*

09.00–12.30
[Fintry – Level 3]
Symposium: *Investigative Imaging*

10.30–11.00 [Lomond Suite – Level 0]
Refreshment Break

09.00–12.25
[Carrick – Level 1]
Symposium: *Bone and Soft Tissue*

10.45–11.15 [Lomond Suite – Level 0]
Refreshment Break

09.00–10.30
[Ochil 1 and 2 – Level 1]
Oral Presentations

10.30–11.00 [Lomond Suite – Level 0]
Refreshment Break

09.00–17.00
[Harris – Level 1]
Association of Clinical Electron Microscopists Companion Meeting

See separate programme

12.30–14.00 [Lomond Suite – Level 0]
Lunch
Poster Viewing and Trade Exhibition

13.30–14.30 [Fintry – Level 3]
Pathological Society's Annual Business Meeting

14.45–17.30 [Fintry – Level 3]
Plenary Presentations

15.30–16.00 [Lomond Suite – Level 0]
Refreshment Break

13.00–14.00 [Carrick – Level 1]
Trainees – Meet the Experts: *Medical Renal Pathology*
Prof ISD Roberts, Oxford

17.30–18.30 [Fintry – Level 3]
Public Lecture: *Clearance of Dying Cells in Control of Inflammation.*
Prof Sir John Savill, Edinburgh

19.30 (for 20.00)**–23.30** [The Hub]
Conference Dinner and Ceilidh
Entertainment provided by the 'Jiggers Ceilidh Band' (for more information see: **www.thejiggers.co.uk**)
Shuttle buses will run from 19.00 *(the alternative is a short walk up a steep hill)*.

08.00 [Reception]
Registration and Coffee

08.00–16.00 [Ochil 3 – Level 1]
Slide Seminar Case Competition Viewing: ***Inflammatory Skin Pathology***

08.30–09.30 [Fintry – Level 3]
Slide Seminar Discussion: ***Inflammatory Skin Pathology***
Dr M Mathers, Edinburgh and Dr A Biswas, Edinburgh.

09.30–12.00 [Fintry – Level 3]
Update Lectures in Dermatopathology

10.00–10.30 [Lomond Suite – Level 0]
Refreshment Break

09.00–12.00 [Carrick – Level 1]
Symposium: ***Testicular Pathology***

10.00–10.30 [Lomond Suite – Level 0]
Refreshment Break

12.00–13.00 [Fintry – Level 3]
BDIAP's Kristin Henry Lecture: ***Bowel Cancer Screening: Extraordinary Conundra for Pathology***
Prof NA Shepherd, Cheltenham

13.00–14.00 [Lomond Suite – Level 0]
Lunch
Poster Viewing

14.00–15.00 [Fintry – Level 3]
Update Lectures in Dermatopathology — *continued*

15.00–16.00 [Fintry – Level 3]
Case Presentations in Dermatopathology

Conference Ends

COMPANION MEETINGS

Wednesday 19 June

09.00–16.45 **[Harris – Level 1]**
Renal Pathology Mini-Symposium and EQA including Renal Oral Presentations

Thursday 20 June

09.10–17.00 **[Harris – Level 1]**
Association of Clinical Electron Microscopists *(see separate programme)*

KEYNOTE AND NAMED LECTURES **[Fintry – Level 3]**

Tuesday 18 June

17.00–17.50
Doniach Lecture: *Simplicity and Complexity – Improving Outcomes in Bowel Cancer*
Prof P Quirke, Leeds

Wednesday 19 June

12.00–13.00
CL Oakley Lecture: *Post-Genomic and Post-Transcriptional Mechanisms in Breast Cancer*
Dr JPC Le Quesne, Cambridge

Thursday 20 June

17.30–18.30
Public Lecture: *Clearance of Dying Cells in Control of Inflammation*
Prof Sir John Savill, Edinburgh

Friday 21 June

12.00–13.00
Kristin Henry Lecture: *Bowel Cancer Screening: Extraordinary Conundra for Pathology*
Prof NA Shepherd, Cheltenham

ORAL COMMUNICATIONS

Sessions will be held as follows:

Wednesday 19 June 09.00–12.00 and 13.30–16.30 **[Carrick – Level 1] and [Ochil 1 and 2 – Level 1]**
Thursday 20 June 09.00–10.30 **[Ochil 1 and 2 – Level 1]**

Note to presenters
Speakers are reminded that no communication may exceed the time allocated on the programme without the consent of the meeting, obtained through the Chairman.

PLENARY ORAL SESSION **[Fintry – Level 3]**

The ten highest-ranked submitted oral abstracts will be presented on Thursday 20 June 14.45–17.30.

Prize
A prize for the best presentation, donated by the *Journal of Pathology* will be presented at the Conference Dinner.

POSTERS, VIEWING AND CHAIRMAN'S ROUNDS **[Lomond Suite – Level 0]**

Poster Size
Poster boards will be size 90 cm x 120 cm (portrait). Please ***do not*** exceed these dimensions. Fixings will be provided.

Viewing
Delegates are encouraged to visit the posters during break times and lunchtimes as well as during the official rounds.

Formal Poster Viewing, Chairman's Rounds and Drinks Reception
Wednesday 19 June 17.30–19.30

Poster round chairs will be circulating during these times to the winners of the following prizes:

BDIAP POSTER PRIZES
Awarded for the best 3 posters relevant to diagnostic pathology.

PATH SOC
Pathological Society's Sir Alastair Currie Prize and second and third poster prizes.

Prize Winners
Winners will be announced at the Conference Dinner on 20 June.

Note to presenters
Ideally, posters should be in place by 10.30 hrs on Tuesday 18 June and removed by 16.00 hrs on Friday 21 June.

Presentation
The presenting author (or another contributor) must attend the meeting and present the poster during the allocated poster rounds in order for the abstract to be published in the *Journal of Pathology On-line Supplement* after the meeting.

SLIDE SEMINAR COMPETITION AND SESSIONS

Competition
Inflammatory Skin Pathology

Viewing Virtual slides **[Ochil 3 – Level 1]**
Slides images will be available for viewing on:

Tuesday 18 June	08.45–18.00	
Wednesday 19 June	08.45–18.00	
Thursday 20 June	08.45–18.00	***(Please note the competition closes at 15.30)***
Friday 21 June	08.00–16.00	

Competition
There will be a slide competition using slide images, which will be available during the days/times shown above and will be available on-line in advance of the meeting.

Prize
A case of champagne. The winner will be announced at the Conference Dinner on Thursday 20 June.
At the discretion of the winner, by tradition, this is shared amongst those present at the dinner!

Competition Case Discussion Session **[Fintry – Level 3]**
Friday 21 June 08.30–09.30

SYMPOSIA

Tuesday 18 June

09.00–12.35	*Future of Translational Research and Molecular Pathology* **[Fintry – Level 3]**
14.00–16.30	*Upper Gastrointestinal Pathology* **[Fintry – Level 3]**

Wednesday 19 June

09.00–12.00	*Gynae-Endometrial Pathology* **[Fintry – Level 3]** **Sponsored by Gedeon Richter (UK) Ltd · Women's Health Division**
09.00–12.00	Mini-Symposium: *Renal Pathology – New Insights into the Pathogenesis of Glomerular Diseases* **[Harris – Level 1]**
13.30–17.00	*Pancreatobiliary Pathology* **[Fintry – Level 3]**

Thursday 20 June

09.00–12.30	*Investigative Imaging* **[Fintry – Level 3]**
09.00–12.25	*Bone and Soft Tissue* **[Carrick – Level 1]**

Friday 21 June

09.00–12.00	*Testicular Pathology* **[Carrick – Level 1]**
09.30–12.00	*Update Lectures in Dermatopathology* **[Fintry – Level 3]**

TRAINEES PROGRAMME

Tuesday 18 June

14.00–17.00 Symposium: *The Part 2 Histopathology Exam and New RCPath Curriculum – What they Mean to You* **[Harris – Level 1]**

Wednesday 19 June

08.00–09.00 Breakfast Session: *Meet the Experts – Post-Mortem Histology* **[Carrick – Level 1]**
Light breakfast will be provided.

Thursday 20 June

13.00–14.00 Meet the Experts: *Medical Renal Pathology* **[Carrick – Level 1]**

UNDERGRADATE SESSION

Tuesday 18 June

14.00–17.00 Undergraduate Forum **[Ochil 1 and 2 – Level 1]**

CONTINUING PROFESSIONAL DEVELOPMENT (CPD)

Royal College of Pathologists

This Meeting has been approved by the Royal College of Pathologists for the purpose of Continuing Professional Development. The following credits will be awarded:

	Full Day
Tuesday 18 June	6 credits
Wednesday 19 June	7 credits
Thursday 20 June	6 credits
Friday 21 June	6 credits

Institute of Biomedical Science (IBMS)

The ACEM Meeting has been approved by the Institute of Biomedical Science (IBMS) for the purpose of Continuing Professional Development. The following credits will be awarded:

	Full Day
ACEM Meeting	4 credits

Delegates who are eligible for CPD points should complete the CPD Certificate Request form which will be provided at the meeting.

TRADE EXHIBITION **[Lomond Suite – Level 0]**

Delegates are encouraged to visit the Trade Exhibition and are requested to support the companies represented there.

LATE REGISTRATION FEES FROM MIDNIGHT (00.01 hr) ON TUESDAY 21 MAY 2013			
Delegate Type	**Fee Categories**	**Per Day or Part Day**	**Conference Dinner**
BDIAP or Pathological Society Members	Ordinary Members, Consultant and/or equivalent position	£ 160	£ 55
BDIAP or Pathological Society Concessionary Members	Biomedical Scientists; Honorary or Senior Members; PhD Students; Post-Doctoral Fellows, Technicians and Trainees	£ 50	£ 55
Undergraduate Students ❇		Free	£ 25
Non-Members	Consultant and/or equivalent position	£ 240	£ 55
Non-Members Concessionary ❇	Biomedical Scientists; PhD Students; Post-Doctoral Fellows, Technicians and Trainees	£ 80	£ 55

REGISTRATION

Registration is via: **www.path.org.uk**

REFRESHMENTS

All refreshments, including lunch, are included in the daily registration fee.

❇ CONCESSIONS

Delegates from categories:

Undergraduate Students
Non-Members Concessionary

must provide an identification document as proof of their student or trainee status, including NTNs where applicable. Proof must be by way of a statement from the Head of Department.
Please email to: **julie@pathsoc.org** (see registration website for template wording).

ADVANCE REGISTRATION

Advance registration will close on Tuesday 4 June 2013. Thereafter delegates may only register on-site on arrival at the meeting.

CANCELLATIONS

A cancellation fee of £20 will be deducted from any refund due for cancellations received in writing by Tuesday 4 June 2013. No refunds will be made after Tuesday 4 June 2013.

DELEGATE ENROLMENT *(AT THE MEETING)*

Enrolment at the Delegate Reception Desk will take place from:

Tuesday 18 June	From 08.00
Wednesday 19 June	From 07.45
Thursday 20 June	From 08.00
Friday 21 June	From 08.00

MEETING WEBSITE

www.path.org.uk

ENQUIRIES

Before the Meeting enquiries should be addressed to:

Pathological Society
2 Carlton House Terrace, London, SW1Y 5AF, UK
Tel: +44 (0)20 7976 1260
Fax: +44 (0)20 7930 2981
Email: **admin@pathsoc.org**

or

BDIAP
PO Box 73, Westbury-on-Trym, Bristol BS9 1RY, UK
Tel: +44 (0)117 907 7940
Fax: +44 (0)117 907 7941
E-mail: **bdiap@blueyonder.co.uk**

VENUE LOCATION

Edinburgh International Conference Centre, The Exchange, Edinburgh EH3 8EE

TRAVELLING TO EDINBURGH

For information visit: **www.path.org.uk**

ACCOMMODATION

Discounted hotel and University accommodation has been reserved for delegates visit: **www.path.org.uk**

ORAL PRESENTATIONS AND LECTURES

PRESENTATION CHECKING AND PREVIEW

Please bring your presentation in PowerPoint (PC/Mac) format. **Note:** If there are movie clips or embedded files included in your presentation you must bring the original files as well.

We would ask you to ensure you check in your presentation at least two hours before you are due to speak (where possible). The speaker preview room for checking in your presentation will be located in the Lomond Foyer at the EICC, located on the ground floor. If you make your way to the Conference Registration Desk on arrival, we will direct you to the room.

Staff will be on-hand in the Speaker Preview room to assist. Presenters do not need to bring a laptop as presentations will be loaded onto a main computer. It is recommended that you bring your presentation on a USB Memory Stick.

INTERNET ACCESS

Internet access will be available in **Ochil 3 – Level 1** and wireless access will also be available.

MESSAGES

During the Meeting, messages for delegates may be left at the following telephone number: **+44 (0)7964 024118**. There will also be a message board located beside the Registration Desk.

REFRESHMENTS

All refreshments will be served in the **Lomond Suite – Level 0** unless stated otherwise in the programme.

BADGES

Delegates are requested to wear their badges ***at all times***.

COATS AND BAGS

Secure facilities will be provided for coats and bags.

DISCLAIMER

The British Division of the IAP and Pathological Society of Great Britain & Ireland cannot be held responsible for any injury or loss sustained during the Meeting.

SOCIAL ACTIVITIES

TUESDAY 18 JUNE, 18.30 – 20.30 *(buses depart from EICC at 18.00)*
Welcome Reception at 'Our Dynamic Earth'.
Places are limited – please reserve your free ticket when registering.
See: **www.dynamicearth.co.uk** for more details.

THURSDAY 20 JUNE, 19.30 – 23.30
Conference Dinner and Ceilidh, at 'The Hub'.
Please reserve your ticket when registering. Tickets cost £55 (£25 for Undergraduates).
Entertainment will be provided by the 'Jiggers Ceilidh Band'.
For more information see: **www.thejiggers.co.uk** and **www.thehub-edinburgh.com**.
Shuttle buses will run from 19.00 *(the alternative is a short walk up a steep hill)*.

LOCAL PLACES OF INTEREST

See: **www.edinburgh.org** for more details.

FUTURE MEETINGS

British Division of the IAP

2013
29–30 November
London
Intestinal Pathology

Pathological Society of Great Britain & Ireland

2014
30 August – 3 September
London
Joint Meeting with the European Society of Pathology

JOINT MEETINGS

of the British Division of the IAP and the Pathological Society of Great Britain & Ireland

2015
23–25 June
Dublin
Dublin Pathology 2015

TUESDAY 18 JUNE

08.00 — **Reception**

REGISTRATION and COFFEE

08.45 – 18.00 — **Ochil 3 – Level 1**

SLIDE SEMINAR CASE COMPETITION VIEWING
Inflammatory Skin Pathology
Please note: Competition closes at 15.30 on Thursday 20 June

08.55 – 12.35 — **Fintry – Level 3**

08.55–09.00 **WELCOME ADDRESS**
Speaker: Prof D Salter, University of Edinburgh

SYMPOSIUM
Future of Translational Research and Molecular Pathology
Chair: Dr MJ Arends, University of Cambridge
Dr RJ Byers, University of Manchester

09.00–09.35 **[S1]** ***Getting Personalised Medicine to the People – The Challenges of Delivering the Genomic Revolution on the Ground***
Ⓟ I Walker; Z Backholer; M Jones; S Johnson; E Shaw; A Tuff-Lacey; T Turtiainen; PWM Johnson

Cancer Research UK, London, United Kingdom

Purpose of the study: Molecular analysis of tumours is increasingly being used to identify patients most likely to benefit from novel targeted therapies. The Cancer Research UK Stratified Medicine Programme (SMP) has demonstrated large scale molecular phenotyping of up to 9000 patients, providing data which can be linked with clinical outcomes enabling research and cohort identification of patients.
Methods: Phase 1 of the SMP is a two year feasibility study delivered within the NHS infrastructure in collaboration with researchers, AstraZeneca, Pfizer and the Department of Health. Through 8 clinical hubs and a supporting network of twenty-five hospitals, consented blood and tumour tissue samples were obtained and submitted to one of three 'technology hubs' for mutation testing. The tests are technically validated and completed in clinically relevant timescales. Recruited patients have clinical data collected and linked to the molecular data and stored in a central data repository hosted within the Eastern Cancer Registry Information Centre.
Results: The study opened across the UK in September 2011 and by December 2012, 5237 samples had been sent for testing and 4734 sets of molecular results had been returned to clinical teams. Test requests and reports are exchanged electronically with standardisation of reporting being developed.
Conclusions: By mid 2013, we hope to have developed a scalable model for routine, high quality, prospective molecular characterisation of tumours for NHS cancer patients, with consent for the collection, storage and research use of population-scale genetic and outcomes data. We will report the emerging results from the SMP with implications and potential issues for wider implementation across the UK healthcare system.

09.35–10.10 **[S2]** ***Influence of Molecular Pathology on Ovarian Cancer Treatment Now and in the Future***
Ⓟ Prof C Gourley

University of Edinburgh Cancer Research Centre, Edinburgh, United Kingdom

Background: Recent molecular and clinical studies clearly show that ovarian cancer should be considered as at least 5 separate entities, based on histology and clinical behaviour. This has major implications for studies of targeted therapies and their subsequent incorporation into routine clinical practice.
Summary of discussion points: Although ovarian cancer is molecularly heterogeneous, subdividing into histotypes allows some enrichment for shared molecular pathways and a small number of clinical studies have utilised this strategy. The completion of The Cancer Genome Atlas Project for ovarian cancer has provided a vast wealth of new information concerning high grade serous ovarian cancer. This has already informed some molecularly stratified novel agent studies (e.g those of PARP inhibitors) in ways which translate into clinical benefit. The extent of molecular characterisation of non high grade serous ovarian tumours is much less impressive. Despite this, evidence is accumulating to suggest some of these histotypes (e.g.low grade serous) may be driven by mutational activation more frequently than high grade serous. This has led to the initiation of studies of novel targeted therapies such as MEK inhibitors. The extent to which these agents should be restricted to tumours containing activating mutations will be discussed. As well as novel agents which target the tumour, anti-angiogenic strategies have recently gained prominence with the licensing of bevacizumab in ovarian cancer. Evidence suggesting pro-angiogenic and non-angiogenic subgroups of ovarian cancer (and methods of identifying these) will be discussed. As in many cancers the development of resistance is a crucial factor hampering the success of novel ovarian cancer therapies. New molecular technologies including next generation sequencing and sequencing of cell free DNA in patients' plasma may help to identify arising mechanisms of resistance on a patient by patient basis.

10.10–10.45 **[S3]** ***Molecular Stratification of Cancer***

Ⓟ Dr D Gonzalez de Castro

The Royal Marsden NHS FT, Sutton, United Kingdom

The speed at which molecular biomarker discovery is currently operating will bring answers to many scientific and clinical questions in the next few years that will allow for fine-tuning of molecular tests for the right therapies. There are critical steps on the implementation of new technologies for molecular stratification of patients, such as sample and test quality, IT infrastructure, commissioning and regulatory issues. New trials are being designed enrolling only molecularly-defined patients to increase power of the analysis with less number of patients leading to implementation of new drugs in the clinic in a timely fashion. The CR-UK Stratified Medicines programme in the UK aims to establish a national network for molecular diagnostics of cancer to facilitate early implementation of molecular – guided therapies across the country.

10.45–11.15 **REFRESHMENT BREAK** **[Lomond Suite – Level 0]**

11.15–11.50 **[S4]** ***Molecular Pathology – The UK NEQAS experience***

Ⓟ Dr S Deans

UK NEQAS for Molecular Genetics, Edinburgh, United Kingdom

The UK National External Quality Assurance Service (UK NEQAS) has provided external quality assessment (EQA) for molecular pathology testing since 2008. These assessments are offered as a collaboration between UK NEQAS for Molecular Genetics and UK NEQAS for Immunocytochemistry and In Situ Hybridisation in order to use the expertise in each area of pathology and to reflect the cross-discipline testing which is performed by diagnostic laboratories across the world. The EQA schemes to date cover molecular analysis in non-small cell lung cancer, colorectal cancer, metastatic melanoma and gastrointestinal stromal tumours along with the external assessment for the Cancer Research UK Stratified Medicine Programme. The primary aim of the EQAs is to provide laboratories with an external measure of the standard of their laboratory testing and to offer help and support to those laboratories with problematic issues. For participants introducing new tests into their testing repertoire then EQA can also play an educational role and advise on areas such as methodology, report content and mutation nomenclature. Data gathered can feed into the development of agreed best practice guidelines for the community. The standard of molecular pathology testing in the UK NEQAS schemes was variable with high genotyping errors detected in the initial EQA runs. The content of the reports were inconsistent and often omitted important information to allow the reader to correctly interpret the result. Improvement has been observed in both genotyping and result reporting. Participation in EQA improves the standard of laboratory testing and ultimately patient care but genotyping errors have been detected in every EQA run to date indicating the need for continual external assessment of laboratory services.

11.50–12.35 **[S5]** ***The Pathologist in Drug Development***

Ⓟ Prof C Womack

AstraZeneca, Macclesfield, United Kingdom

Pathologists have an important role to play in pharmaceutical research and clinical trials although very few are employed full-time in industry. Public/industry research collaboration is a necessity in the complex, long, expensive and regulated process that brings new medicines to patients. Pathologists' general and specialist, diagnostic and research knowledge and skills, in basic and molecular pathology applied day-to-day in hospital practice and university laboratories are all invaluable to the drug development process. Science underpins the understanding of disease mechanisms that informs in the first instance, potential drug target selection and validation biomarkers and later other biomarker types e.g. pharmacodynamic and predictive. There is no prescribed model but in-vitro and in-vivo preclinical activity and toxicology are largely overseen by vetinary pathologists. The preclinical to clinical transition is critical and here relevant to pathologists, robust human tissue tissue biomarkers are refined. These inform proof of mechanism and proof of principle criteria to support first in human studies and efficacy clinical trials later in the drug development pipeline. There is continued reliance on histopathology with established technologies (IHC, FISH) in line with current clinical practice, particularly in oncology. However these technologies have limitations and must be applied in a rigourous manner to ensure consistency. In the meantime the challenges of obtaining repeat tissue samples in clinical trials and the introduction of new technology platforms fuel alternative biomarker approaches. To "future-proof", pathologists must be involved in cross platform comparisons and prepared to adopt, embrace and champion new approaches. Finally, drug and companion diagnostic development requires access to tissue and the pathologist has a further less intellectual but no less important role as sample custodian.

▶ 12.35 – 14.00 **Lomond Suite – Level 0**

LUNCH
POSTER VIEWING AND TRADE EXHIBITION

TUESDAY 18 JUNE — *continued*

▶ 14.00 – 16.30 **Fintry – Level 3**

SYMPOSIUM

Upper Gastrotinestinal Pathology

Chair: Dr KE Robertson, Royal Infirmary of Edinburgh
Prof NA Shepherd, Gloucestershire Cellular Pathology Laboratory, Cheltenham

14.00–14.30 **[S6]** ***Making Sense of Grading and Staging of GI and Pancreatic Neuro-Endocrine Tumours***

Ⓟ Prof TJ Stephenson

Sheffield Teaching Hospitals NHSFT, Sheffield, United Kingdom

The European Neuroendocrine Tumour Society (ENETS) staging system has been shown prognostic in NETs in large number of high quality studies. UK National Cancer Data Set 2012 published by RCPath in consultation with all relevant UK professional organisations recommends its use in preference to AJCC-UICC TNM v7 system, although a few well-evidenced "tweaks" have been introduced. The background is that in 2010 AJCC proposed a new TNM v7 system, that e.g. in the case of pETs, is same as UICC TNM for adenocarcinomas. (TNM v7 doesn't apply to high grade pETs). Evidence for this system, despite distinguished authorship, is inferior to ENETS e.g. AJCC-UICC TNM system for pNETs was validated in only one study and this study had weaknesses. AJCC/UICC never presented any data to justify the category boundaries. Specific additional problems are: 10 year prognosis in ENETS stage 1 pNETs 96%, but for AJCC-UICC T1 is 71% due to inclusion of ENETS stage 2s into the AJCC-UICC T1 category. AJCC-UICC system of limited prognostic value for stratification between stages 2 and 3.
The WHO 2010 classification system for NETs does have the merits of separating out grade from stage for the first time. However, it uses AJCC/UICC stage boundaries, to which the above criticisms still apply. It would have been very convenient to adopt for UK if it were not for the lack of evidence to support AJCC-UICC TNM v7, where it falls short of NHS Evidence Accreditation Standards (now mandatory for the National Cancer Data Sets). This system *may* be adopted in the future if evidence accumulates for it. Recommendation of the ENETS "universal" grading system was straight forward, although a recommendation has been made for a 5% rather than the 2% mitotic index cut point between G1 and G2 for pNETs. pT3 definition for pNETs has also been modified, and the Tang 2008 classification of appendicular goblet cell NETs has been embraced, both well-evidenced

14.30–15.00 **[S7]** ***Mesenchymal Neoplasms of the Gastrointestinal Tract – What's New?***

Ⓟ Dr NAS Wong

Bristol Royal Infirmary, Bristol, United Kingdom

While mesenchymal tumours are relatively rare neoplasms of the gastrointestinal tract, they can be disproportionately difficult to diagnose histologically and/or manage clinically. This talk aims to outline recent advances which particularly contribute to the diagnosis and/or management of such neoplasms. Many of these advances relate to gastrointestinal stromal tumour (GIST) and include the recognition of specific subtypes of GISTs, and the refinement of the immunohistochemical diagnosis, the pathological staging and the prognostication of this neoplasm. There has been greater understanding of the molecular pathology of wild type GISTs, and increased interest in the role of adjuvant chemotherapy for GIST. In the 'post-GIST' era, true smooth muscle neoplasms of the gastrointestinal tract are still recognised and some advances have been made in their pathological classification, immunohistochemical markers and prognostication. Finally, several newly described mesenchymal type neoplasms of the gastrointestinal tract will be discussed.

15.00–15.30 **REFRESHMENT BREAK** **[Lomond Suite – Level 0]**

15.30–16.00 **[S8]** ***Getting Genetics into the Clinic – Can We Stage Oesophageal Adenocarcinomas Better?***

Ⓟ Mr CJ Peters

London Deanery, London, United Kingdom

The incidence of oesophageal and junctional adenocarcinoma has increased 6 fold in the last 30 years and 5 year survival remains ~20%. Current staging is limited in its ability to predict survival which has ramifications for treatment choices. In other cancers such as breast there is some evidence molecular signatures can be used to predict outcome and help make management decisions. In oesophageal cancer the field is less advanced but there is a growing body of literature suggesting numerous molecular prognostic markers. This talk shall summarise the current published work on molecular predictors of outcome and propose a way that these tests can be combined with other clinical features to improve patient management and ultimately outcome. It shall also describe the multi centre OCCAMS collaboration which has been created to coordinate the collection of both patient data and tissue to help develop a greater understanding of the molecular biology of oesophageal cancer.

16.00–16.30 **[S9]** ***The Pathologist's Role in the Management of Coeliac Disease***

Ⓟ Prof NA Shepherd

Gloucestershire Cellular Pathology Laboratory, Cheltenham, United Kingdom

Coeliac disease (CD) is common. It accounts for 5% of all cases of iron deficiency anaemia in the UK and occurs in about 1% of the population. Thus duodenal biopsies for a potential/possible diagnosis of coeliac disease are very common: I report at least 500 a year myself! The disease gets commoner as one goes North and West

in Europe. Thus Ireland and Iceland have relatively high rates. It has been suggested that this is due to the evolution and migration of wheat-associated farming in Europe. Although the histological features of CD are not entirely specific, histology remains the gold standard test. Serology for TTG is a useful screening procedure and EMA serology can add specificity but a histological assessment is always required to allow appropriate management. It must be appreciated, however, that a histology report should only indicate "in keeping with untreated coeliac disease" and that the features are not diagnostic. There is increasing evidence that biopsies of D1 are useful, both in children and in adults, and many now regard two large biopsies from D1 and two from D2 as standard for pathological assessment. There is also a role for pathology in the assessment of patients apparently failing to respond to treatment, namely a gluten-free diet. The pathological quandaries of CD are its patchiness, requiring biopsy protocols as above, the wide differential diagnosis associated with intra-epithelial lymphocytosis with a normal villous architecture/lymphocytic duodenosis, on the one hand, and villous atrophy, on the other, and finally the assessment of the complications of CD, especially refractory coeliac disease, collagenous sprue, ulcerative jejunitis and enteropathy-associated T-cell lymphoma. Many of these conditions may require additional investigations, including immunohistochemistry and molecular assessments, to allow a definitive diagnosis. Coeliac disease will keep GI pathologists busy for many years to come!

▶ 14.00 – 17.00 Harris – Level 1

TRAINEES' SYMPOSIUM

The Part 2 Histopathology Exam and New Royal College of Pathologists' Curriculum – What They Mean to You

Chair: Dr A Green, Guys and St Thomas' NHS Foundation Trust
Dr NP West, University of Leeds

14.00–14.15 **[S10]** ***FRCPath – Evolution not Revolution***

Ⓟ Dr KP West

Royal Colege of Pathologists, London, United Kingdom

Fellowship of the Royal College of Pathologists is an internationally recognised qualification. In the 50 years since it was founded the College's examinations have changed substantially. Some of the drivers to change have been scientific and others educational. For example, when FRCPath (now FRCPath) was first introduced immunocytochemistry was not used in diagnostic histopathology and molecular pathology was still years away. The Primary (now Part1) was relatively standardised with all candidates taking the same multiple choice examination and practical. The Final MRCPath (now Part 2) was taken in numerous centres by 2-4 candidates and each group of candidates saw completely different material. From an educational perspective the Part 2 had to change and did. The part 2 examination is now blueprinted against a detailed curriculum. The bulk of the examination is set centrally and candidates attend centres in groups of approximately 20. Future changes will also be determined by developments in technology and training. Molecular pathology as applied to histopathology will assume a greater significance and there are already discussions within the College about training in this field. The Part 1 examination could be computer based and taken in local centres. Virtual slides offer the opportunity for all candidates to see the same material without attending a large examination centre. Specific training would be required before this technology could be introduced. Any centralised examination might then be reduced in duration and concentrate on face to face interactions. This approach, coupled with robust work place based assessments, could radically change the face of the FRCPath. However, such innovations cannot be introduced quickly as they will rely on substantial changes to training and approval by the GMC.

14.15–14.30 **[S11]** ***The 2010 Histopathology Curriculum: Moving Towards Modular Training and Credentialing***

Ⓟ Dr DM Bailey

Royal College of Pathologists, London, United Kingdom

The introduction of the PMETB standards for curricula and assessment systems in 2010 forced all of the Royal Colleges to review their specialty training curricula. In the case of Histopathology, we made some major changes to our curriculum design, to reflect the changing terms of service amongst histopathology departments across the country. Less than half of UK histopathologists currently undertake autopsies, and changes to cervical screening methodology and reconfiguration of pathology services have resulted in increasingly reduced numbers of cervical screening pathologists. These aspects persuaded us to make these two areas optional modules in the new curriculum. Modular credentialling has been previously considered by the General Medical Council and the ongoing Shape of Training Review sponsored by the Academy, COPMED, the GMC, HEE and the departments of health of the devolved nations is likely to recommend significant changes to the way hospital specialists are trained in the UK. This presentation takes a look how training in pathology specialties may change in the next 5 to 10 years, and examines what the changes to the current histopathology curriculum mean for trainees currently in post.

14.30–14.50 **[S12]** ***How to Approach the Cytopathology Component of Part 2 FRCPath***

Ⓟ Dr NH Anderson

Royal Victoria Hospital, Belfast, United Kingdom

The aim of the Cytopathology component of the Part 2 FRCPath examination is to identify candidates with a level of knowledge and interpretive skills appropriate for their stage of training. For those in the old curriculum, there are eight cervical cytology cases and eight diagnostic cytology cases; for those in the new cuuriculum, there are eight diagnostic cytology cases only. The cervical cytology cases are considered to be clear cut examples and require a short description of the morphology together with a diagnosis and appropriate

TUESDAY 18 JUNE — *continued*

management recommendation. The diagnostic cytology cases will be a mix of FNA and exfoliative cytology specimens. Again, most cases used are considered to be clear cut diagnostic samples with only very rare equivocal cases included. If two slides are included for a case, diagnostic material will be present on both slides. The answers should consist of a short description together with a diagnosis and recommendations for further investigation where appropriate. Rather than state MDT discussion advised, candidates are encouraged to make specific suggestions regarding further investigation. "Trick" cases are not included and it is best to approach the cases from this perspective. Negative cases often cause the greatest problems and candidates should familiarise themselves with normal morphology in common specimens.

14.50–15.00 **Discussion**

15.00–15.30 **REFRESHMENT BREAK [Lomond Suite – Level 0]**

15.30–15.50 **[S13]** ***The FRCPath Part 2 Exam: How to Survive and Thrive***

Ⓟ Dr JA Henry

Queen Elizabeth Hospital, Gateshead, United Kingdom

The presentation will outline the structure of the current FRCPath Part 2 examination in histopathology, and the underling philosophy of the exam. The presentation aims to advise candidates on how to approach the examination, and present themselves to their best advantage on the days of the exam.

15.50–16.10 **[S14]** ***How to Fail the Part 2 Exam***

Ⓟ Dr N Kirkham

Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom

In the RCPath competency-based curriculum, the basis of training in the specialty, the competencies necessary to exit stage C of training are defined as the ability to (1) independent cut-up all specimens; (2) report most histopathology and non-cervical cytopathology specimens; (3) appropriately refer for specialist/second opinion and (4) demonstrate appropriate time management and task prioritisation for the stage of training.
The forms of assessment to exit the stage are: (1) workplace-based assessments 18 in total, 12 directed (during stage); (2) multi-source feedback 1 completed (during year 3) and satisfactory; (3) FRCPath Part 2 pass (earliest opportunity at 21 months in stage); (4) educational supervisor's report satisfactory and (5) ARCP satisfactory outcomes (1 or 2). The Part 2 Exam continues to be a major hurdle, with a high failure rate. One route to examination success is to read the question and then attempt to answer it. A major component of the Exam remains the '*Surgicals*' and the approach to these is equally applicable to the other parts of the Exam. For the *Surgicals* the question, stated at the top of the page, is: '*You should provide a written report to the requesting clinician including a description of the lesion, a clear final diagnosis, and a clinical comment putting your diagnosis into its clinical context. You may suggest additional investigations as appropriate*.' To pass this part of the examination not only does the candidate need to make a clear diagnosis but they also need to put their diagnosis into its clinical context. In this presentation there will only be time to show a few examples, but slides from recent Exams, as well as examples of answers, are available at:
www.virtualpathology.leeds.ac.uk/frcpath/
You can fail the exam by evading, waffling and endlessly listing differentials. Success awaits those who read the questions and answer them. Good luck!

16.10–16.30 **[S15]** ***The Autopsy Exam – Then and Now***

Ⓟ Prof SB Lucas

St Thomas' Hospital, London, United Kingdom

Since its inception in the 1960s, the MRCPath diploma in Histopathology has included an autopsy component - until 2012, when autopsy training and the modular exam became optional. The original format of the exam was increasingly unsatisfactory with respect to testing the knowledge and competences of those who passed, and were thus deemed 'fit for independent practice'. In 2005, the exam was augmented in length and depth and, critically, mandated knowledge of all the legislation relevant to autopsy work in the UK. But persistent concern over the variation in standard of the examination across the various centres led to the 2012 version. Here there is a phase 1 of assessment of technical competence in autopsy dissection and drawing conclusions from gross evidence; then a whole-day OPSE which tests candidates in the evaluation of the many scenarios of death. Whether this more complex exam will improve autopsy quality – a main intention – is unclear. The problems in providing consistent quality autopsy training are evident. And the expectations of those who commission most autopsies (coroners and fiscals) are so variable, that events outwith the RCPath may be even more important. The presenter passed this exam in 1978, and was involved in the evolving changes in 2005 and 2012.

16.30–16.50 ***Autopsy Examination, the Centralised OSPE/Phase 2***

Ⓟ Dr H Shawki

Royal Liverpool University Hospital, United Kingdom

16.50–17.00 **Discussion**

▶ 14.00 – 17.00 **Ochil 1 and 2 – Level 1**

UNDERGRADUATE FORUM

The Part 2 Histopathology Exam and New Royal College of Pathologists' Curriculum – What They Mean to You

Chair/Facilitator:
Dr RJ Byers, University of Manchester
and General Secretary-Elect, Pathological Society

▶ 17.00 – 17.50 **Fintry – Level 3**

PATHOLOGICAL SOCIETY OF GREAT BRITAIN & IRELAND'S 10th DONIACH LECTURE

Chair: Prof IO Ellis, University of Nottingham
and President, Pathological Society of Great Britain & Ireland

[S16] ***Simplicity and Complexity – Improving Outcomes in Bowel Cancer***

Ⓟ Prof P Quirke

Leeds University, England, United Kingdom

Pathology has been able to strongly influence and in some cases drive the improvements in bowel cancer outcome. Starting 30 years ago with simple pathology observations it was possible to Identify why local recurrence occurred in rectal cancer and prove the importance of following anatomical planes and excellent surgical technique. Further simple observations led to changes in techniques in low rectal cancer and subsequently colon cancer surgery. Embedding pathology studies in major clinical trials allowed us to define the relative importance of high quality surgery, preoperative radiotherapy (MRC CR07) and chemotherapy (NCRI Foxtrot), the equivalence of laparoscopic and open surgery (MRC Clasicc) and now we are investigating robotic against laparoscopic surgery (EME Rolarr). Comparative studies of pathology and radiology validated Magnetic Resonance Imaging as an important tool in the NCRI Mercury and NCRI Mercury 2 studies and Pathology protocols are now central to international colorectal cancer trials. Educational courses and national audits are changing practice in bowel cancer worldwide. Better quality of surgery, better preoperative therapy and faecal occult blood and flexisigmoidoscopy screening is improving bowel cancer survival towards those of breast cancer. Digital and molecular pathology are developing strongly and these technologies are set to change the face of pathology. New digital viewing platforms, 3 dimensional Pathology and next generation sequencing are creating a new understanding of bowel cancer biology and treatment.

Funding from Yorkshire Cancer Research, Medical Research Council, Cancer Research UK, National Institute of Health Research, Pelican Centre, Experimental Cancer Medicine Centre, CRUK Leeds Cancer Centre, Pathological Society of Great Britain & Ireland.

▶ 18.30 – 20.30 *Buses depart 18.00* **Our Dynamic Earth**

WELCOME RECEPTION

WEDNESDAY 19 JUNE

07.45 — **Reception**

REGISTRATION and COFFEE

08.00 – 09.00 — **Carrick – Level 1**

TRAINEES' BREAKFAST SESSION

Post-Mortem Histology

Chair: Dr G Hutchins, University of Leeds

Speaker: Prof SB Lucas, St Thomas' Hospital, London

Light breakfast will be provided. Slides will be available on the website in advance of the meeting.

08.45 – 18.00 — **Ochil 3 – Level 1**

SLIDE SEMINAR CASE COMPETITION VIEWING

Inflammatory Skin Pathology

Please note: Competition closes at 15.30 on Thursday 20 June

09.00 – 11.50 — **Fintry – Level 3**

SYMPOSIUM

Sponsored by Gedeon Richter (UK) Ltd · Women's Health Division

Gynae-Endometrial Pathology

Chair: Prof M Wells, University of Sheffield
Dr ARW Williams, University of Edinburgh

09.00–09.40 **[S17]** ***Recognition of High Risk Endometrial Hyperplasias and Metaplasias Using Endometrial Intraepithelial Neoplasia Criteria***

Ⓟ Prof GL Mutter

Harvard Medical School, Boston, United States of America

Endometrial hyperplasias are a mixed bag of hormonally altered and precancerous lesions that often demonstrate altered differentiation ("metaplasia"). These can be divided into two broad categories of clinical disease with quite different management implications: premalignant clonal outgrowths which confer an increased risk of future endometrioid endometrial carcinoma through malignant transformation of their component cells (Endometrial Intraepithelial Neoplasia), compared to an endometrial field demonstrating changes secondary to an abnormal hormonal state (true hyperplasias). The clonal character of EIN lesions confers large-scale "topographic" features, which in many cases is informative in distinguishing localized precancers from the diffuse field effects of hormonal change. Although immunostains for biomarkers (PTEN and PAX2), computerized morphometry, and clonal analysis have all been useful tools to develop EIN diagnostic criteria, none are essential for its implementation using standard H&E slides in routine practice. Within the geographic confines of EIN the area of glands exceeds that of stroma, and there is a change in cytology relative to residual background normal glands which may be seen next to, and/or commingled with the lesion. Sometimes the cytologic alteration is one of a changed differentiation state, including alterations in cytoplasmic appearance. Incorporation of these insights into diagnosis, including reduction of the number of diagnostic entities to two (EIN vs benign al hyperplasia) matches the scientific evidence base, improves diagnostic reproducibility, and better stratifies future cancer risk.

09.40–10.20 **[S18]** ***Dilemmas in Reporting of Endometrial Carcinomas***

Ⓟ Prof WG McCluggage

Royal Hospitals, Belfast, United Kingdom

Endometrial carcinoma is the most common malignancy of the female genital tract in developed countries. Accurate pathological reporting is necessary for optimal patient management and prognostication. There are a number of areas of pathological difficulty which are discussed. These include: **[1]** Difficulties in tumour typing (low grade endometrioid versus serous; typing of grade 3 carcinomas; clear cells in endometrial carcinomas). **[2]** Distinction between endometrial and cervical adenocarcinoma (morphology and immunohistochemistry). **[3]** Unusual patterns of myometrial invasion (diffusely infiltrative, MELF). **[4]** Lymphovascular invasion (true, artefactual). **[5]** Assessment of cervical involvement (multiple problems). **[6]** Synchronous endometrial and ovarian adenocarcinomas.

10.20–10.50 **REFRESHMENT BREAK** **[Lomond Suite – Level 0]**

10.50–11.20 **[S19]** ***Spindle Cell Tumours of the Uterus***

Ⓟ Dr A Al-Nafussi

Lothian University Hospitals, Edinburgh, United Kingdom

The great majority of uterine spindle cell lesions are benign leiomyomas. These are easily recognizable by gynaecologists, radiologists and pathologists alike. Some spindle cell tumours however may create great

challenges for pathologists. These include the leiomyomas and the leiomyosarcomas which exhibit no clear smooth muscle differentiation such as the myxoid and epithelioid variants. Another problem is the vascular, cystic and dissecting leiomyomas that can be confused especially radiologically with ovarian cysts or malignancy. Other uterine mesenchymal tumours include the various subtypes of endometrial stromal sarcoma, undifferentiated uterine sarcoma, mixed Mullerian tumours and the other rare non-gynaecological mesenchymal tumour that present as primary uterine tumours. Examples of the latter are solitary fibrous tumour and PNET. The importance of structured histological approach to the diagnosis of these tumours with the aid of the immunohistochemisty is discussed.

11.20–11.50 **[S20]** ***Endometrial Effects of Progesterone Receptor Modulators***

Ⓟ Dr ARW Williams

University of Edinburgh, Edinburgh, United Kingdom

Progesterone receptor modulators (PRM) are members of a class of compounds that interact with the progesterone receptor and may exert agonist, antagonist or mixed effects in target tissues. Development of PRMs has been slow, but we now see several compounds in use or undergoing investigation for a range of clinical conditions, including non-oestrogen containing contraception, treatment of uterine fibroids and endometriosis. The endometrium is an important target for PRMs, and effects are seen in treated patients that have not been encountered with other agents. In 2006, a coordinated assessment of treated endometrial biopsies from a range of clinical trials of PRMs identified a constellation of histological changes termed "PRM-associated endometrial changes" (PAEC). Changes include cystic glandular dilatation, inactive glandular epithelium, non-physiological secretory effects, glandular apoptosis with mitoses, vascular changes and compact non-decidualised stroma. Two recent clinical trials of the PRM ulipristal acetate (UPA) demonstrated that UPA-treated patients showed shrinkage of fibroids, rapid control of abnormal uterine bleeding and an absence of hypo-oestrogenic side effects. In these studies, over 60% of endometrial biopsies showed PAEC after 3 months treatment, returning to baseline appearances 6 months after treatment cessation. UPA is now licensed in Europe for presurgical treatment of uterine fibroids, the license limiting duration of treatment to 3 months. Ongoing studies are addressing the important issues of safety and reversibility of longer term administration. It is likely that diagnostic histopathologists will soon see endometrial biopsies from patients treated with UPA or other PRMs. It is important they are able to recognise the specific histological changes of PAEC, to avoid misdiagnoses of endometrial hyperplasia.

▶ 09.00 – 12.00 — Harris 1 and 2 – Level 1

RENAL PATHOLOGY MINI-SYMPOSIUM

New Insights into the Pathogenesis of Glomerular Diseases

Chair: Dr COC Bellamy, University of Edinburgh
Prof ISD Roberts, Oxford University Hospitals

09.00–09.40 ***Recent Advances in Understanding Idiopathic Membranous Nephropathy***

Ⓟ Prof P Brenchley

University of Manchester, United Kingdom

09.40–10.20 **[S21]** ***Focal Segmental Glomerulosclerosis (FSGS): Pathogenesis***

Ⓟ Prof VD D'Agati

Columbia University Medical Center, New York, NY, United States of America

Once considered a single disease, FSGS is now viewed as a group of clinical-pathologic syndromes sharing a common glomerular lesion and mediated by diverse insults directed to or inherent within the podocyte. FSGS and related disorder, minimal change disease (MCD), are quintessential podocyte diseases or "podocytopathies". In both conditions, podocyte injury leads to effacement of the podocyte foot processes, which is the major structural correlate of nephrotic proteinuria. This change in podocyte shape requires rearrangement of the actin cytoskeleton, a process that is typically reversible with glucocorticoid therapy in MCD, but irreversible and progressive in FSGS, leading to podocyte depletion as the critical pathogenetic event. Proliferation of parietal cells and facultative stem cells lining Bowman capsule may provide reparative cover for the segmentally denuded glomerular tuft. Despite major advances in our understanding of pathogenesis, the majority of cases of FSGS remain idiopathic (known as primary FSGS). Candidate permeability factors include soluble urokinase receptor (suPAR), an acute phase reactant, and cardiotrophin-like cytokine 1, a member of the IL-6 family. Secondary forms include: genetic causes due to mutations in specific podocyte genes (such as nephrin, podocin, alpha-actinin-4, transient receptor potential cation 6, laminin β2, inverted formin 2, phospholipase Cε1, mitochondrial products, and apolipoprotein L1), viral etiologies (HIV and parvovirus B19), drug toxicities (heroin, interferons α, β or γ, lithium, pamidronate, sirolimus, anabolic steroids) and adaptive forms mediated by adaptation to elevated glomerular capillary pressures and flows in situations of reduced renal mass (such as unilateral renal agenesis) or enhanced filtration demand (such as obesity). A working classification has defined 5 histologic variants (not otherwise specified, perihilar, cellular, tip and collapsing), whose pathogenetic correlates will be discussed.

10.20–11.00 **[S22]** ***IgA Nephropathy***

Ⓟ Prof J Feehally

University of Leicester, Leicester, United Kingdom

IgA nephropathy (IgAN) is the commonest glomerular disease in most parts of the world where renal biopsy is widely practiced. Defined by the dominant mesangial deposition of IgA, IgAN is remarkably heterogeneous. There are wide variations in clinical presentation, pathological features, natural history, and risk of transplant

recurrence. In different racial groups there are substantial variations in prevalence and clinical features. A number of immune abnormalities have been identified in IgAN, including altered glycosylation of IgA1 and variations in mucosal immune response. Genetic analyses have not yet been highly informative. There is still no definite evidence that the entity we now call IgAN is a single disease with a single aetiology and pathogenesis, nor evidence that it is the same disease in all parts of the world. Risk of progression can be predicted to some extent by the evolution of clinical features, and to some extent by pathological features, as best defined in the recent Oxford classification. However there is still no consensus on an optimal clinicopathological score for the prediction of individual prognosis. No treatment has been developed which interrupts glomerular deposition of IgA. Treatments are aimed at more generic aspects of glomerular inflammation and progression. These include use of antihypertensive and antiproteinuric therapy, and also corticosteroids and other immunosuppressive therapies which are only required in a minority of patients. The evidence on which treatment choices can be based is limited, and apparent variations in response to therapy in different racial groups are a further confounder in making appropriate therapeutic choices.

11.00–11.20 **REFRESHMENT BREAK [Lomond Suite – Level 0]**

11.20–12.00 **[S23]** ***Antibody-Mediated Rejection: Critical Appraisal of Diagnostic Criteria***

Ⓟ Dr COC Bellamy

University of Edinburgh, Dept. of Pathology, Edinburgh, United Kingdom

Technical developments are enabling more specific and sensitive detection of anti-donor antibodies in serum. However, the clinical relevance to both risk assessment for and the diagnosis of antibody-mediated rejection (AbMR) is not always clear, while other anti-donor antibodies cannot yet be routinely sought. Hence, direct histologic and immunohistologic appraisal of allograft biopsies for tissue injury and reaction remains central to the recognition of AbMR in its various guises. Nevertheless, the histological criteria are themselves in evolution as we appreciate better the frailty and foibles of some assessments (C4d), the incomplete specificity of others (transplant glomerulopathy, thrombotic microangiopathy) and the sensitivity but debatable reproducibility and specificity of still others (microcirculation inflammation, ultrastructural changes). These and other developments, such as indications that arteritis without tubulitis and arterial intimal neofibrosis can be manifestations within the spectrum of antibody-mediated vascular injury have all come within a relatively short interval and renal transplant pathologists find themselves on shifting sands, in no danger of succumbing to monotony. Some of these paradigm shifts have been prompted by expression array data on biopsy portions, others by improved serology or clinical correlation. Indeed, developing an iteration between serology, histology, immunohistology and expression analysis promises to provide stepping stones to more accurate diagnosis of AbMR as each modality reveals findings that allow the others to hone their performance.

▶ 09.00 – 12.00 Carrick – Level 1

ORAL COMMUNICATIONS

Categories: ***Gastrointestinal; Hepatobiliary/Pancreas***

Chair: Prof RFT McMahon, University of Manchester
Dr D Worrall, Western General Hospital, Edinburgh

09.00–09.15 **[O1]** ***Improved Tissue Sections for Medical Liver Biopsies by Changing to 16g Biopsy Needles***

Ⓟ T Palmer[1]; I Georgiades[2]; A Wright[3]; D Treanor[4]; J Wyatt[1]

[1]St James University Hospital, Leeds, United Kingdom; [2]Bradford Royal Infirmary, Leeds, United Kingdom; [3]University of Leeds, Leeds, United Kingdom; [4]University of Leeds and St James University Hospital, Leeds, United Kingdom

Medical liver biopsy(MLB) is used to investigate diagnosis and stage of liver disease when not clear from non-invasive tests. Most biopsies are taken in radiology departments. A recent audit of UK liver biopsies[1] showed 70% of 2262 MLB used 18g and 13% 16g needles[1]. RCPath Tissue Pathways recommends >6 portal tracts (PT) for diagnosis, with >10 required for staging. The count of PTs varies with area of tissue, and can be increased by using wider gauge needles or multiple passes. Our laboratory processes liver biopsies from 2 hospitals, hospital A 2 passes of 18g needle, hospital B 1 pass of 16g needle.

Aim: To compare section quality and PT number by biopsy practice as evidence base for liver Tissue Pathways.

Method: First 50 MLB in 2011 identified. Number of passes recorded. Complete PT counted from slides (IG). Length, number of fragments, area and max width measured by Aperio image analysis (JW).

Results: Cases excluded if not 18g hospA (1 case) or 16g hospB (9 cases). 32/49 (65%) hospA and 1/41 (2%) hospB had 2 passes.Data analysed per case and per pass. Significant improvements with 16g included: less fragmentation (75% 18g v 29% 16g, p<0.001); wider (Max width 0.74+/-0.07mm v 1.03 +/-0.1mm p<0.001; average width 0.53mm v 0.88mm); larger (area per pass 7.89mm^2 v 11.36mm^2) The median (range) complete portal tracts per case was 6 (1-15) for 18g and 7 (3-14) for 16g (p=NS). A single pass of the needle achieved >6PTs in 18% 18g and 71% 16g p<0.001.; taking 2 passses with 18g resulted in >6 PTs in 75% cases. Only 5/49 18g and 7/41 16g cases had >10PTs.

Conclusion: 16g needles generated significantly improved tissue sections for MLB, equivalent to taking 2 passes with an 18g needle. The RCR audit demonstrated no increase risk with 16g needles. This study supports recommending 16g needles as standard for MLB diagnosis; 2 passes would be needed for reproducible staging.

1 Radiology 2012;265(3);819-831

09.15–09.30 **[O2]** ***DNA Polymerase Beta Protein Expression May Predict Response to Irinotecan in the MRC Focus Trial***

Ⓟ SD Richman; JH Barrett; GJ Hemmings; MT Seymour; P Quirke

Leeds Institute of Molecular Medicine, Leeds, United Kingdom

Prediction of response to the non-targeted agents Oxaliplatin and Irinotecan is important to minimise the use of ineffective drugs. We have investigated 6 key proteins within their metabolic pathways to determine whether they will predict response. Tissue microarrays were constructed from the MRC FOCUS trial (n=908). Protein expression was determined by immunohistochemistry for key transporter proteins (ABCB1 and ABCC2), base excision repair proteins (XRCC1 and DNA Polymerase Beta), copper efflux transporter (ATP7Beta) and Glutathione S-transferase i (GSTPi). Expression was correlated to progression free survival (PFS) and overall survival (OS), using proportional hazards survival analysis, stratified by treatment. Predictive analysis: patients on irinotecan with high compared with low expression of DNA Polymerase Beta, showed weak evidence of worse PFS (HR=1.42, p=0.045 (95% CI 1.01-2.00), p-value for marker-treatment interaction 0.089) and also worse OS (HR= 1.38, p=0.086 (95% CI 0.96-1.98). Higher levels of the other 5 biomarkers were not predictive for either PFS or OS. Immunohistochemical assessment of 6 drug metabolic pathway proteins identified that DNA Polymerase Beta predicted a poorer PFS when treated with irinotecan. The size of this effect is small and there is no clear evidence for marker-treatment interaction. Taken with our experience of IHC of topoisomerase 1 and thymidylate synthase with 5FU therapy, a single protein IHC approach appears inadequate to predict chemotherapy response. This is probably due to the complex network of pathways involved in the metabolism of non-targeted chemotherapeutic agents.

09.30–09.45 **[O3]** ***pT1 cancers in the Bowel Cancer Screening Programme: The London Experience***

Ⓟ M Mitchison[1]; V Sheshappanavar[2]; A Giles[3]; WH Chong[4]; P Cohen[5]; L Panchal[6]; R Owen[2]; H Shaikh[7]; E Wilson[8]; M Rodriguez-Justo[1]

[1]University College London, London, United Kingdom; [2]Barts Healthcare Trust, London, United Kingdom; [3]Lewisham University Hospital, London, United Kingdom; [4]St George's Healthcare Trust, London, United Kingdom; [5]Imperial College Healthcare NHS Trust, London, United Kingdom; [6]Northwick Park and St Mark's NHS Trust, London, United Kingdom; [7]King's College Hospital, London, United Kingdom; [8]Queen's Hospital, Romford, United Kingdom

Background: Studies evaluating recurrence of pT1 cancers have identified histological factors with prognostic significance which might impact the management of these lesions, e.g. incomplete resection, high tumour grade, lymphovascular invasion (LVI) and tumour budding. However it is well known the poor reproducibility of these features and the lack of inter- and intraobserver agreement. This audit includes all pT1 colorectal cancers diagnosed in the London SHA under the bowel cancer screening programme (BCSP).
Results: 183 pT1 cancers were diagnosed (114 M: 69 F), with an average size of 15.31 mm. 86% pT1 cancers were found in the sigmoid or rectum. Only 16 (8.7%) were reported as poorly differentiated. 60 (32.8%) polyps showed budding; but in 82 polyps this parameter was not recorded. The Haggitt/ Kikuchi levels were sm1=23, sm2=22, sm3=5; Haggit1-3=68 and Haggit 4=1 but this parameter was not recorded in 64 (34.9%) of the cases (piecemeal, poor orientation...). Out of 82 R1 (adenocarcinoma <1mm from margin) / Rx (not assessable) with subsequent surgical resection only 15 (18.2%) showed residual carcinoma. Seven surgical cases (7.9%) had nodal involvement, pN1 (6/7) and pN2 (1/7). Two cases had metastatic disease, none of them associated with known risk factors.
Conclusion: Less than 20% of cases with incomplete / not assessable resection at polypectomy had residual neoplasia in the bowel following resection. Only 7.9% of cases with histological risk factors had lymph node involvement. Review of guidelines and careful characterisation of risk factors in pT1 cancers is essential to avoid over treating patients, taking into account the surgical complication [30 day post-operative mortality rate following colorectal surgery 1.1% in the screening population and 2.8% in the same age group of non-screening population].

09.45–10.00 **[O4]** ***The Expression of Retinoic Acid Metabolising Enzymes in Colorectal Cancer***

Ⓟ GT Brown[1]; B Cash[2]; A Alnabulsi[2]; GI Murray[1]

[1]University of Aberdeen, Aberdeen, United Kingdom; [2]Vertebrate Antibodies, Aberdeen, United Kingdom

Colorectal cancer is the third most common cancer in the UK with over 50% of patients presenting at an advanced stage where metastasis to lymph nodes and beyond has occurred. Retinoic acid is a metabolite of vitamin A and is essential for normal cell growth. Previous research has indicated that aberrant retinoic acid metabolism is implicated in tumourigenesis. This study has profiled the expression of three retinoic acid metabolising enzymes in normal colonic mucosa and colorectal cancer tissue. A tissue microarray (TMA) containing duplicate cores of Dukes A, B and C colorectal cancers (n=650) and normal colonic mucosa (n=50) was created from blocks of formalin fixed, wax embedded colorectal cancer resections. Immunohistochemistry was performed on the TMA using monoclonal antibodies which we have developed to the retinoic acid metabolising enzymes CYP26A1, CYP26B1 and CYP26C1. Immunohistochemistry was assessed by light microscopy followed by a semi-quantitative scoring to determine expression. The monoclonal antibodies to each CYP26 isoform were effective on formalin fixed wax embedded tissue sections and in colorectal cancers for both CYP26A1 and CYP26B1 were localised to the cytoplasm tumour cells. Moderate or strong expression of CYP26A1 was observed in 32.5% of cancers compared to 10% in normal tissue ($p<0.01$). CYP26B1 was moderately or strongly expressed in 25.2% of tumour specimens but was not expressed at these levels at all in normal tissue ($p<0.01$). CYP26C1 was not expressed in either colorectal cancer or normal colonic mucosa. In this study monoclonal antibodies to individual retinoic acid metabolising enzymes have been developed that are effective on formalin fixed wax embedded tissue and shown that the retinoic acid metabolising enzymes CYP26A1 and CYP26B1 are significantly overexpressed in colorectal cancer.

WEDNESDAY 19 JUNE — *continued*

10.00–10.15 **[O5]** ***Large Scale Mutation Detection in Normal Mucosa and Early Lesions of Colorectal Cancer***

Ⓟ KM Sutton; L Stead; P Chambers; P Quirke

Leeds Institute of Molecular Medicine, Leeds, United Kingdom

Introduction: The application of next generation sequencing (NGS) with targeted resequencing allows for the detection of mutations at a minimum level of 1% in multiple targets in multiple samples. We have previously identified KRAS mutations in cancer-associated normal mucosa and now have used the fluidigm access-array system to investigate the mutational profiles of a number of genes in normal mucosa and tumour at different stages in development.
Methods: A panel of 10 commonly mutated CRC genes was designed for use with the fluidigm access array system to sequence 157 amplicons in 240 patient samples. These consisted of colorectal mucosa that was cancer-associated normal, adenoma-associated normal plus the matched tumour samples alongside normal mucosa controls from healthy patients.
Results: Mutations were found in all 10 genes in carcinoma and adenoma. The associated normal mucosa also had mutations but at different locations within the genes and at a lower allele frequency. Mutations were also found at low level frequencies in mucosa from healthy patients.
Discussion: The access-array system has allowed us to interrogate 37,680 mutational sites in 240 samples in a single NGS run whilst maintaining sensitivity. This has allowed us to identify multiple clonal populations within the normal mucosa.

10.15–10.30 **[O6]** ***Can We Predict Response to Short-Course Radiotherapy in Rectal Cancer Using Biomarkers?***

Ⓟ JD Nicholls[1]; E Tinkler-Hundal[1]; GJ Hemmings[1]; D Sebag-Montefiore[2]; P Quirke[1]; NP West[1]

[1]University of Leeds, Leeds, United Kingdom; [2]Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom

Pre-operative short-course radiotherapy (SCRT) in high risk rectal cancer reduces the risk of disease recurrence, however, there is no effective method at present for predicting response. We have previously shown that high baseline tumour cell density (TCD) and high expression of protein 53 (p53) predicted a greater response to SCRT. We aimed to further quantify the value of these biomarkers and investigate the optimum cut-offs for predicting response. Seventy one cases of rectal adenocarcinoma treated with SCRT were investigated. TCD and immunohistochemistry for p53, geminin and Ki67 expression were performed on the pre-treatment biopsy (baseline) and post-treatment resection specimen for each case. The response to SCRT was determined by the change in TCD from the biopsy to the resection specimen. High baseline TCD predicted a better response with the lowest quartile having a significantly poorer response when compared to the other quartiles (12% vs. 72%, p=0.018). High expression of p53 predicted a better response but this did not significantly differ according to the percentage of cells staining. The median expression of geminin and Ki67 within the tumour was 23% and 35% respectively with a positive correlation between these two markers (R=0.433, p<0.0001). There was a poorer response with lower geminin expression when dichotomised by the lowest quartile, although this did not achieve statistical significance (p=0.082). Ki67 expression did not significantly predict response when using either the median (p=1.000) or quartiles (p=0.756). When combined, high expression of p53 and geminin (dichotomised by the median) predicted a significantly greater response (81% vs. 48%, p=0.012). High baseline TCD and high expression of p53 (+/- high geminin expression) predicted a significantly greater response to SCRT in rectal cancer. Further large scale confirmatory studies are now urgently required before such biomarkers can influence selection in routine clinical practice.

10.30–11.00 **REFRESHMENT BREAK** **[Lomond Suite – Level 0]**

11.00–11.15 **[O7]** ***Comparison of the Histogenesis of Regenerative Nodules in Patients with Cirrhosis of Different Aetiologies***

JP Gabriel[1]; M Komuta[2]; T Roskams[2]; NA Wright[1]; SA McDonald[1];Ⓟ MR Alison[1]

[1]Barts Cancer Institute, London, United Kingdom; [2]University Hospitals Leuven, Leuven, Belgium

Liver cirrhosis is characterised by regenerative nodules of hepatocyte parenchyma surrounded by fibrous septae. The conventional wisdom has been that these nodules are created when groups of hepatocytes are entrapped between these bands of extracellular matrix. We have recently shown that such nodules may be clonally derived from cholangiocyte-derived hepatic progenitor cells, providing a new paradigm for nodule formation. We now extend our studies to cirrhotic nodules in human liver disease with different aetiologies. Using mitochondrial DNA (mtDNA) mutations as markers of clonal expansion we investigated the clonal origins of regenerative nodules in cirrhosis of different aetiology. Mutated cells were identified phenotypically by deficiency in the predominantly mtDNA encoded cytochrome c oxidase (CCO) enzyme by histochemical and immunohistochemical methods. Hepatocytes were laser-capture microdissected from frozen sections of human liver containing CCO-deficient nodules from age-matched non-alcoholic steatotic hepatitis (NASH) and alcohol liver disease (ALD) patients with cirrhosis. Mutations were identified by polymerase chain reaction sequencing of the entire mtDNA genome. Regenerative nodules analysed from both aetiologies were clonal for mtDNA mutations suggesting a stem cell origin in both conditions. We further demonstrate that adjacent regenerative nodules can have identical mtDNA mutations, implying a single ductular reaction can form multiple regenerative nodules during the histogenesis of cirrhosis. These data suggest a unifying hypothesis for the formation of regenerative nodules in human cirrhosis, namely their creation from the clonal amplification of liver stem cells.

11.15–11.30 **[O8]** ***Transplantation for ALD: Lessons From the Explant***

Ⓟ JG Brain[1]; S Masson[2]; AD Burt[3]

[1]Newcastle University, Newcastle upon Tyne, United Kingdom; [2]Freeman Hospital, Newcastle upon Tyne, United Kingdom; [3]University of Adelaide, Adelaide, United Kingdom

A retrospective study of Explants performed for alcohol related liver disease in our centre was performed. A total of 84 explants were scored blinded by two pathologists using a predetermined scoring pro forma relevant clinical information was then revealed. 4 patients had mixed alcohol and hepatitis C whereas the remainder had only alcohol related liver disease. One patient was found to have pre-septal cirrhosis; all other patients had either mixed or macronodular cirrhosis with a significant number having evidence of re-modelling. A total of 9 (10.7%) patients had evidence of Alpha-1 anti-trypsin deficiency, of these only 4 had abnormally low levels of Alpha-1 anti-trypsin, though the remaining 5 had levels that were in the low end of normal range. 39 (46.4%) patients had parenchymal siderosis with 19 (48.7%) having grade 3-4. Consistent with a significant period of abstinence, a total of 67 (79.8%) patients had induced cell change, interestingly 47 (56%) of patients had the recently described "abstinent cell" phenotype. While 46 (54.8%) of patients had Mallory-denk bodies, 22 (22.6%) patients had both abstinent cells and Mallory-denk bodies. 45 (53.6%) of patients had ballooning and 31 (36.9%) patients had steatosis. In terms of pre-malignant and malignant change; 14 (16.7%) had at least one HCC, 15 (17.9%) had dysplastic nodules, 20 (23.8%) had small cell change and 50 (59.5%) large cell change. As described previously phlebosclerosis and parenchymal extinction were universal findings. These findings demonstrate that despite a period of abstinence of at least 6 months, over half of patients had residual Mallory-denk bodies and ballooning, while none had any evidence of acute alcoholic hepatitis. 56% of patients had the recently described abstinent cell phenotype. These findings indicate that presence of Mallory bodies should not be used as evidence of continued alcohol consumption, the presence of induced or abstinent cells correlates more strongly with abstinence

11.30–11.45 **[O9]** ***Systematic Review and Meta-Analysis of Immunohistochemical Diagnostic Markers for Pancreatic Ductal Adenocarcinoma***

Ⓟ D Ali

University of Glasgow, Glasgow, United Kingdom

Purpose of the study: Pancreatic ductal adenocarcinoma (PDAC) has an overall 5 year survival of only 2%. Diagnosis involves cross sectional imaging followed by endoscopy with cytology and is important for patient management. Cytology involves the distinction of PDAC from non-neoplastic pancreas, which can be difficult, especially in chronic pancreatitis. Immunohistochemical (IHC) biomarkers could help but none are yet routinely used. This study provides a systematic review and meta-analysis on diagnostic IHC biomarkers for PDAC.
Methods: The literature was searched using EMBASE and MEDLINE databases from inception to March 2012. We sought publications on IHC markers differentially expressed between human PDAC and non-neoplastic pancreas.We catalogued study characteristics including specimen type, biomarkers assessed and staining results. In the meta-analysis, for each biomarker, coupled forest plots, bivariate summary estimates and combined summary receiver operating characteristic curves were generated, in turn, then compared and ranked according to pooled sensitivity/specificity.
Summary of results: 2089 papers were initially identified. 57 studies reporting 32 biomarkers were selected for systematic review. From these, 45 studies reporting 16 biomarkers progressed to meta-analysis. Meta-analysis of IHC biomarkers assessed in resection specimens showed 11 differentiating PDAC from non-neoplastic pancreas. The highest ranked biomarkers according to pooled sensitivity/specificity values were: S100P (100% sensitivity/100% specificity); maspin (92%/97%); KOC (85%/98%); and MUC4 (82%/93%).Meta-analysis of cytology specimens showed seven biomarkers. The highest ranked were: KOC (85%/100%); SMAD4 (80%/100%); S100P (91%/91%); and mesothelin (64%/92%).
Conclusions: The highest ranking IHC markers for PDAC were KOC and S100P, followed by maspin, mesothelin and MUC4. These markers may be appropriate for further clinical validadation and potentially routine use in difficult cases.

11.45–12.00 **[O10]** ***Novel Strategy to Diagnose and Grade Hepatocellular Carcinoma***

Ⓟ RM Mehboob

King Edward Medical University, Lahore, Pakistan

Hepatocellular carcinoma (HCC) is among the most common malignancies worldwide, particularly in South and South East Asia. Unfortunately due to lack of appropriate facilities and awareness only limited information is available about its early diagnosis. Aim of the present study was to determine the efficacy of p53 by immunohistochemistry and Argyrophilicnucleolar organizer regions (AgNORs) in diagnosis of HCC and cirrhosis of liver. A total of 100 liver biopsies were studied, it included 20 cases of HCC, 60 cases of cirrhosis of the liver and 20 cases of normal liver from autopsy specimens as a control. Out of 20 cases of HCC, 15 were positive for p53 stain and 5 were negative. None of the 60 cases of cirrhosis or 20 with normal histology revealed p53expression. A statistically significant ($p < 0.001$) difference was observed between mean AgNOR counts of normal (1.57 +/- 0.13), cirrhotic (4.70 +/- 0.66) and HCC tissues (14.96 +/- 1.18). In contrast the mean AgNOR count of biopsies with alcoholic cirrhosis (1.57 +/- 1.62) was significantly less ($p < 0.001$) than post-hepatitic cirrhosis and was similar to that of normal liver tissue. AgNORs differentiates post-hepatitic and alcoholic cirrhosis.HCV and HBV were found to be the main causative agents in HCC and Cirrhosis of liver. Mean age of HCC patients was slightly higher than liver cirrhosis patients.It is concluded that p53 and AgNORs can act as a good adjuvant to histology in diagnosing liver diseases. It helps in differentiation from well differentiated to moderately and to poorly differentiated HCC.

WEDNESDAY 19 JUNE — *continued*

▶ 09.00 – 12.00 **Ochil 1 and 2 – Level 1**

ORAL COMMUNICATIONS
Categories: *Breast*
Chair: Prof AM Hanby, University of Leeds
Dr J Thomas, Western General Hospital, Edinburgh

09.00–09.15 **[O11] *Laminin Protein Expression is an Independent Predictor of Poorer Survival in Indigenous Black Breast Cancer***

Ⓟ AOJ Agboola[1]; AA Musa[1]; BS Salami[1]; AAF Banjo[1]; C Nolan[2]; EA Rakha[2]; IO Ellis[2]; AR Green[2]

[1]Olabisi Onabanjo University, Sagamu, Nigeria; [2]Division of Pathology, School of Molecular Medical Sciences, Nottingham University Hospital and University of Nottingham, Nottingham, United Kingdom

Immunogenic activities of Laminin have been demonstrated to be essential for BRCA1-deficient breast carcinogenesis, suggesting that it may be a useful biomarker and a potential therapeutic target. In this study, protein expression of Laminin was investigated immunohistochemically in TMA preparations of 255 of Nigerian women and results were correlated with clinicopathological features, clinical outcome and the expression of 17 relevant biomarkers to demonstrate its biological and clinical significance in black women.
Results: Laminin expression showed an inverse association with hormone receptors (ER and PgR), E-cadherin, DNA-damage-repair (DDR) proteins (BRCA-1 and BARD-1), p27 and positive correlation with BRCA1 inhibitor ID4, other DDR proteins UBC9, PIAS, PARP-1, MTA-1, p53, the proliferation (Ki67 and PI3KCA) and basal-associated markers (EGFR, CK5/6 and P-cadherin) and with the triple-negative and basal-like phenotypes. Interestingly, Laminin expression was a predictor of poorer outcome independent of tumour size, histological grade and lymph node involvement.
Conclusion: Our observations indicate that laminin expression may play a significant role in breast cancer and its expression is related to the basal-like triple-negative and BRCA-1 deficient breast cancer phenotypes and is associated with prognosis in black BC. Laminin may have potential application in sub classification breast cancer in black women.

09.15–09.30 **[O12] *Oestrogen Receptor Status of Screen-Detected Invasive Breast Cancer in Scottish and UK Regions 2008–11***

Ⓟ A Al-Mohtaseb[1]; JS Thomas[2]

[1]Royal Infirmary, Edinburgh, United Kingdom; [2]Western General Hospital, Edinburgh, United Kingdom

Screen-detected invasive breast cancer is oestrogen receptor (ER) positive in about 90% of cases against 80% for symptomatic disease. Consistency of testing is important for patient management and participation in the national quality assurance scheme (NEQAS) is mandatory. The purpose of the study was to examine region-to-region and year-on-year variation in ER reporting in the UK. We reviewed ER status in the six Scottish screening centres for the years 2008-2011 using public domain data published by the Information and Statistics Division of National Services, Scotland. We compared our results with national UK data published by the British Association of Surgical Oncology (BASO) for the same period - a total of 37,000 UK cases of newly diagnosed screen-detected invasive breast cancer. Each UK region reports approximately 1000 cases of newly diagnosed screen-detected invasive breast cancer per annum. There is a region-to-region and year-to-year variation of ER positivity of up to 4% (88-92%). Data from four of the six Scottish screening centres showed a comparable rise/fall/rise of ER positivity (93%; 86% and 95%) over this period. Three of these four units used the same antibody and the fluctuation did not correlate with reported tumour grade. Examination of Allred scores of one unit showed a year-on-year shift of scores that would explain the variation. ER positivity in screen-detected breast cancer varies within and among UK regions and year-on-year of the order of +/- 2%. Regions with smaller case-loads are more sensitive to fluctuations as evidenced by the individual Scottish centres and Northern Ireland. It is possible that some of the variation seen is due to batch-to-batch variation of antibodies as suggested by the shift of Allred scores seen in one Scottish centre.

09.30–09.45 **[O13] *Male Breast Cancer: Study of a Large Series From a Single Institution***

Ⓟ N Raut[1]; IO Ellis[2]; EA Rakha[2]

[1]University of Nottingham, Nottingham, United Kingdom; [2]Nottingham City Hospital, Nottingham, United Kingdom

Purpose of the study: Data on male breast cancer (BC) are derived from either small series or population-based studies. This study aimed to audit male BC in a large single-institution over a 25-year period.
Methods: Pathology databases at Nottingham City Hospital, UK were queried for patients presenting with BC. Clinicopathological and outcome information was retrieved. Features of male BC were compared to those of female BC.
Summary of results: Of 13,000 BC patients, 59 (0.4%) were male. Of male breast diagnostic biopsies, 9% were invasive carcinoma. Patient age ranged from 37-to-89 years (median 58). Tumours ranged in size from 3-to-47mm (mean 20mm). Compared to female BC, all males underwent mastectomy in one operation-setting but with less frequent axillary surgery. Although a higher percentage of male BC were associated with positive lymph-nodes compared to female BC (48% in male BC Vs 38% in female BC), the number of positive nodes in male BC was usually low (one node+ in 57%). Male BC shows the oestrogen receptor-positive/HER2-negative phenotype with no triple-negative tumours identified. Outcome data showed low-incidence of local recurrence however male BC was associated with shorter 5-year and 10-year survival compared to female BC.
Conclusions: Male BC is likely to be presented at older age, treated by mastectomy and typically shows the hormone receptor-positive-HER2-negative-phenotype. Although axillary surgery was less common, node positivity was more frequent than female BC, which may explain the poorer outcome of male BC patients.

09.45–10.00 **[O14]** ***Expression of the Protein Inhibitor of Activated STAT Family Members (PIAS1 and PIASγ) and Their Significance in Human Breast Cancer***

Ⓟ AT Alshareeda; AR Green; C Nolan; IO Ellis; EA Rakha

University of Nottingham, Nottingham, United Kingdom

Introduction: PIAS1 and PIASγ are members of the PIAS family that interact with and modulate the activities of a variety of cellular function including DNA damage repair (DDR). Previous studies of these proteins in normal tissue have reported diverse functions. In this study we aim to assess the expression of PIAS1 and PIASγ in breast cancer (BC).
Methods: A well-characterized annotated series of 2195 BC including a subset with BRCA1-germline-mutation was investigated using TMA and immunohistochemically. Results were correlated to clinicopathological features and molecular markers with emphasis on DDR proteins.
Results: Expression of PIAS1 was observed in the nuclei (nPIAS1) and cytoplasm (cPIAS1) of malignant cells whilst expression of PIASγ was seen in the nuclei. Loss of nPIAS1 and expression of cPIAS1 were significantly associated with features of aggressive behaviour including higher-histological grade with high-mitotic frequency, triple-negative phenotype and absence of HR markers (BRCA1, RAD51 and CHK1) but with expression of the NHEJ marker KU70/KU80 ($p<0.001$). On the other hand, loss/weak expression of nPIASγ showed an association with lower nodal stage, expression of progesterone receptor and HR-markers and lower expression of NHEJ-marker. BRCA1-associated tumours showed expression of nPIASγ and cPIAS1 and lacked nPIAS1. Outcome analysis showed as association between loss of nPIAS1 and expression of cPIAS1 and worse breast cancer specific survival and disease free interval. No such associations were found with nPIASγ.
Conclusion: These findings confirm the diverse function of PIAS proteins, emphasis the role of subcellular localisation and provide further evidence on the complexity of DDR mechanisms.

10.00–10.15 **[O15]** ***Impact of HER2 Copy Number in IHC HER2 2+/FISH Positive Breast Cancer on Outcome of Adjuvant Trastuzumab Treatment***

Ⓟ A Borley[1]; T Mercer[2]; M Morgan[3]; P Barrett-Lee[1]; B Jasani[4]

[1]Velindre Hospital LHB, Cardiff, United Kingdom; [2]School of Medicine, Cardiff University, Cardiff, United Kingdom; [3]Department of Cellular Pathology, Cardiff & Vale LHB, Cardiff, United Kingdom; [4]Institute of Cancer & Genetics, School of Medicine, Cardiff University, Cardiff, United Kingdom

Adjuvant trastuzumab (T) is a standard treatment in conjunction with chemotherapy for patients with HER2 positive early breast cancer. A retrospective review of this treatment in a community setting in a South East Wales Cancer Network (SEWCN) showed comparable outcomes to the multinational trials such as HERA. Positive HER2 status was defined in line with the prevailing guidelines HER2 IHC 3+ or as HER2 IHC 2+/HER2 FISH+ (HER2 copy number/CEP17 copy number >2.0). The aim of this study was to investigate the degree to which HER2 amplification in terms of HER2 gene copy numbers in HER2+ (IHC2+) cancers affected the outcome in the same set of patients. All 311 consecutive SEWCN patients presenting between 1st January 2005 and 31st December 2008 were included. Amongst 3+ cases 163 received T vs 66 no-T. 5 year disease-free survival was 84% (T) vs 70% (no-T). Amongst 2+ cases 59 received T vs 22 no-T. Amongst 59 treated cases n=28 had >12, n=13 had 6.1-12, and n=18 had 2-6 HER2 gene copies, respectively. The time to progression and overall survival of high and low copy number patients was similar and better than the intermediate copy number and the untreated cohorts. Although based on small numbers of patients, high HER2 copy number (>12) appears to be associated with consistently better response compared to patients with intermediate HER2 copy numbers (6-12). Our findings are at variance with those of HERA which compared outcomes with HER2 copy numbers without segmenting HER2 2+ from 3+ IHC cases.

10.15–10.30 **[O16]** ***Epithelial Mesenchymal Transition in Early Invasive Breast Cancer: Further Evidence Using Reverse Phase Protein Array***

Ⓟ MA Aleskandarany[1]; OH Negm[2]; EA Rakha[3]; MAH Ahmed[1]; CC Nolan[1]; PJ Tighe[2]; AR Green[1]; IO Ellis[1]

[1]Division of Pathology, School of Molecular Medical Sciences, University of Nottingham, Nottingham, United Kingdom; [2]Division of Immunology, University of Nottingham, Nottingham, United Kingdom; [3]Pathology Department, Nottingham City Hospital, NHS Trust, Nottingham, United Kingdom

Background and purpose: Although Epithelial Mesenchymal Transition (EMT) has been reported in-vivo, the occurrence of events remains unclear. This study aimed at exploration of the EMT portraits of breast cancer (BC) with relevance to triggering molecular pathways and molecular subtypes.
Methods: Hierarchical and k-means clustering were performed on a well-defined series of invasive BC (n=1656), prepared as tissue microarrays, utilising data of immunohistochemical (IHC) biomarkers including cadherins, TGFβ1, PIK3CA, pAkt, cytokeratins, Twist2, Erb-family members and hormone receptors. Reverse phase protein array (RPPA) was performed on proteins extracted from formalin-fixed paraffin-embedded tissues of a subset of cases from the same series (n=49).
Results: Clustering analyses resulted in four molecular subtypes (Luminal 1&2, HER2+, and basal-like (BLBC)), showing differential IHC expression of EMT markers. BLBC tended to express lower E-cadherin, higher P-cadherin, SMA and PIK3CA, relative to HER2+ BC that expressed highest levels of N-cadherin, TGFβ1 and PIK3CA. Although distribution of EMT markers/triggers using RPPA was not statistically significant, their mean expression levels were variably expressed within BC molecular classes. E-cadherin was reciprocally expressed with N-cadherin in luminal and HER2+ BC. Moreover, pAkt-S473 was maximally expressed in luminal BC and minimally expressed in TN-basal BC, while PIK3CA was maximally expressed in HER2+. However, TGFβ1 was maximally expressed in TN-Basal class, followed by HER2+ BC.
Conclusions: EMT in BC appears to occur in synergy with TGFβ1 and PIK3/Akt pathways activation. RPPA findings validate quantitatively the findings observed using IHC, therefore opening promising avenues for monitoring subtle quantitative changes in protein expression in different molecular pathways. These findings could help developing targeted therapies against EMT-associated/triggering pathways.

WEDNESDAY 19 JUNE — *continued*

10.30–11.00 **REFRESHMENT BREAK** [Lomond Suite – Level 0]

11.00–11.15 **[O17]** ***Optimisation of the Estimation of Lymphovascular Invasion in Primary Breast Cancer Patients: Single or Multiple Blocks?***

Ⓟ A Mukherjee[1]; M Craze[2]; WH Nyan Soe[2]; A Loona[3]; E Rakha[1]; IO Ellis[1]

[1]University of Nottingham, NUH NHS, Nottingham, United Kingdom; [2]University of Nottingham, Nottingham, United Kingdom; [3]Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom

Purpose: The prognostic significance of lymphovascular invasion (LVI) in breast cancer (BC) using immunohistochemistry (IHC) is well documented. Although assessment of LVI on H&E stained sections involves multiple slides, IHC is often limited to a single tumour block. The optimum number of tumour quadrants requiring IHC has not been determined. Such quantification would help optimise LVI assessment.
Methods: Sections were cut from multiple tumour quadrants of 87 BC cases (n=286) and peritumoural LVI ascertained using the lymphatic endothelial marker D2-40. Difference in LVI status as adjudged from one or more blocks by IHC was analysed.
Results: 47 (54%) cases were LVI positive. Assessment of LVI status in the corresponding tumour sections revealed that LVI status would have been concordant in 49 cases (56.3%) even if a single tumour block was stained. Of these, 9 cases were LVI positive. In 38 (43.7%) LVI-positive cases, there was a probability of underdiagnosing LVI, if analysis was limited to 1 tumour block ($p< 0.001$). Of these, 8 cases had 25%, 10 cases 33%, 12 cases 50%, 5 cases 66% and 3 cases 75% probability of achieving the correct IHC diagnosis by single block staining. 31 patients in the series developed distant metastases. Of these, 14 were lymph node (LN) negative. 8 of them were LVI positive on multi-block analyses and 7 would have been under-called otherwise. 17 distant metastases cases were LN positive. 11 were LVI positive on multi-block IHC; 8 would have been under-called otherwise. In this series, LVI by IHC improved on H&E in 34 cases (39%), either by reversing the H&E call (23%) or by helping to make a definitive diagnosis (16%).
Conclusion: The study indicates that IHC on more than one tumour block is required when supplementing H&E with objective LVI analysis. Objective LVI assessment is superior to H&E assessment in predicting outcome.

11.15–11.30 **[O18]** ***Nottingham Prognostic Index Plus (NPI+): A Modern Clinical Decision-Making Tool in Breast Cancer***

Ⓟ E Rakha[1]; D Soria[1]; C Lemetre[2]; A Green[1]; D Powe[3]; C Nolan[1]; J Garibaldi[1]; G Ball[2]; IO Ellis[1]

[1]University of Nottingham, Nottingham, United Kingdom; [2]Nottingham Trent University, Nottingham, United Kingdom; [3]Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom

Current management of breast cancer (BC) relies on risk stratification based on well-defined clinicopathologic factors incorporated into tools such as the Nottingham Prognostic Index (NPI). Global gene expression profiling studies have demonstrated that BC comprises distinct molecular classes with clinical relevance. In this study, we hypothesized that the molecular features of each class BC are key drivers of tumour behaviour and that clinicopathological variables included in tools such as the NPI would differ in relevance and strength in each class. In the current study, a panel of 10 biomarkers with relevance to BC was applied to a well-characterised seris of 1,073 cases of BC, using immunohistochemistry. Seven core BC molecular classes (3 luminal, 2 HER2 and 2 basal-like) were identified using cluster analysis methodology. Subsequently, each class was further interrogated to identify those clinicopathologic variables of prognostic relevance in the class. These variables were combined into bespoke formulae, collectively known as the Nottingham Prognostic Index Plus (NPI+), which were able stratify each of the different molecular classes. NPI+ was then used to predict outcome in the different molecular classes with consideration to systemic therapy. Outcome analysis showed that use of bespoke NPI formulae for each biological breast cancer class provided improved patient outcome stratification, superior to the traditional NPI. This study provides proof-of principle evidence for the use of methods like NPI+ in supporting improved individualised clinical decision making.

11.30–11.45 **[O19]** ***The Biological and Clinical Significance of p-JNK1/2 in Human Breast Cancer***

Ⓟ DA Jerjees; RF Abduljabbar; AR Green; IO Ellis; EA Rakha

City Hospital, Nottingham, United Kingdom

Background: c-Jun N-terminal kinase (JNK) is a member of MAPK pathway involved in a diversity of cellular function including signal transduction, apoptosis, proliferation and cellular differentiation. Previous studies of JNK in breast cancer (BC) have produced contrasting results. In this study we aimed to assess the clinicopathological and biological significance of phospho JNK 1 and 2 (p-JNK1/2) expression in BC using immunohistochemistry and a large well-characterized series of clinically and molecullary annotated (n=1950) series prepared as TMA.
Results: p-JNK1/2 expression was associated with features of good prognosis including smaller tumour size, lower grade and up-regulation of luminal-enriched proteins (ER, PgR, AR, CK7/8, CK18, CK19, MUC1), ER-coactivators, differentiation-related and other ER-related proteins (CARM1,TFF3, XBP1, BEX1 and AGTR), proapopotic gene Bcl2 and the p53-inhibitor MDM2. Negative association was observed between pJNK1/2 and expression of HER2, HER4, proliferation-related genes (Ki67, TK1 and PI3K) and p53. When cases were stratified according to ER-expression, association with HER2 disappeared however, when tumours were stratified according to HER2-status, association with ER was maintained in the HER2-negative tumour but not in HER-positive subgroup. Outcome analysis showed p-JNK1/2 is an independent factor of poor survival only for ER-HER2-cases.
Conclusion: these finding indicate p-JNK1/2 is associated with luminal phenotype and its expression is related to ER-pathway. Association with HER2 appears to be ER-dependent. P-JNK1/2 was an independent prognostic factor in the ER-HER2- cases but not the whole series.

11.45–12.00 **[O20]** ***Liver Receptor Homolog 1 Expression and its Correlation to the Breast Biomarkers in a Large Cohort of Breast Cancer Patients***

Ⓟ RF Abduljabbar[1]; E Rakha[1]; DA Jerjees[1]; C Nolan[1]; f Lai[2]; L Buluwela[2]; S Ali[2]; IO Ellis[1]

[1]University of Nottingham, Nottingham, United Kingdom; [2]Imperial College, London, United Kingdom

Liver Receptor Homolog-1 (LRH-1) is an orphan receptor belongs to Nuclear Receptor Superfamily (NR) of transcription factors that includes the oestrogen receptor (ER). Recent studies have shown that LRH-1 expression is oestrogen-regulated in breast cancer cells and have determined that LRH-1 regulates breast cancer (BC) cell growth and promotes cell motility and invasion. While LRH1 gene expression has been shown to be elevated in ER-positive BC, clustering analysis has grouped it with other NRs that are elevated in HER2-positive BC. In this study, we have assessed LRH-1 protein expression in a large well-characterised annotated cohort of BC patients (n=1200) to determine its biological and clinicopathological significance.
Results: LRH-1 expression was observed in the nuclei and cytoplasm of the malignant cells and both were significantly correlated (r2= 0.66, p< 0.001). 3% of the tumours showed complete absence of expression. Although LRH1 expression (Nuclear H-score > 20) showed positive association with tumours grade (p<0.001) and HER2-positivity (p=0.01), it was highly expressed in ER-positive and androgen receptor-positive tumours (p= 0.002 and p< 0.001 respectively) and its expression was low in Triple Negative BC. Outcome analysis showed that LRH1 is not an independent predictor of survival.
Conclusions: These findings indicate that LRH-1 is associated with both ER and HER2 expression in BC. The lack of prognostic value of LRH-1 may be a reflection of its complex and diverse functions in BC.

▶ 12.00 – 13.00 — Fintry – Level 3

PATHOLOGICAL SOCIETY OF GREAT BRITAIN & IRELAND'S 31st CL OAKLEY LECTURE

Chair: Prof CS Herrington, University of Dundee,
and General Secretary, Pathological Society of Great Britain & Ireland

[S25] ***Post-Genomic and Post-Transcriptional Mechanisms in Breast Cancer***

Ⓟ JPC Le Quesne[1]; A Modelska[2]; J Beaton[2]; J Warren[2]; P Pharoah[3]; C Caldas[2]

[1]Addenbrooke's Hospital, Cambridge, United Kingdom; [2]CRUK Cambridge Research Institute, Cambridge, United Kingdom; [3]University of Cambridge, Cambridge, United Kingdom

Purpose: I will discuss some of the approaches that we have used recently to investigate post-transcriptional alterations to gene expression in breast cancer, and their contribution to the malignant phenotype.
Methods: We have used collections of archival tissue in tissue microarrays as a platform in which to investigate correlations with the malignant phenotype, using LNA *in situ* hybridisation assays for micro-RNA expression and immunohistochemistry for protein expression. The expression and subcellular localisation of Dicer protein was investigated by immunofluorescence in cultured cells and by immunohistochemistry in archival tumour tissue. Expression of key translation initiation factors (notably eiF4A and PDCD4) was modulated in cultured cells by standard methods, and alterations in growth and cell cycle were assayed. Polysome isolation, gene expression microarrays and deep sequencing were used to measure the effects of these factors upon the transcriptional and translational profiles of cultured cells.
Summary of Results and Conclusions: The micro-RNAs *let-7b* and *miR-205* are found to be predictors of good outcome in ER positive breast cancer, and to have distinct correlations with the tumour phenotype. MicroRNAs have potential as biomarkers and therapeutic targets. Dicer protein is found to be expressed in the nuclei of breast epithelial cells as well as the cytoplasm. Nuclear expression is related to good outcome in ER positive disease, but cytoplasmic expression predicts poor outcome. I present a model to explain these findings. Several translation initiation factors are shown to be highly predictive of poor outcome, whereas the eIF4A inhibitor PDCD4 predicts good outcome. Furthermore, alterations in the expression of PDCD4 and eIF4A in cultured cells affect cell growth and the cell cycle. This is accompanied by changes in cellular translation, with groups of mRNAs being moved into or out of polysomes.

▶ 12.30 – 14.00 — Lomond Suite – Level 0

LUNCH
POSTER VIEWING AND TRADE EXHIBITION

▶ 13.30 – 17.00 — Fintry – Level 3

SYMPOSIUM
Pancreatobiliary Pathology

Chair: Prof F Campbell, University of Liverpool
Dr KE Robertson, Royal Infirmary of Edinburgh

13.30–14.15 **[S26]** ***Viral Infection in the Pathogenesis of Type 1 Diabetes***

Ⓟ Prof AK Foulis[1];Ⓟ Dr SJ Richardson[2]

[1]GG&C Pathology Department,, Glasgow, United Kingdom; [2]University of Exeter Medical School, Plymouth, United Kingdom

An increasing body of circumstantial evidence has implicated enteroviral infection of islet beta-cells as an important factor in the aetiology of type 1 diabetes in the majority of human patients. Using two rare sample

collections of formalin-fixed paraffin embedded autopsy pancreatic tissue from young persons with recent onset type 1 diabetes – a large UK cohort collected 30 years ago and the more recent JDRF nPOD cohort from the USA, the presence of an enteroviral infection in islet beta cells and the host response to that infection have been examined and compared. It has become clear that in diabetes, such infections do not follow the typical course in which phases of large scale viral replication lead to extensive cell lysis. Rather, the infections appear to be atypical in that they do not cause acute damage to beta cells. Instead, these infections appear to exist in a latent (more persistent) form such that viral replication occurs only very slowly and leads to more subtle changes in islet cell physiology, which ultimately culminate in the development of autoimmunity rather than cell lysis.

14.15–14.50 **[S27]** ***Intraductal Papillary Neoplasms of the Bile Duct (IPNB): Keys to their Molecular Pathogenesis***

Ⓟ Prof I Esposito

Institute of Pathology Technische Universität München, Munich, Germany

Purpose of the study: Intraductal papillary neoplasms of the bile duct (IPNB) are precursors of cholangiocarcinoma (CC) and share morphological similarities with intraductal papillary mucinous neoplasms (IPMN) of the pancreas. However, little is known concerning their subtype stratification, their molecular pathogenesis and their biological behaviour.
Methods: These issues were analyzed through a multicenter study in a large European cohort. IPNB from 45 patients were characterized using immunohistochemistry (Muc1, Muc2, Muc5AC, Muc6, CDX2, p53, Smad4, EGFR, Her2neu, beta-catenin) and molecular analyses (Kras, GNAS, p16). 22 intra- and extrahepatic classical CC were used as controls.
Summary of results: IPNB mainly showed a pancreato-biliary (36%) or intestinal (29%) differentiation, followed by gastric (18%) and oncocytic (13%) subtypes. An adenoma-carcinoma sequence progressing from low- to high-grade lesions to invasive carcinoma was detected at the morphological and the molecular level. KRAS mutations, p53 overexpression and loss of p16 were early events, whereas loss of SMAD4 was found in the late phases of tumor development. Alterations of HER2, EGFR, beta-catenin and GNAS were rare. IPNB patients showed a slightly better overall survival than patients with CC (Hazard Ratio (CC vs. IPNB): 1.40; 95% CI: 0.46 to 4.30; p=0.552).
Conclusions: IPNB show similar differentiation to pancreatic IPMN with different distribution of the subtypes. A stepwise activation of common oncogenic pathways supports their progression to CC. CC originating through a papillary carcinogenetic pathway seems to be less aggressive than classical CC.

14.50–15.15 **REFRESHMENT BREAK** **[Lomond Suite – Level 0]**

15.15–15.50 ***Endocrine Tumours of the Pancreas***

Ⓟ Prof G Kloppel

Technical University, Munich, Germany

15.50–16.25 ***Cystic Neoplasms of the Pancreas***

Ⓟ Prof F Campbell

University of Liverpool, United Kingdom

16.25–17.00 **[S28]** ***Utilising Pre-clinical Models to Refine Immune Modulation in Pancreatic Cancer***

Ⓟ Dr T Hagemann

Barts Cancer Institute, London, United Kingdom

ABSTRACT RETRACTED

Recent developments o[illegible] for patients with solid tumours. Howeve[illegible] disease pro[illegible]gression still occurs invariably in the vast m[illegible] consequence, 2 year survival rate for advan[illegible] carcinoma is naturally resistant to current chemo- and radiation-therapy. Therefore there is an urgent need for the improvement of current therapy. Immunotherapy recently gained significant momentum with new therapeutic options at the horizon. There is a[illegible] in the tumour microenvironment[illegible] tumour immune responses as well a[illegible] PDAC th[illegible] overcome i[illegible]. However the immune suppressive microenvironment of pancreatic cancer has not yet been systematically characterised. However, human and mouse immunity demonstrate significant differences and studies are needed to define patient immunity in detail to develop and improve immune therapies. Our work aims to define the immunity in pancreatic cancer patients in a spatio-temporal manner and to redefine therapeutic points of intervention.

RENAL PATHOLOGY MINI-SYMPOSIUM — *continued*

Chair: Dr COC Bellamy, University of Edinburgh
Prof ISD Roberts, Oxford University Hospitals

13.30–14.00 **[S24]** ***Role of Electron Microscopy in the Assessment of Renal Transplant Biopsies***

Ⓟ Dr CA Roufosse

Imperial College Healthcare NHS Trust, London, United Kingdom

Electron microscopy (EM) is an ancillary technique that is standard of care for the examination of native renal biopsies in a proportion of cases. Despite its cost, it is essential for the diagnosis of some diseases (such as thin basement membrane lesion, Alport syndrome, and fibrillary/immunotactoid glomerulonephritis), and adds value to biopsy interpretation in a number of other cases. The role of EM in the examination of renal transplant biopsies is more controversial. The main indication for EM in transplant biopsies is glomerular disease, which can be discovered either by the clinical detection of proteinuria and/or haematuria, or by abnormal glomeruli on light microscopy examination. Glomerular disease is not a common finding in transplant biopsies, but increases with time post-transplant, and contributes to allograft loss. It can be related to recurrent or de novo glomerulopathies, or to rejection, in the form of glomerulitis and transplant glomerulopathy (TG). Immunofluorescence examination and/or EM help to distinguish alloimmune glomerular disease from immune complex-related glomerulonephritis. A possible future application for EM in the transplant biopsy is the early detection of chronic antibody-mediated damage, but the validity and cost-effectiveness of EM in this context have not been established.

References: Role of electron microscopy in transplant renal pathology. Herrera GA, Isaac J, Turbat-Herrera EA. Ultrastruct Pathol. 1997 Nov-Dec;21(6):481-98. Electron Microscopy in Renal Biopsy Interpretation – When and Why We Still Need It. Haas M. US Renal Disease 2007 (Touch Briefings)

14.00–15.00 ***Renal Pathology EQA***

Ⓟ Prof ISD Roberts

Oxford University Hospitals, Oxford, United Kingdom

15.00–15.20 **REFRESHMENT BREAK [Lomond Suite – Level 0]**

15.20–15.50 ***Renal Transplant EQA***

Ⓟ Dr D Neil

Queen Elizabeth Hospital, Birmingham, United Kingdom

15.50–16.15 ***RCPath and Renal Registry Issues***

Ⓟ Prof T Cook

Imperial College, London, United Kingdom

16.15–16.30 **[O41]** ***Fibrillary Glomerulonephritis: Clinico-pathologic Series of 13 Cases with Glomerular Proteomic Analysis in 5 Cases***

Ⓟ EP Dinneen[1]; JA Gilbertson[2]; N Rendell[2]; GW Taylor[2]; A Burns[3]; PS Bass[1]; HJ Lachmann[2]

[1]Department of Histopathology, Royal Free Hospital London, London, United Kingdom; [2]National Amyloidosis Centre, Royal Free Hospital London, UCL Medical School, London, United Kingdom; [3]UCL Centre for Nephrology Royal Free Hospital London., London, United Kingdom

Fibrillary Glomerulonephritis (FGN) is a rare primary glomerular disease characterized by electron microscopy feature of straight, non-branching, randomly arranged fibrils (ranging from 10 – 30nm in diameter) deposited diffusely in the GBM and the mesangium. Here we report the first UK based case series. The characteristics of 13 patients with FGN referred to a single institution are detailed. The most common LM pattern was mesangial proliferative/sclerosing followed by membranoproliferative GN. At the time of biopsy, mean age was 48 years (range 27 – 75 years). Mean proteinuria at biopsy was 5.91g/24 h (range 0.5 – 11g). Mean serum creatinine at biopsy was 174 µmol/l (range 49 – 426 µmol/l), and 62% of patients had renal insufficiency. Average follow-up period was 45.4 months. Four patients progressed to ESRF, another 4 have progressive renal disease CKD 4, 3 have progressive renal disease, and 2 had partial remission of disease. Five patients' renal biopsy tissue was obtained for laser microdissection (LMD) and tandem mass spectrometry (MS). Glomerular proteomics demonstrated universal complement deposition, presence of Igs in 4 of 5 cases, and proteins typically associated with amyloid in 2 cases. Glomerular proteomics in FGN using LMD and MS has never been reported previously in the literature. In conclusion, the clinico-pathologic series demonstrates findings, which whilst entirely consistent with previous studies on FGN, emphasise the high degree of heterogeneity in the presentation, the histology, co-morbidities and prognosis of patients with FGN. Now for the first time there is also evidence to suggest a heterogeneous glomerular proteomic profile also. Taken together, this suggests that the histological features of FGN results from a spectrum of different pathological pathways which all result in protein fibrillogenesis within the glomerulus.

16.30–16.45 **[O42]** ***Report of Two Cases of Crescentic Membranous Glomerulonephritis with Linear IgG Immunofluorescence Staining.***

Ⓟ DT Kipgen

Southern General Hospital, Glasgow, United Kingdom

Membranous glomerulonephritis (MGN) rarely takes the form of crescentic rapidly progressive glomerulonephritis (RPGN). This report describes the clinical presentation, renal biopsy findings, and clinical progress of two patients with crescentic MGN.
Case 1: a 23 year old man who presented with haematuria, proteinuria, low serum albumin and serum creatinine of 129 µmol/L. ANCA, ANA and anti-GBM antibody serology was negative. Renal biopsy showed active crescents in 10 of 15 glomeruli with mild chronic damage. Immunofluorescence: linear IgG glomerular capillary wall staining. Electron microscopy showed intramembranous electron dense deposits. He was treated with methylprednisolone, cyclophosphamide and mycophenolate mofetil and initially responded. His renal function has subsequently deteriorated and a repeat biopsy 4 years later shows a marked increase in global glomerulosclerosis and chronic tubulointerstitial damage.
Case 2: a 62 year old woman who presented with acute deterioration in renal function (serum creatinine 546 µmol/L). Anti GBM antibody titres were strongly positive. Renal biopsy showed active crescents in 6 of 8 glomeruli and mild chronic tubulointerstitial damage. Immunofluorescence: linear glomerular capillary wall staining with IgG. Electron microscopy showed subepithelial electron dense deposits. She was treated with plasma exchange, cyclophosphamide, prednisolone and co-trimoxazole. She did not recover renal function and remains dialysis dependent.
Conclusions: The two cases show prognosis more consistent with RPGN or anti-GBM GN than MGN. Given recent and ongoing advances in knowledge of pathogenesis of MGN it would be interesting to know anti phospholipase A2 receptor antibody status in these patients. Possible pathogenetic reasons for a combination of anti-GBM GN and MGN include abnormal exposure of basement membrane antigens and increased expression of podocyte antigens.

▶ 13.30 – 15.00 Carrick – Level 1

ORAL COMMUNICATIONS
Categories: ***Neuropathology/Ophthalmic; Osteoarticular/Soft Tissue; Lymphoreticular***
Chair: Prof D Salter, University of Edinburgh
Prof JE Martin, Barts and the London School of Medicine and Dentistry and Barts Health NHS Trust

13.30–13.45 **[O21]** ***Lentiviral Vector Mediated Haematopoietic Stem Cell Gene Therapy for the Treatment of Lysosomal Disease***

Ⓟ JH McDermott[1]; A Langford-Smith[1]; A Sergijenko[1]; KJ Langford-Smith[1]; A Liao[1]; SA Jones[2]; JE Wraith[2]; RF Wynn[3]; FW Wilkinson[1]; BW Bigger[1]

[1]Stem Cells & Neurotherapies, University of Manchester, Manchester, United Kingdom; [2]St Mary's Hospital, Manchester, United Kingdom; [3]Blood and Marrow Transplant Unit, RMCH, Manchester, United Kingdom

Mucopolysaccharidosis type III (MPS III) is a lysosomal storage disorder which results from mutations in the genes coding for a number of heparan sulphate (HS) degrading enzymes. The disease is characterised by progressive HS accumulation and subsequent neuronal degeneration during childhood. Current therapies fail to restore sufficient brain enzyme activity and, as a result, patients rarely live past their second decade. Hematopoietic stem cell transplantation (HSCT), is an effective treatment for other MPS disorders, but is ineffectual for MPS III. We propose that insufficient enzyme is produced by donor-derived brain microglial cells to achieve a clinical response following transplantation. To overcome this dose-effect we created several lentiviral vector constructs containing genes encoding for the absent enzyme under either the myeloid specific CD11b (LV-CD11b) or ubiquitous PGK promoter (LV-PGK). Vector expression was achieved in vitro and hematopoietic stem cells (HSCs) were transduced over repeated rounds to maximise the number of viral copies per cell. Significant increases in the average copy number were achieved and importantly this transduction technique was shown to not affect the normal lineage behaviour of the HSCs. An in vivo study was subsequently initiated examining the efficacy of HSCT for MPS III mice where allogenic WT stem cells had been transduced with LV-CD11b compared with HSCT alone. Our data suggests that, although HSCT alone was able to increase enzyme activity above MPS III control levels in the periphery, LV-CD11b HSCT had a significantly enhanced effect; fully correcting the enzyme defect in the periphery and, most strikingly, providing a 9.5% restoration of WT enzyme activity in the brain. This level of restoration has been associated with disease correction and therefore we suggest that vector-mediated HSCT may offer an alternative therapeutic strategy for the treatment of MPS III.

13.45–14.00 **[O22]** ***The Balloon Cell Vascular Niche: Anatomical Evidence of a Stem Cell-Blood Vessel Relationship in Epilepsy-Associated Malformations of Cortical Development***

Ⓟ MA Hollingworth[1]; SML Paine[1]; K Latak[2]; A Gapapathi[2]; K Miller[2]; F Becherini[2]; JH Cross[1]; W Harkness[1]; BN Harding[1]; TS Jacques[1]

[1]Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom; [2]Institute of Child Health, London, United Kingdom

Purpose of study: Epilepsy is the most common severe neurological disease of childhood. Focal cortical dysplasia (FCD) is the most common neuropathological finding in those undergoing surgery for drug resistant focal seizures. Evidence suggests that balloon cells (BC) in focal cortical dysplasia type IIb (FCDIIb) and the genetic disease tuberous sclerosis (TS) are related to stem cells. As stem cells in the developing brain have an essential relationship with blood vessels, the so-called 'vascular niche', we hypothesized that the distribution of BC would be related to blood vessels (BV).
Methods: Using the immunohistochemical markers β1 integrin and von Willebrand factor, we analyzed the distribution of BC and BV in cases of FCD with (FCDIIb) and without (FCDIIa) BC, cortical tubers from children with tuberous sclerosis (TS) and in normally-formed neocortex from children with epilepsy.
Summary of results: Overall, the blood vessel density in areas of dysplasia with BC in TS and FCDIIb cases was reduced compared to the surrounding tissue. However, the vascular density (MVD) immediately adjacent to BC was increased. We conclude that these data support the hypothesis that BC and BV are not randomly distributed; this raises the possibility that BC occupy a stem cell-like vascular niche.

14.00–14.15 **[O23]** ***Precision of Needle Biopsy in the Diagnosis of Soft Tissue Sarcomas***

Ⓟ DG Gent; AJ Freemont

Manchester Medical School, Manchester, United Kingdom

Background: Whereas once surgery was the primary treatment for all sarcomas increasingly presurgical radiotherapy/chemotherapy are now used to improve patient outcome. Use of these therapies is diagnosis specific. Diagnosis is usually based on needle core biopsy. This study examined the diagnostic accuracy of needle biopsy in patients coming to surgical resection of soft tissue sarcomas, using the resection specimen diagnosis as definitive.
Methods: A retrospective review was undertaken of the GMOSS database at Manchester Royal Infirmary (2 specialist sarcoma pathologists) for the period 1/06 to 12/2012. 127 patients with both core needle biopsies and resection specimens were identified. The reliability of core needle biopsies was determined by comparing it with the resection specimen result. Patients were included only if they had a resection diagnosis of sarcoma.
Results: The correct subtype and grade of sarcoma (eg. Myxoid liposarcoma, grade 2 myxofibrosarcoma) was identified using needle biopsy in 67.7% (n=86, 86/127) of cases. The exact subtype of sarcoma was refined using the resection specimen in 11.0% (n=14, 14/127) of cases. A completely different type of sarcoma was identified by the resection specimen compared to the needle biopsy in 21.3% (n=27, 27/127) of cases.
Conclusions: Needle biopsies are a useful diagnostic tool, but for certain subtypes of sarcoma, (e.g. epitheloid sarcoma) the diagnosis was less easily made. The main differences between the needle biopsy and the resection related to sampling of heterogeneous tumours and limitations of information derived from immunohistochemistry in some settings.

14.15–14.30 **[O24]** ***Prevalence and Cytological Characterisation of a Mixed Arthritis with Monosodium Urate and Calcium Pyrophosphate Crystals***

Ⓟ EL Heselden; AJ Freemont

University of Manchester, Manchester, United Kingdom

Purpose of Study: The aim of this study was to investigate the existence of an arthritis in which monosodium urate (urate) and calcium pyrophosphate (CPP) crystals co-existed in synovial fluid (SF).
Methods: Synovial fluid analyses of 33000 samples were reviewed, identifying those which contained urate and CPP crystals. Synovial fluid cell count, presence of organisms, and differential cell count, together with patient age and sex were retrieved from a computerised database spanning 22 years of SF analysis.
Summary of Results: Crystals were identified in 6983 (21%) cases. Of these CPP were found in 3685 cases, urate in 3127, and both in 171 (0.5%). These 171 cases were deemed to have a mixed crystal arthropathy (MCA). MCA sufferers were 77% male and 23% female, and the highest incidence was found in people aged 76–80 yrs.
The most common pattern (69.4%) was that of high numbers (>20/10HPF) of both crystals and an acute inflammatory cell count – "True" MCA. In most of the remainder (23.8%) there were low numbers of CPP and many of these had proven osteoarthritis (OA). This pattern we call OA with gout. Of these 29% had evidence of acute gout at the time of aspiration, the remainder were considered to have "quiescent gout".
Conclusion: This study confirms the existence of a disease that has been suspected but never hitherto characterised – true MCA. This diagnosis can only be made by SF microscopy. We describe its diagnostic SF features and demography, but there is still a need to characterise it clinically and define its management.

WEDNESDAY 19 JUNE — *continued*

14.30–14.45 **[O25]** ***Splenic Marginal Zone Lymphoma: Mutation Landscape by Exome Sequencing***

Ⓟ AJ Clipson[1]; AJ Watkins[1]; M Ashton-Key[2]; L de Leval[3]; A Wotherspoon[4]; G Vassiliou[5]; MQ Du[1]

[1]University of Cambridge, Cambridge, United Kingdom; [2]Southampton General Hospital, Southampton, United Kingdom; [3]Institut Universitaire De Pathologie, Lausanne, Switzerland; [4]Royal Marsden Hospital, London, United Kingdom; [5]Wellcome Trust Genome Campus, Hinxton, United Kingdom

Splenic marginal zone lymphoma (SMZL) is a low grade B-cell lymphoma with remarkably variable clinical outcome. Currently, it is not possible to predict the prognosis of patients with SMZL and stratify their treatments accordingly. This is largely due to a lack of understanding of the genetics and molecular mechanisms underlying the lymphoma development. SMZL lacks recurrent chromosome translocation, and is characterised by frequent 7q deletion, but the gene(s) targeted by the deletion remain elusive. By exome sequencing 15 cases of well-characterised SMZL, we have identified recurrent mutations in multiple signalling pathways including NOTCH, NF-κB, BCR, TLR and WNT signalling, as well as in several chromatin remodelling genes. There was no apparent correlation between the various signalling pathway mutations and the 7q deletion status or IGVH usage. We are in the process of validating these mutations in a large cohort of SMZL by targeted re-sequencing and will then examine their incidence, potential association and utility in prognosis and treatment stratification.

This work is supported by a Path Soc Research Grant.

14.45–15.00 **[O26]** ***Prognostic Impact of D2-40 Expression and BCL6 Gene Rearrangement in Diffuse Large B-Cell Lymphoma.***

AA Al-Sissi; MI Mourad; NA El-Sissy; SM Abd El-Aziz;Ⓟ AA Shalaby

Mansoura University, Mansoura, Egypt

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma, accounting for 30-40% of newly-diagnosed cases. Lymphatic invasion is correlated with worsening prognosis including increased risk of nodal metastasis, decreased survival and long term or distant recurrence. D2-40 expression is a good predictor of lymphatic invasion and can be considered as a potential target for therapy. Studies of BCL6 gene rearrangement in DLBCL has yielded contradictory results, demonstrating favorable, intermediate, and adverse outcomes. In this study we evaluated D2-40 expression by immunohistochemistry and BCL6 rearrangement by FISH technique in DLBCL cases and correlated both with each other and with the established prognostic and clinical parameters. This study was conducted on formalin fixed paraffin embedded sections of 30 cases of DLBCL of cervical lymph nodes. Cases were evaluated clinically on the basis of Ann Arbor Staging and International Prognostic Index (IPI). The relationships between D2-40 expression, BCL6 break apart and other clinicopathologic features revealed a highly significant inverse correlation between IPI and BCL6 rearrangement ($P<0.001$), overall survival (OS) as well as disease free survival (DFS) ($P<0.001$). BCL6 rearrangement was associated with good overall survival and disease free survival ($P <0.001$). On the other hand, BCL6 rearrangement showed a highly significant negative correlation with D2-40 immunoreactivity, lymph vessel density (LVD) and lymph vessel invasion (LVI) ($P <0.001$). These results support the use of D2-40 expression as an indicator of lymphatic invasion in combination with clinical parameters such as IPI and Ann Arbor Staging. The combination of CD2-40 expression and BCL6 gene rearrangement may help to develop a more patient-tailored therapy.

15.00–15.30 **REFRESHMENT BREAK** **[Lomond Suite – Level 0]**

▶ 15.30 – 16.30 Carrick – Level 1

ORAL COMMUNICATIONS

Categories: ***Cardiovascular/Pulmonary; Technical Advances; Head and Neck***

Chair: Prof D Salter, University of Edinburgh
Dr TR Helliwell, Royal Liverpool University Hospital

15.30–15.45 **[O27]** ***Diagnostic Efficacy of Cell Block Preparation in Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration – A Retrospective Review in the West of Ireland***

Ⓟ D Abu-Sinn; M Tan Chien Sheng

University Hospital Galway, Galway, Ireland

Endobronchial Ultrasound-guided Transbronchial Needle Aspiration (EBUS-TBNA) has proven to be a highly specific and sensitive diagnostic outpatient procedure for lung cancer staging and evaluation of mediastinal lymphadenopathy. Cytological smears and cell blocks are routinely performed in the majority of hospitals offering this service. A retrospective study was conducted over one year to assess the diagnostic efficacy of cell block preparations in the assesment of EBUS-TBNA samples. The diagnostic yield between smears and cell block preparations is compared. One hundred and fifty patients (296 lymph nodes) underwent EBUS-TBNA in 2012. On-site evaluation was done in 6 (4%) cases. The aspirates were diagnostic in 134 (89.3%) cases. The diagnoses were atypical/suspicious, benign/granulomatous lymphadenitis and malignant in 16 (12%), 73 (54.5%) and 45 (33.5%) cases respectively. Of the malignant cases, 38 (84%) were primary lung cancer metastases, of which 10 (26.3%)small cell, 18 (47.3%) adenocarcinoma, 9 (23.7%) squamous cell carcinoma, 1 case was adenosquamous/ mucoepidermoid. There were no NSCLC-NOS cases. Of the 16 (10.7%) non-diagnostic cases, 2 had repeat EBUS-TBNA, while 9 had concomitant specimens which were all diagnostic for malignancy. The diagnostic material

was found on cell block in 97.7% of malignant cases, and in 90.4% of benign cases; while diagnosis was based on smear only in 1 (2%) of the malignant cases and 7(9.5%) of the benign cases. EBUS-TBNA remains a highly specific and sensitive method in diagnosing mediastinal disease despite the lack of onsite evaluation. In a high percentage of cases diagnosis can be made without a single smear preparation. This finding conclude the reliability of a cell block as a sole modality in the diagnosis of EBUS specimens. In the minority of cases where the diagnosis is based on smears, only one of these cases showed evidence of malignancy.

15.45–16.00 **[O28]** ***Evaluation of Cell Pellet Usage in Endobronchial Ultrasound-Guided Fine Needle Aspirations (EBUS-FNAS)***

Ⓟ HK Iftikhar; A Rice; A Montero; S Chikte; J Sills; AG Nicholson

Royal Brompton Hospital, London, United Kingdom

Background: Endobronchial ultrasound (EBUS) guided fine needle aspiration of mediastinal lymph nodes is a minimally invasive procedure for cytological sampling of the mediastinal lymph nodes that has been successfully applied in nodal staging of lung carcinomas, their restaging after adjuvant therapy, diagnosing mediastinal lymphoma, other extrathoracic metastatic malignancies and also non neoplastic entities such as sarcoidosis and tuberculosis. It has evolved as a mainstay of diagnostic practice over the past 10 years, with the management of samples constantly evolving to meet clinical needs. Initially EBUS-FNA specimens were solely reviewed via cytology (PAP-stained, Diff-Quick-stained, Thin Prep slides dependent on local practices), with cell blocks being increasingly made for ancillary investigation (genetic testing) in positive cases only over the last 5 years. In our department, a cell pellet had until June 2012 been prepared for positive After discussion in the department in relation to complexity of diagnosis in such cases, we decided to make cell pellets for all TBNA specimens.
Aims: The aim of this audit was to establish whether making cell pellets for all TBNAs was best practice or unnecessary in relation to accuracy of diagnosis.
Methodology: We reviewed the results of 97 EBUS-FNAS from June 2012 to January 2013 to establish the role of the cell pellet in the management of TBNA specimens.
Results: Our results showed that, in 19 out of 100 consecutive cases (19%), a diagnosis was made on the cell pellet when the cytology specimen alone had been negative for a specific diagnosis was not possible without a cell pellet. Of the 19 cases, there were 12 cases of non-necrotising granulomatous inflammation, 5 were cases of neoplastic disease and 2 cases were called suspicious on cytology but were felt to be benign on cell pellet. There were no cases where the cytology was positive and the cell pellet was negative.

16.00–16.15 **[O29]** ***Variation in Cellular Pathology Department Specimen Handling Processes in the Cancer Research UK Stratified Medicine Programme***

Ⓟ EC Shaw[1]; VP Collins[2]; D Gonzalez de Castro[3]; AM Hanby[4]; D Harrison[5]; D Neil[6]; B O'Sullivan[6]; K Oien[7]; P Taniere[8]; AG Nicholson[9]; D Rassl[10]; PWM Johnson[1]

[1]Cancer Research UK, London, United Kingdom; [2]Addenbrookes Hospital and University of Cambridge, Cambridge, United Kingdom; [3]The Institute of Cancer Research and Royal Marsden NHS Foundation Trust, London, United Kingdom; [4]Leeds Institute of Molecular Medicine, Yorkshire Cancer Research and Liz Dawn Pathology and Translational Sciences Centre, Leeds, United Kingdom; [5]NHS Lothian and University of St Andrews, Edinburgh, United Kingdom; [6]University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; [7]University of Glasgow, Glasgow, United Kingdom; [8]University Hospital Birmingham and University of Birmingham, Birmingham, United Kingdom; [9]Royal Brompton & Harefield NHS Foundation Trust and Imperial College London, London, United Kingdom; [10]Papworth Hospital NHS Foundation Trust, Cambridge, United Kingdom

Purpose of the study: To establish a baseline and assess variation in current NHS cellular pathology department specimen handling. This will be an essential step in developing optimised protocols in anticipation of the increasing requirement to analyze nucleic acids from formalin-fixed, paraffin-embedded tumour specimens.
Methods: Somatic cancer gene mutation profiling has been underway since September 2011 in the Stratified Medicine Programme. Close collaboration between genetics and cellular pathology services delivering this testing has led to the identification of variation in specimen handling practices and laboratory processes that may account for differences in the success rate of subsequent genetic analysis. The areas implicated include tissue fixation, processing and microtomy. A survey of laboratories involved in the programme is currently underway and the results will be presented for the first time at the meeting.
Summary of results: Tumour samples from a total of 5735 English, Scottish and Welsh patients have undergone analysis with a total of 24122 gene tests. Marked differences have been found in the success rates of genetic analysis on different types of specimen as well as the same tumour types from different NHS organizations. The failure rates for genes linked to currently licensed drugs in samples from different centres are as follows: 3-12% for EGFR in lung carcinoma, 0-11% for BRAF in advanced melanoma and 0-5% for KRAS in colorectal carcinoma. The underlying reasons for these variations are being explored through the collaborative multidisciplinary network of researchers involved in the programme.
Conclusions: There is variation in specimen handling in NHS cellular pathology departments. To facilitate the future delivery of predictive molecular analysis for stratified cancer medicine, multidisciplinary and inter-departmental collaboration is required to establish and implement optimised protocols for specimen and nucleic acid preservation.

16.15–16.30 **[O30]** ***Immunohistochemical Assessment of DNA Damage Repair Pathway Activation in Head and Neck Squamous Cell Carcinoma, is it Related to Hypoxia?***

Ⓟ GNJ Betts[1]; H Jones[2]; D Oakes[2]; H Valentine[3]; CML West[3]; C Womack[2]

[1]The Christie, Manchester, United Kingdom; [2]AstraZeneca, Alderly Edge, United Kingdom; [3]University of Manchester, Manchester, United Kingdom

Head and neck squamous cell carcinoma (HNSCC) is characterised by frequent chromosomal aberrations, including loss of the DNA damage response (DDR) kinase ataxia telangiectasia mutated (ATM). DDR capability and tumour hypoxia are known to influence HNSCC radiosensitivity. We measured the expression of biomarkers linked to DDR activation in a cohort of HNSCC tumours already characterised by their hypoxia and p16 status. FFPE sections from 104 patients with primarily surgically treated HNSCC were stained using immunohistochemistry (IHC) for RAD51, p53, pH2AX, 53BP1, ATM, Ki-67 and geminin. Homologous recombination (HR) deficiency was identified as high geminin (S/G2/M marker) to RAD51 ratio. Scores were determined by image analysis based upon the percentage of cells stained positive. Published scoring criteria were used for p53 and 53BP1. Hypoxic status was determined in 42 tumours using a gene expression based hypoxia score. Significant correlations were seen between pH2AX and ATM (p=0.014, Kruskal-Wallis) and RAD51 (p=0.02). HR deficiency was associated with 53BP1 positivity (p=0.003) and high UICC stage (p=0.008). HR deficiency, loss of 53BP1 and loss of ATM were only seen in p16 negative tumours. No relationship was seen between DDR markers and hypoxia although hypoxia was inversely correlated with the proliferation markers Ki-67 (rho=-0.49, p=0.001) and geminin (rho=-0.33, p=0.03). The observation that DDR marker deficiency is confined to the p16 negative population shows that IHC assessment of DDR markers is practical and can reflect tumour biology. The observed association between HR deficiency and 53PB1 may provide an indicator of genomic instability.

▶ 13.30 – 15.00 Ochil 1 and 2 – Level 1

ORAL COMMUNICATIONS

Categories: ***Breast; Experimental Tumour Pathology; Technical Advances***

Chair: Dr J Loane, University of Edinburgh
Dr E Rakha, University of Nottingham

13.30–13.45 **[O31]** ***Screen-Detected DCIS in the UK 2003–2012: A Review of Pathology Practice and Data in 7500 Cases from the Sloane Project***

Ⓟ JS Thomas[1]; AM Hanby[2]; SE Pinder[3]; G Balls[4]; K Clements[5]; G Lawrence[5]; AM Thompson[6]

[1]NHS Lothian, Pathology, Edinburgh, United Kingdom; [2]University of Leeds, Leeds, United Kingdom; [3]Division of Cancer Sciences, King's College, London, United Kingdom; [4]Nottingham Trent University, Nottingham, United Kingdom; [5]West Midlands Cancer Intelligence Unit, Birmingham, United Kingdom; [6]Dundee Cancer Centre, University of Dundee, Dundee, United Kingdom

Purpose: The Sloane Project, a prospective UK audit of patients with screen-detected non-invasive carcinomas and atypical hyperplasias of the breast detected by the National Health Service Breast Screening Programme (NHSBSP), closed to new cases of DCIS in March 2012 and has over 12000 cases. Data have been gathered relating to imaging, surgery, pathology and radiotherapy. We have studied these data to give insight into current practice and guide future management of DCIS.
Methods: We reviewed data from 7537 patients with pure DCIS with pathology, radiology and treatment records. Included are 2624 conservation cases with a complete dataset for disease extent, grade, comedo necrosis and margin width to allow comparison of our cases with previously published series including those of the UK/ANZ DCIS 1 Trial and those used to derive the Van Nuys Prognostic Index (VNPI).
Results: 70% of cases were treated by breast conservation surgery (BCS). Patients treated by mastectomy had significantly more extensive disease (median 36mm) than those treated by BCS (median 13mm). Disease extent correlated positively with grade and negatively with ER status. 64% of DCIS was high grade but there was a wide range in the reporting of this by different laboratories (20-80%). Age had no influence on the grade distribution of disease or the operation type offered to patients. Only100 cases (<4%) fell into the worst VNPI category. Preliminary analysis of 135 local recurrences shows a narrower margin of clearance compared with non-recurrences.
Conclusions: The Sloane Project is an invaluable data resource that will inform the management of DCIS in the future. The VNPI will require modification to provide a useful prognostic tool for screen-detected DCIS and more follow up data will inform this process.

13.45–14.00 **[O32]** ***Epithelial-Stromal Cross-Talk in Breast Cancer: miR-26b Within Carcinoma-Associated Fibroblasts Regulates Epithelial Cancer Cell Migration and Invasion***

Ⓟ ET Verghese; R Drury; CA Green; DL Holliday; X Lu; C Nash; V Speirs; H Thygesen; A Zougman; MA Hull; AM Hanby; T Hughes

Leeds University, St James Hospital Leeds, Leeds, United Kingdom

Bi-directional epithelial:stromal interactions are important in breast breast cancer biology. Fibroblasts within cancer stroma, carcinoma-associated fibroblasts (CAFs), are phenotypically different from normal fibroblasts (NFs). Roles of miRNAs in regulating CAF function are largely unknown. We have previously reported that miR-26b is down-regulated in CAFs compared to NFs in clinical breast cancer samples and a tissue culture model. Here, we investigate the importance of miR-26b in CAFs with respect to CAF and epithelial cancer cell

behaviour. We manipulated miR-26b expression in immortalized breast fibroblasts using transient and stable lentiviral strategies. Reduced miR-26b resulted in increased migration and invasion of fibroblasts in scratch-closure and transwell assays. Fibroblasts with reduced miR-26b expression, or control fibroblasts, were directly co-cultured with the breast cancer epithelial cell line MCF-7. Reduced miR-26b fibroblasts resulted in increased migration and invasion of MCF-7 cells in both 2-D and 3-D models. We used label free mass spectrometry to determine changes in protein expression associated with reduced miR-26b. Pathway analyses revealed that glycolysis and the TCA cycle, and cytoskeletal regulation by Rho GTPases are down-stream of miR-26b. Using an false discovery rate set at <0.1 we identified 3 individual miR-26b targets (TNKS1BP1, CPSF7, COL12A1). To examine the clinical significance of these targets we interrogated publically available breast cancer stromal gene expression profiles. All 3 targets were upregulated in breast cancer stroma, in accordance with the miR-26b down-regulation we have observed, and high expression predicted recurrence. In summary, we have identified miR-26b in breast CAFs as a regulator of breast cancer behaviour and have identified genes and molecular pathways that act down-stream of miR-26b in CAFs.

Funding: PathSoc, MRC, BCC

14.00–14.15 **[O33]** ***Differential Expression of MicroRNAs in Breast Cancers From Four Different Ethnicities***

JA Pollard[1]; PA Burns[1]; TA Hughes[1]; G Mukherjee[2]; JL Jones[3]; C Ho-Yen[3]; GO Omoniyi Esan[4]; NA Titloye[5]; AM Shaaban[6];Ⓟ V Speirs[1]

[1]University of Leeds, Leeds, United Kingdom; [2]Kidwai Memorial Institute of Oncology, Bangalore, India; [3]Barts Cancer Institute, London, United Kingdom; [4]Obafemi Awolowo University, Ife Ife, Nigeria; [5]Kwame Nkrumah University of Science & Technology/Komfo Anokye Teaching Hospital, Kumasi, Ghana; [6]St James's University Hospital, Leeds, United Kingdom

Breast cancer outcomes vary across different ethnic groups. MicroRNAs (miRs) are small non-coding RNA molecules that regulate gene expression across a range of pathologies, including breast cancer.The aim of this study was to evaluate the presence and expression of miRs in breast cancer samples from 4 different ethnic groups; British, Nigerian, Indian and British Black. Four cases from each group were identified and matched according to patient age, tumour grade/type and 10x10µ sections taken. Tumour area was macrodissected, total RNA extracted and cDNA synthesised. cDNA was applied to human miScript PCR arrays allowing quantification of 84 of the most abundantly expressed/best characterised miRs. Differential expression of 9 miRs was seen across the 4 groups. In particular significantly higher levels of miR-140-5p, miR -194 and miR-423-5p were seen in Nigerian breast tumours compared with other ethnic groups (all p<0.0001, ANOVA). miR-423-5p, located on chromosome 17 is of particular interest as it harbours the SNP rs6505162. Bioinformatics analysis showed this SNP was associated with different ethnicity with Europeans mainly AC (57%), Asians mostly CC (~60%) and Africans mainly AA (~60%). In conclusion, although numbers are modest, this study has emphasised the divergent roles of miRs in breast cancer and, importantly, suggests that specific genetic variants in miR genes may affect breast cancer risk in different ethnic groups. Predicted targets of miR-423-5p may uncover useful biomarkers that could have clinical value in breast cancers of different ethnicity.

14.15–14.30 **[O34]** ***Pathological Evaluation of the Staging Axillary Lymph Nodes: A National Survey in the United Kingdom***

R Verma; Ⓟ S Sundara Rajan; E Thomas; K Horgan; AM Hanby; S Lane

Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom

The handling of sentinel lymph node for the presence of metastasis is critical in the assessment of axillary lymph nodes (ALN). Differences in practice between pathological units can lead to variability in patient management between centres. Such variability is increasingly relevant when there is ongoing debate on the need for axillary dissection following positive sentinel lymph node. The aim of this survey was to investigate the practice followed by different pathological laboratories in various hospitals across the United Kingdom in the evaluation of ALN for breast cancer staging.

Methods: A structured questionnaire approved by the NHSBSP pathology Big 18 committee was circulated amongst all pathologists in the United Kingdom through the Breast Screening Quality Assurance Reference Centres.

Results: Amongst 160 respondents, the majority performed sentinel lymph node biopsy (SLNB) (92%) for staging. Most laboratories had a protocol for processing staging ALN (97%). Most laboratories examined the ALN after formalin fixation and paraffin embedding (FFPE) (85.6%). However a few used some initial intra—operative procedures such as PCR (7.5%), frozen section (3.8%) and touch imprint cytology (3.1%), with or without subsequent FFPE examination.

Currently 33% perform serial sectioning of the FFPE blocks with the majority (75%) staining 3 sections using H&E. 67% performed standard sectioning at 1-2 mm followed by H&E evaluation of one section. Most units (85%) performed immunohistochemistry evaluation only when suspicious cells were detected in the H&E stained sections.

Conclusion: Most of the breast units perform SLNB and FFPE for analysis of the axillary lymph nodes for staging. There is considerable variation in the way lymph nodes are sectioned and evaluated histopathologically, however majority of the laboratories adhere to the national guidelines for evaluating staging ALN.

14.30–14.45 **[O35]** ***An Ex-Vivo Tumour Model Using Core Biopsy Explants Validate Carbonic Anhydrase IX (CAIX) as a Therapeutic Target in Breast Cancer***

Ⓟ C Ward[1]; J Meehan[1]; DJ Harrison[2]; IH Kunkler[1]; SP Langdon[1]

[1]University of Edinburgh, Edinburgh, United Kingdom; [2]University of St Andrews, St Andrews, United Kingdom

The development of hypoxic foci in breast and other tumours is associated with the development of aggressive disease and increased mortality. It is estimated that 40% of all breast cancers and 50% of locally advanced breast cancers include hypoxic regions. Adaptive mechanisms to potentiate tumour cell survival under hypoxic

conditions include increased rates of aerobic glycolysis causing external acidosis as cells secrete lactic acid and protons to preserve intracellular pH. CAIX, a hypoxia-inducible protein, is established as an important pH regulator in breast tumours. Previous studies associate expression of CAIX with poor prognosis and increased metastasis in breast cancer. Using an ex-vivo breast cancer explant model, which includes core biopsies from different breast cancer subtypes, it was determined that several novel CAIX inhibitors used at concentrations between 1 and 100 μM, could inhibit tumour invasion of a collagen matrix; complete inhibition was achieved using concentrations of 3 μM. Established invasion regressed by 75% over a period of 5 days after a single 30 μM treatment; while explant area was decreased by 16% within 5 days of treatment using 1 μM inhibitor. Immunohistochemical evaluation of treated and untreated explants showed that increased CAIX expression appears to associate with the invasive capacity of explants and that CAIX inhibitors decrease the numbers of CAIX expressing cells present. Staining for cleaved caspase 3 and Ki67 illustrate that both increased apoptosis and decreased cell proliferation are involved in the responses of this primary tumour explant model to these novel CAIX inhibitors.

14.45–15.00 **[O36]** ***Comparison of Ion Torrent and Pyrosequencing in the Detection of* TP53 *Mutations***

Ⓟ B Doyle[1]; CC Lee[2]; TT Harkins[2]; R Petraroli[2]; P Smyth[1]; K Sheahan[3]; JJ O'Leary[1]; O Sheils[1]

[1]Trinity College, Dublin, Ireland; [2]Life Technologies, Foster City, CA, United States; [3]St. Vincent's University Hospital, Dublin, Ireland

Background: Detection of mutations in tumour tissue is increasingly important to pathologists due to the number of targeted therapies that are only effective in tumours displaying specific mutations. At present, much of the testing to detect these mutations is performed using individual assays. This has proven to be an effective method as the number of 'drugable' mutations is currently relatively low. However, the number of targeted therapies (and therefore targets to be assessed) is expected to rise significantly. This has lead to the development of assays capable of assessing mutations across multiple gene panels. Here we assess one new technology (Ion Torrent's PGM), comparing the results to those obtained with pyrosequencing, an established technology used in many molecular diagnostic laboratories.
Methods: DNA extracted from 8 cell lines with known *TP53* mutations (CCRF-CEM, SW 837, NCI-H23, U251, MDAMD231, SKBR-3, CALU6, C33a) was sequenced using Ion Torrent (Ion PGM sequencer, Life Technologies) and Pyrosequencing (PyroMark Q24, Qiagen) technology.
Results: The Ion Torrent results matched those achieved using pyrosequencing in all 8 cases. The results also matched the known mutations for these cell lines in the TP53UMD mutation database. In one case (M246I mutation in NCI-H23 cells) the Ion Torrent detected 3 different bases, T, A and C. Each of these mutant bases would lead to expression of the same mutant isoleucine amino acid. Interestingly, this may indicate increased depth of sequencing associated with Ion Torrent and also potential heterogeneity within the cell line population.
Conclusion: Results achieved with the Ion Torrent PGM were comparable to that seen using pyrosequencing. As the number and complexity of tests required to inform clinicians increases technologies such as this, with high throughput and scope for expansion may prove beneficial to diagnostic molecular pathology laboratories.

15.00–15.30 **REFRESHMENT BREAK** **[Lomond Suite – Level 0]**

▶ 15.30 – 16.30 — Ochil 1 and 2 – Level 1

ORAL COMMUNICATIONS
Categories: ***Experimental Tumour Pathology; Gynaecological; Cellular/Molecular Pathology***
Chair: Prof M Wells, University of Sheffield
Dr ARW Williams, University of Edinburgh

15.30–15.45 **[O37]** ***Combination of HER2-Targeted Antibodies (Trastuzumab + Pertuzumab) is Effective Against HER2 Amplified Ovarian Cancer Xenograft Models***

Ⓟ SP Langdon[1]; AH Sims[1]; DJ Harrison[2]

[1]University of Edinburgh, Edinburgh, United Kingdom; [2]University of St Andrews, St Andrews, United Kingdom

New therapeutic strategies are required for ovarian cancer and current studies are focussing heavily on targeted therapy approaches. The HER2 cell surface receptor is currently the target of multiple inhibitor strategies with the recognition that use of dual inhibitor approaches are markedly more effective than single inhibitors for the treatment of HER2-positive metastatic breast cancer. This has led to consideration of a HER2 combination approach in other disease types in which HER2 is either amplified or ovexpressed. HER2 is amplified in certain ovarian cancers and while the HER2-targetted antibodies trastuzumab and pertuzumab have limited clinical activity as single agents, combination use may be more effective. We evaluated the combination of trastuzumab and pertuzumab in 6 xenograft models of human ovarian cancer. HER2 was amplified in two of these models (HOX424 and SKOV3) and in both models the combination of antibodies produced regression of tumours. The combination of agents was more effective than treatment with single antibodies alone. This contrasts with progressive growth on treatment in 4 xenograft models (OV1002, HOX 516, HOX 486, HOX 493) in which HER2 was not amplified or overexpressed. In the responsive models, growth response was associated with a reduction of ERK signalling and an increase in expression levels of both p21 and p27 as measured by quantitative immunohistochemistry (AQUA). Apoptosis as indicated by cleaved caspase 3 was also increased in these models. These results support consideration of the use of this dual HER2-targeted antibody approach for the treatment of HER2-positive ovarian cancer.

15.45–16.00 **[O38]** ***Use of Reverse Phase Protein Arrays to Identify Biomarkers of Response to PI3K/mTOR Inhibitors in Ovarian Cancer Models***

Ⓟ G Tashkandi[1]; P Mullen[2]; A Goltsov[3]; JL Bown[3]; DJ Harrison[2]; SP Langdon[1]

[1]Division of Pathology, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, United Kingdom; [2]School of Medicine, University of St Andrews, St Andrews, United Kingdom; [3]Centre for Research in Informatics and Systems Pathology (CRISP), University of Abertay, Dundee, United Kingdom

Ovarian cancer is the leading cause of death in women from gynaecological malignancy with the majority of patients developing resistance to initial chemotherapy. One of the major pathways responsible for chemoresistance in ovarian cancer is the PI3K/PTEN/Akt/mTOR pathway. This pathway is associated with malignant transformation, proliferation and cell survival and is currently under intense investigation as a target for new therapeutic agents. We are investigating the effects of the PI3K specific (LY294002), mTOR specific (Rapamycin) and dual PI3K/mTOR (BEZ235) inhibitors on the growth and signaling of a panel of ovarian cancer cell lines in order to assess the association of drug response with pathway activation. This panel has been selected to represent a range of cell lines containing mutations in PTEN and PI3K as well as wild-type models which are commonly found in ovarian cancer clinical samples. A reverse phase protein array (RPPA) strategy is being used as a high throughput proteomic approach to study dynamic changes in cell signaling over multiple time points. Antibodies to phospho-activated proteins are being used to assess response and include pAKT(Ser473), pERK (Thr202/Tyr204), pPTEN (Ser380/Thr382/383), pmTOR(Ser2448) and pS6K1 (Thr421/Ser424). Initial results indicate that heregulin stimulation of pAKT is enhanced by Rapamycin in the PE04 and A2780 cell lines but inhibited by LY294002 and BEZ235. In contrast heregulin-stimulated activation of pERK is enhanced by LY294002 and Rapamycin in these two models. Heregulin-stimulated p-mTOR is reduced by BEZ235, but the effects of Rapamycin and LY294002 are more complex and time-dependent. We are using computational modeling of the pathway to help identify the usage of feedback loops and also biomarkers that best identify the nature of the response.

16.00–16.15 **[O39]** ***Endometrial Cancer Biopsy Reporting – What is the Problem with Diagnosis?***

Ⓟ T Palmer[1]; N Wilkinson[1]; P Cross[2]; A Ralte[2]; B Williams[1]

[1]St James University Hospital, Leeds, United Kingdom; [2]Queen Elizabeth Hospital, Gateshead, United Kingdom

Endometrial carcinoma is the most common malignancy of the female genital tract and the incidence is increasing in part due to an increasing prevalence of the metabolic syndrome. Appropriate staging and treatment is dependent on the accuracy of biopsy diagnoses; the criteria for the diagnosis of atypical complex hyperplasia (ACH) and endometrial carcinoma are associated with significant intraobserver and interobserver variation.

Aim: to establish the level of consistency in diagnosis of ACH and endometrial carcinoma referred into the regional cancer centres.

Method: comparison of the original and review diagnoses for all endometrial biopsies for cases referred to the multidisciplinary team meetings at two large UK regional cancer centes during 2010. When the patient underwent definitive surgery, the final hysterectomy diagnosis was recorded.

Results: 288 biopsies were reviewed; the original and review diagnoses correlated in 204 (70.4%) cases. Three problematic areas were identified:

- cases of endometrioid adenocarcinoma were reported as ACH
- there was under-grading of endometrioid carcinoma
- type 2 carcinomas were not always recognised.

Hysterectomy diagnoses were available for 208 of the cases reviewed; the diagnoses in these specimens matched the review biopsy diagnoses in 76% of cases compared to 59% of the original biopsy reports.

Discussion: the diagnostic issues identified are thought to have arisen due to a combination of poor reproducibility of the current diagnostic criteria and de-skilling of non-specialist cancer unit pathologists. As histological misinterpretations such as those identified above can lead to significant patient mismanagement, cognisant of the poor reproducibility of the diagnostic criteria for endometrial carcinoma vs ACH, we recommend an alternative approach for management of these patients such that the correct surgical procedure is performed. We discuss an approach to the diagnosis of type 2 carcinomas.

16.15–16.30 **[O40]** ***Insights into the Epigenetic Regulation of HPV16 Oncogene Expression During Cervical Carcinogenesis***

IJ Groves; CG Scarpini; MR Pett; D Ward; Ⓟ N Coleman

University of Cambridge, Department of Pathology, Cambridge, United Kingdom

Cervical squamous carcinogenesis is characterised by deregulated expression of high-risk human papillomavirus (HRHPV) early genes in basal epithelial cells, usually as a result of virus integration into host DNA. Multiple integration events may occur in a mixed population of HRHPV-infected cells, with subsequent clonal selection of the virus integrant that provides the greatest growth advantage. However, the factors that provide a competitive advantage to a particular integrant in a mixed cell population remain poorly understood.

We used the W12 model system to investigate mechanisms of transcriptional deregulation of integrated HPV16 during cervical carcinogenesis. From a single parental population of cervical keratinocytes naturally infected with extra-chromosomal (episomal) HPV16, we generated a panel of 24 isogenic clones that differed only by the site of HPV16 integration into host chromosomes. The integration sites observed were typical of those seen in cervical carcinomas in vivo. Across all clones suitable for analysis, levels of virus oncogene transcription per DNA template varied ~40 fold, with only ~30% of clones showing significantly greater oncogene expression than the episome-containing parental cells. Detailed epigenetic profiling of the HPV16 long control region (LCR; 850bp) showed that virus oncogene expression levels correlated with multiple chromatin modifications and with RNA polymerase-II recruitment and activation. These data indicate that different levels of HPV16 oncogene expression from integrated virus DNA are associated with epigenetic changes at the LCR and that integration does not necessarily lead to elevated oncogene levels. The epigenetic modifications associated with high E6/E7 expression are novel therapeutic targets in cervical carcinoma cells.

WEDNESDAY 19 JUNE — *continued*

▶ 17.30 – 19.30 **Lomond Suite – Level 0**

CHAIRMAN'S POSTER ROUNDS
DRINKS RECEPTION

CATEGORY	POSTER NUMBER	CHAIR
Autopsy/Forensic	P1–P8	Dr EW Benbow, Manchester and Dr C Bryce, Edinburgh
Breast	P9–P25	Prof AM Hanby, Leeds and Dr J Thomas, Edinburgh
Cardiovascular/Pulmonary	P26–P29	Dr T Helliwell, Liverpool and Dr H Monaghan, Edinburgh
Head and Neck	P30–P34	
Cellular/Molecular Pathology	P35–P43	Dr RJ Byers, Manchester and Dr S Langdon, Edinburgh
Experimental Tumour Pathology	P44	
Technical Advances	P45–P47	
Education and Audit	P48–P55	Dr M Mathers, Edinburgh and Dr H Shawki, London
Gastrointestinal	P56–P65	Prof RFT McMahon, Manchester and Dr D Worrall, Edinburgh
Hepatobiliary/Pancreas	P66–P67	
Genitourinary/Renal	P68–P79	Dr C Bellamy, Edinburgh and Prof S Fleming, Dundee
Gynaecological	P80–P86	Dr KE Robertson, Edinburgh and Dr ARW Williams, Edinburgh
Lymphoreticular	P87–P94	Dr RJ Byers, Manchester and Dr N Rooney, Bristol
Neonatal/Paediatric	P95–P97	Dr A Biswas, Edinburgh and Dr P Ramani, Bristol
Neuropathology/Ophthalmic	P98	
Skin	P99–P102	
Osteoarticular/Soft Tissue	P103–P112*	Prof AM Flanagan, London and Prof D Salter, Edinburgh

** P111 has been withdrawn*

THURSDAY 20 JUNE

08.00 — **Reception**

REGISTRATION and COFFEE

08.45 – 18.00 — **Ochil 3 – Level 1**

SLIDE SEMINAR CASE COMPETITION VIEWING
Inflammatory Skin Pathology
Please note: Competition closes at 15.30 on Thursday 20 June

09.00 – 17.00 — **Harris – Level 1**

COMPANION MEETING
Association of Clinical Electron Microscopists (ACEM)
See separate programme *(all are welcome to attend)*

09.00 – 10.30 — **Ochil 1 and 2 – Level 1**

ORAL COMMUNICATIONS
Categories: *Gastrointestinal; Cellular/Molecular; Skin*
Chair: Dr T Brenn, University of Edinburgh
Prof NA Shepherd, Gloucestershire Cellular Pathology Laboratory, Cheltenham

09.00–09.15 **[O43]** ***Are We Following Royal College Guidelines for Colorectal Cancer Reporting? A Completion of Audit Cycle***

K Gopalakrishnan;Ⓟ A Azam

University Hospitals Coventry & Warwickshire, Coventry, United Kingdom

Objectives: (1) Are we complying with minimum dataset for colorectal cancer reporting as per the Royal College of Pathologists' guidelines? (2) Comparison of the results with previous audit.
Standards & Target: All the colorectal cancer resection reports should follow the minimum dataset by RCPath. This includes documentation of all the parameters in the dataset. The target for each parameters was set at 100%.
Methodolgy: Type of audit: Retrospective, Time period: From Nov 2011-Dec 2012 (14 months) 6 months after the previous audit, Inclusion criteria: All cases of colorectal cancer resection reported at GEH, Exclusion criteria: none, Data source: SNOMED codes & Pathology ULTRA system for retrieving, Audit tool: Excel spreadsheet.
Results: A total of 67 colorectal cancer resections were reported from 01/11/2011 to 24/12/2012 (14 months) by five pathologists at GEH. The mean age of these patients was 66.5 years (Range 43-90 years). Male to female ratio was about 1:1 (34:33), The findings were recorded as follows: A) Clinical details: All clinical details were mentioned in all reports.B) Macroscopic description: The site of tumour and maximum diameter was mentioned in 100% of the cases. Relation of tumour to APR was mentioned in all rectal tumours however TME was not graded in 2/16 cases. C) Microscopic description: The type of tumour and local invasion was mentioned in all of these reports . However, tumour differentiation and maximum distance of spread beyond MP was not mentioned in 3/67 reports (4.5%). D) Pathological staging: Complete resection at all surgical margin was omitted in 7 out of 53 reports (13%), In 14of them, although it is mentioned that histologicaly there is no distance metastasis but M doesn't mentioned in TNM staging. Conclusion:The overall target of 100% was only achieved in 17/28 core items. There was better reporting in all areas but we can improve in few areas, Maximum distance beyond MP, Plane of surgical excision, Distance to nearer cut-end.

09.15–09.30 **[O44]** ***Mathematical Modelling of Murine Stem Cells in Intestinal Epithelium and Adenomas***

S Kozar;Ⓟ E Morrissey; R Kemp; S Tavaré; L Vermeulen; D Winton

Cancer Research UK Cambridge Institute, Cambridge, United Kingdom

The intestinal epithelium is characterised by rapid cellular turnover sustained by stem cells located at the base of glandular crypts. Though the intestinal stem cells are known to reside at the base of the crypts, it is unclear exactly where at the base they reside. Based on marker expression and location, several different populations have been put forward as intestinal stem cells.
In this talk we will describe the use of a novel marker-free strategy, which in combination with mathematical modeling allows us to predict stem cell numbers and dynamics.
We first apply our approach to intestinal epithelium and find that previously described neutral dynamics of intestinal stem cell replacement remain constant with age. We also show that there are significant regional differences in stem cell number and rate of stem cell replacement along the length of the intestine.
We then apply our model to intestinal adenomas and show that the adenomas are fuelled by a small number of stem cells with an accelerated replacement rate.

09.30–09.45 **[O45]** ***STAT3 Exerts a Paradoxical Effect on β-Catenin Expression and Function***

S Ibrahem;Ⓟ S AlGhamdi; K Baloch; B Mohamed; W Fadhil; D Jackson; AS Nateri; M Ilyas

University of Nottingham, Nottingham, United Kingdom

We have previously shown that STAT3 can regulate Wnt signalling through altering levels of β-catenin transcription in five different colorectal cancer (CRC) cell lines. In this study, we extended these studies to include another four cell lines and investigated the biological interaction of the Wnt and STAT3 signalling pathways. STAT3 and β-catenin were individually knocked down in a total of nine different CRC cell lines. The effects of knockdown of each gene on the mRNA and protein levels of the other gene were assessed. These effects were validated by modulation of STAT3 signalling and Wnt signalling through IL-6 stimulation and dominant-negative (DN)-TCF4 expression respectively. The biological interaction between STAT3 and Wnt signalling was tested by knocking down STAT3 and β-catenin individually and in combination in the CRC cell line SW620 and testing the effects on cell proliferation, apoptosis and motility. STAT3 knockdown resulted in a reduction in β-catenin mRNA and protein levels. In contrast, neither β-catenin knockdown nor DN-TCF4 expression affected STAT3 levels. STAT3 activation with IL6 resulted in increased β-catenin mRNA. Knockdown of β-catenin and STAT3 individually inhibited cell proliferation although the effect of β-catenin knockdown was more pronounced. Simultaneous knockdown of STAT3 and β-catenin had a significantly weaker effect than knockdown of β-catenin alone . Knockdown of STAT3 and β-catenin, individually and together, inhibited cell motility but there was no evidence of interaction. β-catenin is in part transcriptionally regulated by STAT3 resulting in altered levels of β-catenin protein. Conversely β-catenin does not regulate STAT3. The biological interaction between STAT3 and β-catenin is complex but may result in partial loss of the proliferative activity of β-catenin. This may indicate biological differences in tumours where both STAT3 and β-catenin are activated compared to those where only one of these is activated.

09.45–10.00 **[O46]** ***P63 and NF-KB Expression in Primary Cutaneous B-Cell Lymphomas; Correlation with Proliferation and Further Evidence for Pathogenetic Heterogeneity***

Ⓟ Z Shukur[1]; P Coates[2]; A Subtil[3]; W Kempf[4]; D Sahni[5]; S Morris[1]; A Robson[1]

[1]St John' Institute, St Thomas' Hospital, London, United Kingdom; [2]University of Dundee, Dundee, United Kingdom; [3]Yale University, New Haven, United States; [4]University of Zurich, Zurich, Switzerland; [5]Boston University, Boston, United States

Over-expression of the transcriptional activator p63 has been demonstrated in various tumours, although it is not clear whether p63 halts or enhances tumour growth. Through alternate promoters the TAp63 isoform transactivates p53 target genes and induces apoptosis, whereas the delta-Np63 isoform conveys a dominant-negative effect on p53/TAp63. p63 expression in nodal follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) has been correlated with proliferative index and mortality. Constitutive activation of the NF-KB signaling pathway is a key feature of DLBCL lymphomagenesis. However, the significance of p63, whether it correlates with proliferative index, and any relationship with NF-KB, in cutaneous B-cell lymphoma has yet to be elucidated. We assessed p63, NF-KB and Ki-67 expression in primary cutaneous follicle centre cell lymphoma (pcFCCL) and diffuse large B-cell lymphoma, leg type (DLBCLL), which differ morphologically, immunophenotypically and prognostically. Using a generic p63 antibody 16/21 DLBCLL cases had diffuse strong expression, compared with only 3/16 pcFCCL (p=0.002). Further labelling of 8 DLBCLL and 5 pcFCCL using an antibody specific to the delta-Np63 isoform failed to show expression, indicating the observed expression was of TAp63. Ki-67 staining was stronger in p63 positive cases (p=0.005) suggesting an association with proliferative index. Staining for NF-KB revealed no statistically significant difference (p=0.371) in expression in DLBCLL (4/19 positive) compared with pcFCCL (1/9 positive), although all NF-kB positive cases showed strong expression of p63. This study suggests that p63 expression, specifically the TAp63 isoform, differs in pcFCCL and DLBCLL. Furthermore p63 expression appears to correlate with proliferative index. This emphasises the different biology of these lymphomas, and might reflect one mechanism for their disparate clinical behaviour.

10.00–10.15 **[O47]** ***Immunocytochemical Expression of IMP-3 by Dysplastic Epidermis and Cutaneous Squamous Cell Carcinoma: A Novel Biomarker Associated with Invasion and Aggressive Disease***

Ⓟ K Aljefri[1]; MS Ally[2]; H Fassihi[3]; N Attard[3]; F Lewis[3]; J Mellerio[3]; C D'Arrigo[4]; L Igali[5]; A Robson[6]

[1]Newcastle Royal Infirmary, Newcastle, United Kingdom; [2]Stanford University, Stanford, United States; [3]St John's Institute of Dermatology, London, United Kingdom; [4]Dorset County Hospital Histopathology Department, Dorchester, United Kingdom; [5]Histopathology Dept Norfolk & Norwich University Hospital, Norwich, United Kingdom; [6]Dermatopathology Dept, St John's Institute of Dermatology, London, United Kingdom

Purpose: Insulin-like growth factor II mRNA-binding protein 3 (IMP-3) is an oncoprotein important in cell growth and migration in foetal development. Lu et al reported that IMP-3 expression in dysplastic cervical lesions is closely associated with their invasive potential, and with more aggressive clinical behaviour of cervical squamous carcinoma. To date, reports have been limited to cervical, renal, urothelial carcinomas and malignant melanoma. We studied the expression of IMP-3 by a series of 116 dysplastic and/or invasive squamous lesions of the skin. These included 47 dysplastic or in-situ (SCCIS) of various types and 62 squamous cell carcinomas (SCC), 13 of which had a co-existing in-situ component.
Methods: Paraffin-embedded blocks were retrieved from the departmental archives, processed and stained with IMP-3 (Dako, IgG monoclonal 69.1, dilution 1/100, EDTA antigen retrieval pre-treatment). The stained slides were then reviewed for presence and location of immunostaining.
Results: Six of 47 dysplastic lesions or SCCIS had diffuse strong IMP-3 expression and 4 of these had adjacent normal epidermis that was immuno-negative. Four vulval lesions were negative. The 5 examples of PUVA-induced dysplasia were negative. IMP-3 expression was significantly more common in the SCC group in

comparison to SSCIS/benign lesions (p<0.0088) Twenty-nine of 62 SCC had expression of IMP-3, usually strongly and diffusely, including 2 of 6 tumours arising following renal transplantation. Five of 10 SCC's arising in epidermolysis bullosa (EB) were positive; Follow-up data is currently being retrieved but, thus far, 2 of the positive cases were metastatic lesions and 3 of the EB patients with positive tumours have died of widespread malignancy.
Conclusions: Expression of the oncoprotein IMP-3 is associated with invasive but not in-situ squamous cell carcinomas, and IMP-3 expression is associated with aggressive SCC.

10.15–10.30 **[O48]** ***A Structured Approach to the Diagnosis of Borderline Melanocytic Skin Lesions***

Ⓟ N Kirkham[1]; Y Bury[1]; N Thampy[1]; S Upadhye[2]

[1]Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom; [2]Northumbria Healthcare NHS Trust, North Shields, United Kingdom

In 3 areas the RCPath recommends double reporting of biopsies: (1) for high grade dysplasia of Barrett's oesophagus and inflammatory bowel disease (2) for pT1 cancers in the Bowel Cancer Screening Programme (3) cutaneous melanocytic dysplasias (melanomas and severely atypical naevi).
Recently the RCPath reported that '*Double-reporting may be misconstrued as providing an independent expert opinion, whereas having the opinion of a second individual who is not a specialist in a particular field may inappropriately reinforce the views of the first pathologist. Most importantly, double-reporting does not prevent false negative* (or false positive) *reporting of biopsies*'. Detailed guidance is strikingly absent on how to recognise and categorise these dysplasias and achieve a reproducible final diagnosis. Over recent decades there has been a striking increase of diagnoses of Stage 1 melanoma that has not been matched by an accompanying increase in mortality, suggesting the possibility of a degree of over-diagnosis: of the mis-classification of pre-tumourous melanocytic proliferations as melanoma. In this study a structured approach to diagnosis was devised using a list of 15 morphological variables described in a recent review of *Dysplastic Naevi*. Each of the 15 variables was scored on a 5-point scale using the morphological definitions given in the review, from benign naevus, through dysplastic naevus, to melanoma, with uncertainty catered for by allowing scoring between each of the three major categories. 10 slides of thin melanomas and atypical naevi were scored blind, without clinical information. On the basis of the pattern of scores achieved a final diagnosis was then made based on the balance of scores achieved across the 15 features. This combination of a structured approach, clearly described criteria and multiple variables achieved a good level of intra- and inter-observer agreement and is readily applicable to routine diagnostic practice.

10.30–11.00 **REFRESHMENT BREAK** **[Lomond Suite – Level 0]**

▶ 09.00 – 12.30 — Fintry – Level 3

SYMPOSIUM
Investigative Imaging
Chair: Prof M Ilyas, University of Nottingham
Dr ARW Williams, University of Edinburgh

09.00–09.30 **[S29]** ***Development of Fluorescence Imaging Technologies as Preclinical Tools in Oncology***

Ⓟ Dr VG Brunton

University of Edinburgh, Edinburgh, United Kingdom

A major challenge in cancer research is to reduce cancer cell survival in the tumour niche and prevent tumour spread. In reductionist terms, this means stopping the cancer cells breaking free as isolated cells, or groups of cells that migrate collectively, preventing local invasion or the initiation of new metastases. In common with other hallmarks of cancer, understanding and inhibiting invasion and metastasis is complicated by the multiplicity of mechanisms, the plasticity of cancer cell behaviour and the evolving nature of the microenvironment. Our research has focused on understanding the adhesion network that drives metastatic spread using protein/peptide technologies, genetic intervention and quantitative intravital imaging that permits visualization of multiple cancer cell phenotypes in vivo using mouse models. Use of intravital fluorescence microscopy through optical windows provides robust and quantitative read-outs of cancer cell behavior, such as invasion and proliferation, cell-cell adhesion dynamics and the intracellular movement and activity of cancer-associated proteins. More recently we have coupled two-photon excited fluorescence (TPEF) microscopy with Coherent Anti-stokes Raman Scattering (CARS). CARS is a form of 'fast acquisition' Raman spectroscopy that allows visualisation based on the vibration of particular chemical bonds. In principal, this will permit label-free imaging in a number of contexts, such as disease versus normal tissue and drug imaging based on distinct Raman spectral properties. We are developing the use of this multi-modal intravital imaging approach to image drug uptake, localisation and retention times in vivo which can be correlated with markers of response and phenotypic outcome using fluorescence reporters of cell cycle arrest, apoptosis and invasion that we have developed. We hope that this will provide a comprehensive approach to select optimal novel agents and combinations to take forward into the clinic.

09.30–10.00 **[S30]** ***Imaging Inflammation and Tracking Macrophages with MRI Using Ultra-Small Particles of Iron Oxide (USPIO)***

Ⓟ Dr SIK Semple

University of Edinburgh, Edinburgh, United Kingdom

A novel class of magnetic resonance imaging (MRI) contrast agent consist of ultra-small superparamagnetic particles of iron oxide (USPIO). Because of their size (commonly 10-30nm in diameter), after intravenous

administration these particles escape immediate detection by the reticuloendothelial system and persist for long enough in the blood stream to undergo macrophage phagocytosis. USPIO-MRI therefore presents a non-invasive methodology for macrophage tracking throughout the body, and can be used to asses accumulation within vascular and lymphatic tissues. These particles have been used to investigate joint inflammation or infection, as well as in a range of cardiovascular diseases. Non-invasive assessment of macrophage uptake has been successfully demonstrated in carotid plaque, abdominal aortic aneurysms and in the myocardium following acute infarction and coronary bypass. The non-invasive nature of the technique potentially allows monitoring of inflammatory progression in the acute or chronic state, as well as response to anti-inflammatory therapy. Due to the superparamagnetic nature of these particles, they have an extremely strong effect on the local magnetic field homogeneity resulting in localized signal reduction and change in the magnetic relaxation time T2*. Darker areas are seen around areas of USPIO accumulation on T2*-weighted images. Several groups have developed methodologies to 'quantify' the amount of signal loss through mapping of local changes in T2* which is affected by the presence of USPIO. This presentation summarises the theory behind the technique, presents some recent and currently ongoing applications and discusses potential further applications and developments in this field. Our group have developed a methodology which combines imaging before and after administration of the USPIO agent, spatial registration of the resulting images and quantitative analysis of USPIO uptake. This methodology will be presented.

10.00–10.30 **[S31]** ***Imaging Vascular Calcification and Inflammation Using PET/CT***

Ⓟ Dr MR Dweck

Royal Infirmary of Edinburgh, Edinburgh, United Kingdom

In this talk we will examine how combined positron emission and computed tomography can be used to image calcification and inflammation in the aorta, aortic valve and coronary arteries. We will examine the novel insights that this technique has provided as to the pathophysiology of aortic stenosis and atherosclerosis, how it may prove a useful biomarker of disease activity and its potential to improve risk prediction.

10.30–11.00 **REFRESHMENT BREAK** **[Lomond Suite – Level 0]**

11.00–11.30 **[S32]** ***Imaging and the Autopsy***

Ⓟ Prof ISD Roberts

Oxford University Hospitals, Oxford, United Kingdom

Postmortem imaging is frequently used as a supplement to dissection in the forensic autopsy. CT in particular is sensitive for the detection of fractures, haemorrhage and foreign bodies. Imaging is non-destructive and provides a permanent record of injuries that may be used in court. More recently, imaging has been used as an alternative to traditional Coroner's autopsy. A postmortem MRI service was set up in Manchester in the 1990s in response to a demand from the Jewish community. A cause of death is provided on the basis of MRI without autopsy and accepted by the Coroner in >90% of cases. However, recent validation studies, comparing imaging with full autopsy, have demonstrated postmortem MRI has major weaknesses and will fail to identify the correct cause of death in >40% of Coronial referrals. CT is superior in identifying the cause of death in adults, and when radiologists are confident in the imaging cause of death, there is almost 90% agreement with that based on autopsy. Postmortem MRI and CT have a number of important weaknesses, notably inability to visual coronary artery occlusion. A method of targeted postmortem CT coronary angiography has been developed that appears to be superior to dissection in the visualisation of coronary artery lesions. Trial of a minimally invasive autopsy service employing CT and coronary angiography for investigation of sudden adult deaths referred to the Oxfordshire Coroner achieved a 70% reduction in the number of autopsies required. In this series, imaging detected fractures that were missed at autopsy, changing an apparently natural cause of death to an accidental verdict. If the Oxford postmortem imaging protocol were introduced into routine service, it would reduce the number of Coroner's autopsies by over half and improve the quality of those that are performed; imaging findings can be used to direct dissection and audit autopsy standards.

11.30–12.00 **[S33]** ***Nanoscale Morphomics – Recent Advances with Potential Application in Pathology***

Ⓟ Dr JM Lucocq

University of St Andrews, St Andrews, United Kingdom

Electron microscopy (EM) has undergone a revival of late. The increased use of EM in cell and systems biology is linked to developments that enable widescale quantitation of molecules and nanostructures. These quantities can now be connected to the real 3D data set (the morphome) via rigorous sampling schemes. In this lecture I will explore the state of the art in nanoscale morphomics and speculate on how it might interface with recently developed approaches in electron tomography and dynamic light microscopy.

12.00–12.30 ***Microbubbles in the Identification of the Sentinel Node as an Outpatient Procedure***

Ⓟ Miss K Cox

Maidstone and Tunbridge Wells NHS Trust, United Kingdom

SYMPOSIUM

Bone and Soft Tissue

Chair: Prof D Salter, University of Edinburgh
Prof AJ Freemont, University of Manchester

09.00–09.35 **[S34]** ***Update on Molecular Pathology in Diagnosis and Classification of Soft Tissue Tumours***

Ⓟ Prof C Fisher

Royal Marsden Hospital, London, United Kingdom

Soft-tissue tumours are increasingly associated with genetic aberrations. These fall into three groups. The largest has non-specific genetic alterations and complex karyotypes; most are pleomorphic high-grade sarcomas. The second group, including benign and malignant neoplasms, have diagnostically useful, consistent translocations forming chimeric fusions. Many are long-known, but recently discovered examples include USP6-MYH9 in nodular fasciitis, NAB2-TAT6 in solitary fibrous tumour, WWTR1-CAMTA in epithelioid haemangioendothelioma, EWSR1-POU5F1 in myoepitheliomas, and CIC-DUX4 in small round cell tumours. A gene can pair with various partners. Thus, EWSR1 is rearranged in Ewing sarcoma, desmoplastic small round cell tumour, extraskeletal myxoid chondrosarcoma, or myxoid liposarcoma; and ALK partners with one of several genes in inflammatory myofibroblastic tumour. Conversely, the same translocation can occur in different tumours. EWSR1-CREB1 fusions occur in clear cell sarcoma, angiomatoid fibrous histiocytoma, and primary pulmonary myxoid sarcoma. The third group has non-translocational abnormalities, including somatic mutations (e.g. KIT/PDGFRA in GISTs) that affect signalling pathways; and copy-number abnormalities, such as MDM2, CDK4 and HMGA2 amplification in well-differentiated liposarcoma. Further changes characterise grade progression such as in dedifferentiated liposarcoma. Among benign tumours, mammary-type myofibroblastoma, spindle cell lipoma and cellular angiofibroma are genetically similar. Furthermore, different genetic aberrations can produce different entities within a specific lineage, such as myofibroblastic or fibroblastic neoplasms. Sequencing methods show additional alterations in specific genes.e.g PIK3CA in myxoid/round cell liposarcoma, JUN in dedifferentiated liposarcoma, and TSC2 in PEComa. Knowledge of molecular mechanisms could influence classification and improve targeted therapy.

09.35–10.10 **[S35]** ***Implant-Related Pathology***

Ⓟ Prof NA Athanasou

Nuffield Orthopaedic Centre, Oxford, United Kingdom

Histopathology plays a major role in the assessment of implant failure. Aseptic loosening, the most common cause of arthroplasty failure, usually occcurs several years after the implant has been in place and functioning reasonably. The production of implant-derived wear particles induces a pronounced foreign body macrophage and giant cell response. Wear particle - associated macrophages are capable of differentiating into osteoclasts by RANKL and non-RANKL (pro/inflammatory cytokine)-induced mechanisms, leading to extensive osteolysis around the prosthesis and implant loosening. Implant failure and the formation of necrotising granulomatous pseudotumours have been associated mainly with cobalt-chrome (Co-Cr) metal on metal implants. Production of very large numbers of submicron Co-Cr particles induces necrosis of the macrophages which have ingested the particles, marked connective tissue degeneration and a hypersensitivity reaction characterised by a perivascular lymphoid infiltrate that can be very pronounced; these changes can result in the formation of a tumour-like mass. Histopathology is often required to distinguish septic from aseptic loosening as this requires very different treatment. Septic loosening may be acute, sub-acute or late (occurring more than two years after joint replacement). The presence of more than five neutrophils per HPF on average (after examination of at least 10 HPF) is diagnostic of septic loosening. Fewer neutrophils (1-5 per HPF on average) may be found in low-grade infection. Similar inflammatory changes can be seen in periprosthetic tissues from rheumatoid joints and joints with crystal deposition. In all cases of implant-related pathology it is important to correlate clinical and other findings with histology to identify the cause of arthroplasty failure.

10.10–10.45 **[S36]** ***Paget's Disease of the Bone: New Insights from Genetic Studies***

Ⓟ Dr OME Albagha

University of Edinburgh, Edinburgh, United Kingdom

Paget's disease of bone (PDB) is a common disorder of the skeleton that affects up to 2% of individuals of European ancestry. The disease is characterized by focal areas of increased and disorganized bone remodelling leading to symptoms such as bone pain, bone deformity, pathological fracture, deafness and secondary osteoarthritis. PDB predominantly affects the axial skeleton of individuals above the age of 55 years. Genetic factors are important contributors to PDB risk, and between 15% and 40% of individuals with PDB have an affected first-degree relative. Mutations in *SQSTM1* have been identified in about 10% of sporadic cases and up to 40% of familial cases. Mutations of *SQSTM1* in PDB patients causes disruption in the NFκB signalling pathway leading to enhanced osteoclastogenesis. Recent genetic studies have identified seven additional genetic loci that were associated with increased risk of PDB. Genetic variants within or near *CSF1, TM7SF4, OPTN, RIN3, PML, TNFRSF11A,* and *NUP205* were found to increase the risk of PDB in many European populations (Albagha *et al,* Nat Genet 2011). Some of these genes are known to play important roles in osteoclast differentiation and function (*CSF1, TNFRSF11A, and TM7SF4*) but others (*OPTN, RIN3, PML and NUP205*) highlight new signalling pathways in PDB pathogenesis. Patients with high number of risk alleles defined by the seven loci had 10-fold increase in disease risk compared to those carrying low number of risk alleles suggesting that these variants could be useful in genetic profiling to identify people at high risk of developing PDB. In summary, recent genetic studies have provided new insights into the pathogenesis of PDB and identified several genes that were not previously suspected to play a role in bone metabolism.

THURSDAY 20 JUNE — *continued*

10.45–11.15 **REFRESHMENT BREAK** [Lomond Suite – Level 0]

11.15–11.50 **[S37]** ***Genomic Profiling of Bone Tumours – What it Adds to Patient Management***

Ⓟ Prof AM Flanagan

UCL Cancer Institute, London, United Kingdom

The Wellcome Trust Sanger Institute is currently funding the comprehensive genetic, epigenetic and transcriptomic profiling of 500 primary bone tumours as part of the International Cancer Genome Consortium (2011–2016). This group of tumours, comprising a number of subtypes, represents less than 1% of all cancers, and includes osteosarcoma, chondrosarcoma, chordoma, adamantinoma amongst others. The rarity of the disease and the wide range of histological features mean that providing a diagnosis on core biopsies is challenging. Distinguishing chondrosarcoma from osteosarcoma, and benign from malignant primary bone tumours on microscopic features alone is often impossible. Whereas immunohistochemistry has provided little help in classifying primary bone tumours, genomic and epigenetic profiling of these neoplasms is revealing hallmarks of this disease. Recent studies on chondrosarcoma are already having an impact on how we diagnose these tumours, and this is reducing the diagnostic challenge that histopathologists have faced until now. Using archived collections of these rare tumours it will now be possible to correlate the genetic signatures with clinical outcome, and it is possible for the first time to select patients with bone tumours for clinical trials on the basis of a biological rationale.

11.50–12.25 **[S38]** ***In Vitro and In Vivo Models in the Study of Bone Sarcomas***

Ⓟ Prof JVM Bovee

LUMC, Leiden, Netherlands

In vitro and in vivo models are essential to translate basic research findings to clinical practice. Over the past decade, our knowledge regarding the genetic background and active signalling pathways in bone sarcomas has increased. In order to use these findings for the treatment of these patients, often carrying a poor prognosis, the availability of preclinical models is crucial. Several human derived osteosarcoma, chondrosarcoma and Ewing sarcoma cell lines are available, enabling the study of many cellular processes. A panel of cell lines should be used representative of the heterogeneity observed in human tumours. Furthermore, in vitro models include mesenchymal stem cells that can differentiate towards bone, cartilage and fat. For instance, using 3D pellet culture of mesenchymal stem cells, chondrospheres can be generated that histologically strongly resemble low grade chondrosarcoma. 3D pellet culture of chondrosarcoma cell lines histologically resemble high grade chondrosarcoma. Moreover, mouse mesenchymal stem cells can undergo malignant transformation forming high grade osteosarcoma upon transplantation into mice, providing an excellent model to study osteosarcomagenesis. In vivo animal models have been useful mechanistically, providing further understanding of pathogenesis, and preclinically, in evaluating the effect of novel therapeutic strategies. Xenografts of human tumour cells into immunocompromised mice are most commonly used. Cells are injected either subcutaneously enabling evaluation of the tumor mass by papation or simple measurements, or bioluminescent orthotopic mouse models are being used. Moreover, genetic mouse models of disease are being developed. As an alternative to mouse modelling, zebrafish provide a suitable in vivo model enabling xenografting as well as genetic engineering. Xenografting in a zebrafish embryo model enables the study of tumor cell homing, proliferation, migration and angiogenesis only 3 days after tumour grafting.

▶ 12.30 – 14.00 **Lomond Suite – Level 0**

LUNCH
POSTER VIEWING AND TRADE EXHIBITION

▶ 13.00 – 14.00 **Carrick – Level 1**

TRAINEES – MEET THE EXPERTS
Medical Renal Pathology
Chair: Dr A Green, Guys and St Thomas' NHS Foundation Trust
Speaker: Prof ISD Roberts, Oxford University Hospitals

▶ 13.30 – 14.30 **Fintry – Level 3**

PATHOLOGICAL SOCIETY OF GREAT BRITAIN & IRELAND'S ANNUAL BUSINESS MEETING
— Members only
(Agendas will be sent separately to Members)

PLENARY ORAL PRESENTATIONS

Chair: Prof IO Ellis, University of Nottingham
Prof ISD Roberts, Oxford University Hospitals, Oxford

14.45–15.00 **[PL1]** ***High-Throughput Assessment of MicroRNA Expression in Normal Breast Tissues and in Lesions Representing Different Stages of Breast Cancer Progression***

Ⓟ SM Khoshnaw[1]; JS Reis-Filho[2]; MB Lambros[2]; G Ball[3]; EA Rakha[1]; TM Abdel-Fatah[1]; CC Nolan[1]; Z Hodi[1]; DR Macmillan[1]; IO Ellis[1]; AR Green[1]

[1]Nottingham City Hospital, Nottingham, United Kingdom; [2]Breast Cancer Research Institute, London, United Kingdom; [3]Trent University, Nottingham, United Kingdom

Background: The expression profiling of miRNAs is deregulated in human breast cancer (BC), and the deranged expression has been revealed to be associated with tumour initiation and progression. Although the number of newly discovered human miRNA sequences is rapidly increasing, the availability of miRNA expression profiles in different stages of BC progression is limited.
Methods: miRNA expression profiling was explored in a series of BC patients (n = 7) with distinct stages of tumour progression (normal breast parenchymal tissue, ductal carcinoma in situ -DCIS, primary invasive BC and nodal metastatic BC), using an Agilent miRNA microarray which utilises miRBase 16 to screen for 1,205 human and 144 human viral miRNA candidates. The results from the microarray analysis were validated by TaqMan quantitative RT-PCR.
Results: In addition to confirming the previously reported deregulation of 20 miRNAs in BC, this study revealed 93 unidentified miRNA candidates to be deranged and differentially expressed across the different tissue components representing stages of BC progression. Among the novel miRNA candidates, 82 were downregulated and 11 were upregulated in BC. Seventeen of the downregualted miRNAs (hsa-miR-1915, hsa-miR-762, hsa-miR-3196, ebv-miR-BART13, hsa-miR-1224-5p, hsa-miR-1181, hsa-miR-940, hsa-miR-125a-3p, hsa-miR-874, hsa-miR-3137, hsa-miR-371-5p, hsa-miR-4322, hsa-miR-345, hsa-miR-557, hsv1-miR-H1, hsa-miR-3621 and hsa-miR-145) were progressively lost with BC progression. These differentially expressed miRNAs are potentially influential in the process of transition of cancer cells from one stage to a more advanced stage.
Conclusions: This study confirms previous BC miRNA profiling studies, and reports a set of novel miRNA candidates potentially involved in BC progression. This study further supports the role of miRNAs in BC progression.

15.00–15.15 **[PL2]** ***Breast Cancer Proteomic Profiling Using Reverse Phase Protein Array (RPPA)***

Ⓟ OH Negm[1]; AT Alshareeda[2]; MA Aleskandarany[2]; AG Green[2]; IO Ellis[2]; EA Rakha[2]; PJ Tighe[1]

[1]Molecular Medical Sciences, University of Nottingham, Nottingham, United Kingdom; [2]Division of Pathology, Molecular Medical Sciences, University of Nottingham, Nottingham, United Kingdom

Background and purpose: Reverse Phase Protein Array (RPPA) is a high-throughput technique that provides relative quantitative assessment of multiple known protein targets across a large sample set. In addition, it is applicable to detecting post-translational modifications and has great potential for biomarker analysis.
Methods: Testing the reproducibility and the validity of RPPA was performed before applying it in this study. After optimization, we applied RPPA to examine extracts of formalin-fixed paraffin-embedded human breast cancer (n=49) and cell lines (n=5) detecting a panel of 30 proteins involved in DNA damage repair and epithelial mesenchymal transition (EMT) pathways. RPPA results were compared to conventional immunohistochemical analysis (IHC) and clinicopathological variables.
Results: Testing the reproducibility and the validity of RPPA indicated high reproducibility with co-efficient of variation within the replicates less than 15% for all the analyzed samples. RPPA results revealed that the expression levels of biomarkers included in this study reiterate observations of relative distribution of these markers using IHC in fixed breast cancer tissue and were consistent with the investigated type of cell lines.
Conclusions: RPPA methodologies show good concordance with IHC analysis and therefore offer a viable route to very high throughput cancer sample analysis, applicable to both retrospective and prospective investigations.

15.15–15.30 **[PL3]** ***Clonal Evolution in a Highly Recurrent Astroblastoma of Childhood***

Ⓟ S Popov[1]; A Mackay[1]; W Ingram[2]; D Sturm[3]; A Burford[1]; A Jury[1]; M Vinci[1]; S Pfister[3]; C Jones[1]

[1]The Institute of Cancer Research, Sutton, United Kingdom; [2]University of Queensland, Royal Children's Hospital, Brisbane, Australia; [3]German Cancer Research Centre, Heidelberg, Germany

Astroblastoma is a rare glial tumour of unknown origin, with no established WHO grade, and controversial claims to being a distinct entity. These lesions are characterised by the presence of the astroblastic pseudorosettes composed of tumour cells with a prominent process extending to a central blood vessel and perivascular hyalinization. It is usually presented as a well-demarcated superficially located mass. These lesions most commonly present in children and young adults, and appear to have a reasonably favourable clinical outcome, with differential diagnoses including primitive neuro-ectodermal tumour (CNS-PNET), ependymoma, glioblastoma and embryonal tumour with abundant neuropil and true rosettes (ETANTR). There have been few molecular studies, though chromosomal abnormalities including gains of 9q and 20q, and losses of 13q have suggested a distinct biology. We have studied a unique case of astroblastoma arising in a 6 year old girl, with multiple recurrences over a period of 10 years, by whole exome sequencing and 450k Illumina methylation profiling. Initial presentation of a fronto-parietal tumour was followed after multiple rounds of surgery and chemoradiotherapy with recurrences in the left frontal, left parietal parafalcine, left temporal, sphenoid and

nasal locations. The tumours studied were not mutated for H3F3A/HIST1H3B, ATRX/DAXX, IDH1/2 or TP53, nor harboured amplification of 19q13.42. Copy number profiles showed gains of 9q and 15q, and losses of 9q, 10, 13q and 14q, with a high degree of divergence over each subsequent recurrence. A total of 331 somatic variants with a read depth of >10 in the germline were observed in any tumour sample. Of these, a core list of 29 genes were somatically mutated in all recurrences, indicating a common origin for all tumour samples. These data present a remarkably diverse clonal evolution of astroblastoma during childhood, and argue for its consideration as a distinct biological entity.

15.30–16.00 **REFRESHMENT BREAK [Lomond Suite – Level 0]**

16.00–16.15 **[PL4]** ***Diffuse Large B-Cell Lymphoma: Sub-Classification by Massive Parallel Quantitative RT-PCR***

Ⓟ X Xue[1]; S Barrans[2]; N Zeng[1]; L Worrillow[2]; MA Care[3]; RM Tooze[2]; Z Gao[4]; A Jack[2]; MQ Du[1]

[1]Division of Molecular Histopathology, Department of Pathology, University of Cambridge, Cambridge, United Kingdom; [2]Haematological Malignancy Diagnostic Service, St. James's Institute of Oncology, Leeds, United Kingdom; [3]Section of Experimental Haematology, Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom; [4]Department of Pathology, Health Science Center, Peking University, Beijing, China

Purpose of the study: Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous entity with remarkably variable clinical outcome. Gene expression profiling classifies DLBCL into activated B-cell like (ABC), germinal centre B-cell like (GCB) and type-3 subtypes, with ABC-DLBCL characterised by a poor prognosis and constitutive NF-κB activation. A major challenge for the application of this cell of origin classification in routine clinical practice is to establish a robust clinical assay amenable to routine FFPE (formalin-fixed paraffin-embedded) diagnostic biopsies. In recent studies, we have successfully applied Illumina whole genome DASL assay to RNA samples extracted from FFPE specimens and established a microarray platform-independent classification tool for DLBCL sub-classification. In this study, we investigated the possibility of DLBCL sub-classification by massive parallel quantitative reverse transcription PCR (qRT-PCR) using RNA samples extracted from FFPE biopsies.
Methods: We have systematically designed and validated PCR primers for all of the 27 LLMPP classifier genes and the 6 NF-κB targeted genes that characterise ABC-DLBCL, and established a protocol for massive parallel qRT-PCR using Fluidigm Dynamic Array.
Summary of results: Of the 21 cases of DLBCL investigated so far, for which ABC/GCB classification was available by Illumina DASL array, there was an excellent concordance (20/21=95%) in sub-classification between the Illumina DASL array and the qRT-PCR based approach. As expected, the NF-κB target gene expression is significantly higher in ABC than GCB-DLBCL.
Conclusions: With the inclusion of all of the 27 classifier genes and high sensitivity of PCR, the qRT-PCR based molecular subtyping offers a robust approach for DLBCL sub-classification using routine FFPE diagnostic biopsies.

16.15–16.30 **[PL5]** ***There are Significant Differences in Copy Number Variation Between Microsatellite-Stable and Instable Cases in Stage II/III Colorectal Cancer***

Ⓟ K Southward[1]; G Hutchins[1]; C Beaumont[1]; J Coffa[2]; D Kerr[3]; R Gray[4]; P Quirke[1]

[1]Leeds Institute of Molecular Medicine, Leeds, United Kingdom; [2]MRC-Holland, Amsterdam, Netherlands; [3]RDM Clinical Laboratory Sciences, Oxford, United Kingdom; [4]Clinical Trial Service Unit, Oxford, United Kingdom

Purpose of the study: Abnormalities of the mismatch repair (MMR) genes affect around 12% of colorectal cancers. We have investigated the frequency of chromosome gain and loss using Multiplex Ligation-dependent Probe Amplification (MLPA) in a series of stage II/III colorectal cancers divided into proficient (pMMR) and deficient MMR (dMMR).
Methods: 400 stage II/III colorectal tumours from the QUASAR-1 clinical trial were studied. MMR status was determined by immunohistochemistry of 2 MMR genes hMLH1 and hMSH2. Tumour DNA was extracted from a formalin-fixed paraffin-embedded block. Gain and loss of DNA was analysed using MLPA with simultaneous analysis of 46 probes associated with the development and progression of colorectal cancer. The reaction mix was run on a DNA sequencer and analysed using Coffalyser software.
Summary of results: 304 cases were pMMR, 48 dMMR. Data was unavailable for other cases. pMMR cases showed a significantly higher frequency of loss of sites on chromosomes 8p (p=0.0325), 17p (p=0.0497), 18q (p=0.0286) individually and losses of 17p and 18q (p=0.0477) arms when cases were stratified by MMR. Gains of EGFR (p=<0.0001) were significantly higher in pMMR than dMMR cases.
Conclusion: MLPA appeared a robust method for the cost effective (approximately £5 per case) simultaneous assessment of multiple genomic sites. pMMR cases showed an increased frequency of loss of 8p, 17p and 18q and gain of EGFR compared to dMMR cases.

16.30–16.45 **[PL6]** ***Development and Characterisation of a 3D Tri-Culture Model of Normal Breast as a Tool for Cancer Initiation Studies Shows Overexpression of Her2 and Her3 Alters 3D Epithelial Architecture***

Ⓟ CE Nash[1]; DL Holliday[1]; G Mavria[1]; D Tomlinson[1]; A Hanby[1]; F Berditchevski[2]; V Speirs[1]

[1]The University of Leeds, Leeds, United Kingdom; [2]University of Birmingham, Birmingham, United Kingdom

Multicellular 3D *in vitro* models of normal breast tissue to provide baselines for cancer initiation studies are lacking. We present a model incorporating 3 of the major functional cell types of breast, detail the phenotype and document our breast cancer initiation studies.

Myoepithelial cells and fibroblasts were isolated and immortalised from breast reduction mammoplasty samples collected with ethical approval and labelled with EGFP and dsRed proteins respectively for tracking. 3D collagen 1 cultures were established containing non—tumorigenic HB2 luminal epithelial cells, in parallel with HB2 overexpressing different Her family proteins, together with labelled myoepithelial cells and fibroblasts. Spheroids developed after 3 weeks in culture and were analysed and characterised by confocal microscopy and immunohistochemistry, comparing phenotype to normal breast tissue. Similar to normal breast tissue, immunohistological characterisation with a comprehensive biomarker panel showed polarised epithelial structures with lumen formation and basement membrane production. Quantification of spheroids showed an increased size upon Her2 and Her2/3 overexpression compared to controls (120% increase; p=<0.0001). These had significantly reduced circularity (p=<0.0001) and were less cohesive controls. Her3 overexpressing spheroids were also larger and maintained a more cohesive phenotype akin to controls. Spheroid number remained unchanged upon Her protein manipulation. We have developed a robust 3D tri—cellular model of normal breast which is amenable to quantitative comparable analysis after genetic manipulation of Her proteins. We have illustrated that Her2 overexpression alone or in combination with Her3 is sufficient to alter normal breast epithelial architecture in 3D, but this does not reflect disordered malignant cell phenotype. Going forward, our model is ideally suited to investigate stromal influence in this process.

16.45–17.00 **[PL7]** ***Multiscale Analysis of Colorectal Cancer Cell Lines***

Ⓟ R Briffa[1]; IH Um[2]; D Faratian[2]; Y Zhou[1]; DJ Harrison[3]

[1]The University of Edinburgh, Edinburgh, United Kingdom; [2]The University of Edinburgh No longer an employee, Edinburgh, United Kingdom; [3]University of St Andrews, St Andrews, United Kingdom*

Background: Selecting which colorectal (CRC) patients are likely to respond to therapy remains a challenge. Analysing signalling networks in their entirety at gene, transcript, and protein level is one approach to understanding mechanisms of resistance.
Methods: A panel of 15 CRC cell lines was profiled using array comparative genomic hybridisation, transcriptomics, reverse phase protein arrays, and targeted sequencing of *KRAS* hotspot mutations. Sensitivity to 5-fluoruracil, oxaliplatin, and BEZ-235 was established by calculating drug IC50s. We performed a systematic, array-based survey of gene expression and copy number variations and compared these to sensitivity to these agents. Amplifications of the *TRIB-1* and *MYC* loci were confirmed using FISH in a cohort of 118 CRCs: protein expression for Trib-1 and 14 associated biomarkers were measured by quantitative immunofluorescence.
Results: Frequently gained regions contained *EGFR*, *PIK3CA*, *MYC*, *SMO*, *TRIB-1*, *FZD1* and *BRCA2*, while frequently lost regions contained *FHIT* and *MACROD2*. Pathway analysis revealed significant enrichment for Wnt, EGF receptor, apoptosis, cell cycle, and angiogenesis-related genes in resistant lines. Stepwise integration of copy number and gene expression data yielded 47 candidate genes that were significantly correlated ($p \leq 0.05$) with drug effect. Amongst these, *TRIB-1* and *MYC* were overexpressed in 15.5% and 8%, respectively, and amplifications were significantly correlated ($p \leq 0.0001$). Trib-1 protein expression was significantly correlated ($p \leq 0.01$) with protein expression of pErk, Akt and Caspase 3.
Conclusions: A set of candidate predictive biomarkers for 5-FU, L-OHP, and BEZ235 have been described. *TRIB-1* in particular is a putative oncogene whose amplification we described for the first time in CRC. Inhibition of Trib-1 may be an attractive therapeutic approach, perhaps via a synthetic lethal mechanism with MYC.

17.00–17.15 **[PL8]** ***Methylation Patterns of Clonally-Related Hepatocytes Provide Evidence of a Periportal Stem Cell Niche in the Normal Human Liver***

J Gabriel[1]; TA Graham[2]; H Kocher[1]; NA Wright[1]; M Alison[1];Ⓟ SAC McDonald[1]

[1]Queen Mary, University of London, London, United Kingdom; [2]University of California, San Francisco, San Francisco, United Kingdom

The normal human liver shows little hepatocyte proliferation and there is no direct evidence for the presence of human hepatic stem cells. Animal studies have suggested the hepatic stem cell niche is located at the periportal region, specifically in the biliary epithelium, with hepatocytes 'streaming' from the portal tract to central vein (Zajicek 1985;5(6):293-300, Kuwahara et al, Hepatology 200847(6):1994-2002). Previously we have detected large clonal patches of hepatocytes in the normal liver where each cell within a patch shares a common somatic mitochondrial DNA (mtDNA) mutation, suggesting they originate from a single stem cell (Fellous et al., Hepatology 2009;49:1655). Here we use methylation patterns of CpG islands in promoters of non-expressed genes (*CSX* and *MYOD1*) as a marker of recent cellular ancestry in mutant clonal patches. Such patterns are somatically inherited at mitosis and change over time, as CpG sites become methylated or de-methylated, and the level of diversity (as determined by bisulpite sequencing) is related to how recently a clone was derived from its parent stem cell. We demonstrate that as clonal areas abutting the portal tract increase in size, their methylation diversity increases. This increase is not observed in patches abutting the central vein, implying that recent clonal expansions are only taking place in the periportal region, as opposed to the centrilobular region. Furthermore, the percentage of portal tracts with adjoining clonal mtDNA patches is significantly greater than the percentage of central veins with adjoining clonal patches, confirming that clonal patches are more likely to originate in the periportal region. These data therefore support a hypothesis that the periportal region is the location of the hepatic stem cell niche.

17.15–17.30 **[PL9]** ***Detection Of Venous Invasion To Stage Colorectal Cancer***

Ⓟ AK Foulis[1]; CSD Roxburgh[2]; DC McMillan[2]

[1]Pathology Department, Southern General Hospital, Glasgow, United Kingdom; [2]Surgery, Royal Infirmary, Glasgow, United Kingdom

Purpose of study: Elastica staining of tumour sections increases the sensitivity of detection of venous invasion in colorectal cancer. We compared the prognostic value of elastica detected venous invasion with that of other pathological features in colorectal tumours.
Methods: This was a single-centre clinical outcome study of pathological variables in electively resected colorectal cancer specimens.

Results: 631 resection specimens were analysed. The median follow up was 73 months (24-178) and during this time there were 238 deaths (134 from cancer). Venous invasion was detected in 56% of cases and was a stronger predictor of poor long term cancer-specific survival than other pathological features . On multivariate analysis of all cases the hazard ratio (HR) for failure to survive 5 years for venous invasion =3.94 (P<0.001); HR for lymph node involvement = 1.81, (P<0.001) and HR for T stage = 1.64 (P=0.005). In node negative cases the HR for failure to survive 5 years for venous invasion on multivariate analysis =3.55 (P<0.001) and for T stage was 2.03 (P=0.004). When T stage and venous invasion were considered together, patients could be stratified by risk of 5-year cancer mortality from 100-54% in node negative disease and 100-33% in node positive disease. A novel staging system based only on T stage and venous invasion (TVI) was created. This simple TVI system was at least as predictive as the gold standard TNM system when considering all cases, and provided increased prognostic value in both T1 and T2 tumours, as well as in node negative disease.
Conclusion: Sensitive, accurate detection of venous invasion on elastica stained sections improves its prognostic importance such that it becomes a key pathological characteristic arguably of more importance than nodal status, in determining outcome in patients with colorectal cancer.

▶ 17.30 – 18.30 — Fintry – Level 3

PUBLIC LECTURE
Clearance of Dying Cells in Control of Inflammation
Chair: Prof D Salter, University of Edinburgh
Speaker: Prof Sir John Savill, Edinburgh

▶ 19.30 – 23.30 — The Hub

CONFERENCE DINNER
CEILIDH
Shuttle buses will run from 19.00 *(the alternative is a short walk up a steep hill)*

FRIDAY 21 JUNE

08.00 — **Reception**

REGISTRATION and COFFEE

08.45 – 16.00 — **Ochil 3 – Level 1**

SLIDE SEMINAR CASE COMPETITION VIEWING
Inflammatory Skin Pathology

08.30 – 09.30 — **Fintry – Level 3**

SLIDE SEMINAR DISCUSSION SESSION
Inflammatory Skin Pathology
Chair/Speakers:
Dr A Biswas, Western General Hospital, Edinburgh
Dr M Mathers, Western General Hospital, Edinburgh

09.30 – 12.00 — **Fintry – Level 3**

SYMPOSIUM
Update Lectures in Dermatopathology
Chair: Dr T Brenn, University of Edinburgh
Dr E Calonje, St John's Institute of Dermatology, St Thomas' Hospital, London

09.30–10.00 **[S39]** ***Update on Melanocytic Tumours: The Undiagnosable Small Lesion***
Ⓟ Prof WJ Mooi
VU Medical Centre, Amsterdam, Netherlands

With very few exceptions, melanoma causes death by distant metastasis. The classification of melanocytic tumours therefore is essentially based on a simple binary division: those lesions that have the potential for distant metastasis (melanomas) and those that do not (melanocytic naevi). Since early detection and surgical removal of melanoma increases the likelihood of cure, i.e., eliminates the tumour before distant metastasis has occurred, major efforts have, in the past decades, been made to increase early melanoma detection. We have now reached a stage where most melanomas are cured as a result of early medical intervention. This success comes at a cost. Many of the melanocytic lesions that are submitted to the pathologoist are small and thin, and show only some of the features of melanoma. Over and over, the pathologist has to decide: is this a cat or a baby tiger? Underdiagnosis of a small melanoma that leads to undertreatment and recurrent disease, is a dreaded mistake. There is a heavy pressure on pathologists not to miss the diagnosis of melanoma, and no doubt the required exceedingly high sensitivity of melanoma diagnosis comes at the cost of decreased specificity of that diagnosis. Ironically, such decreased specificity results in higher cure rates of melanoma (i.e. of those lesions diagnosed as melanoma), happy doctors, satisfied hospital managers and grateful patients. The only thing is, these patients with overdiagnosed naevi never had a cancer. What is to be done? This is difficult. Some suggestions and half-answers will be provided in the presentation.

10.00–10.30 **REFRESHMENT BREAK** **[Lomond Suite – Level 0]**

10.30–11.00 ***Update on Skin Adnexal Carcinomas***
Ⓟ Dr E Calonje
St John's Institute of Dermatology, St Thomas' Hospital, London, United Kingdom

11.00–11.30 ***Update on Cutaneous Lymphoma***
Ⓟ Dr P Jansen
Leiden University Medical Centre, Leiden, The Netherlands

11.30–12.00 ***Update on Cutaenous Mesenchymal Tumours***
Ⓟ Dr T Brenn
University of Edinburgh, United Kingdom

FRIDAY 21 JUNE — *continued*

▶ 09.00 – 12.00 **Carrick – Level 1**

SYMPOSIUM

Testicular Pathology

Chair: Prof DM Berney, Queen Mary University of London
Dr C Verrill, Oxford University Hospitals NHS Trust

09.00–09.30 ***Pathogenesis of Testicular Germ Cell Tumours***

Ⓟ Dr VE Reuter

Memorial Sloan-Kettering Cancer Center, New York, USA

09.30–10.00 **[S41]** ***Germ Cell Tumours: Pathology and Therapeutic Decision Making***

Ⓟ Dr JM Theaker

University Hospital Southampton, Southampton, United Kingdom

Although uncommon (approx 2200 UK cases in 2010), testicular germ cell tumours are important as they affect young men and have a relatively high potential to metastasise. Modern chemotherapy is highly effective, even in advanced metastatic disease, with the overall UK survival now reaching 97%. Accurate pathological diagnosis and sub typing is important as GCTs (excluding spermatocytic seminoma) are managed as one of two groups - seminomas and non-seminomatous germ cell tumours (NSGCTs). It is important to appreciate that up to 15% of tumours have combined seminomatous and non-seminomatous elements and are managed along the lines of NSGCTs. Pathology also plays a potentially important role in treatment decision making in Stage 1 tumours with oncologists considering factors such as size and rete invasion in seminoma and the presence of vascular invasion in NSGCT when deciding whether to offer adjuvant chemotherapy. Accurate diagnosis of most tumours can be made with routine histological examination. Seminoma is characterised by relative cytological uniformity but architectural heterogeneity and it is important to recognise the more unusual patterns such as the diffuse intertubular seminoma, those with a dominant inflammatory infiltrate masking small numbers of tumour cells and those which have largely undergone regression. Sometimes, seminoma cells show more amphopyhlic cytoplasm and more nuclear pleomorphism when it must be distinguished from solid embryonal carcinoma. NSGCTs have a very wide range of patterns and different components but are all managed along similar lines except in rare cases such as when there is somatic malignant transformation in a teratoma. Immunohistochemistry is helpful in recognised problem areas (eg distinguishing classical from spermatocytic seminoma or from solid pattern embryonal carcinoma) and is particularly helpful in recognising germ cell tumours when they present as metastases.

10.00–10.30 **REFRESHMENT BREAK** **[Lomond Suite – Level 0]**

10.30–11.00 **[S42]** ***Difficult Issues in Germ Cell Tumour Pathology – Evidence from Central Review of Testicular Tumours***

Ⓟ Dr C Verrill

Oxford University Hospitals NHS Trust, Oxford, United Kingdom

Testicular germ cell tumours are relatively rare, accounting for just over 1% of male cancers in the UK. Cases are centrally reviewed which helps concentrate pathology experience. Although most Stage 1A/1B testicular germ cell tumours are now managed by surveillance rather than with adjuvant chemotherapy, it is sometimes patient or oncologist preference to opt for adjuvant therapy if adverse prognostic histological factors are present. Therefore, accurate assessment of tumour type (s) and prognostic factors such as lymphovascular invasion in non-seminomatous germ cell tumours remains crucial. In Oxford, (the supraregional centre for germ cell tumours in the Thames Valley), a review of a database of all patients discussed at the germ cell tumour MDT between 2004 and 2012 was undertaken in order to compare original local histology reports and the final supraregional reports. 627 cases of testicular tumour were reviewed in Oxford between 2004 and 2012 of which 402 were referred from 11 other hospitals in the cancer network and of these 370 cases had an original report available for review. Overall, there was discrepancy between original and final reports in 116 cases (31.4%). There were alterations of tumour type in 34 cases (9.2%), which were mainly minor changes, but one classical seminoma was reclassified as spermatocytic seminoma. There was a change in stage in 45 cases (12.1%). Commonest discrepancies occurred in assessment of lymphovascular invasion, spermatic cord invasion and rete testis invasion. The Oxford experience of centrally reviewing testicular tumours from 2004-2012 will be used to highlight where most discrepancies and therefore difficult issues in germ cell tumour reporting occur and discuss how these can be clarified and addressed in the future.

11.00–11.30 **[S43]** ***Sex-Cord / Stromal Tumours of the Testis***

Ⓟ Prof DM Berney

Queen Mary University of London., London, United Kingdom

Sex cord stromal tumours of the testis form a rare but heterogenous group which can cause tremendous diagnostic challenges and lead occasionally to inappropriate treatment. The most common are Leydig cell tumours, which are increasingly seen incidentally with increased untrasound screening. Others types include Sertoli cell tumors, granulosa cell tumors, and mixed forms which show different lines of sex cord stromal differentiation. The majority of sex cord stromal tumours are benign, however malignancy is well reported, and associated with size, mitotic count, necrosis, vascular invsaion and infiltration of the surrounding parenchyma. Malignant Sertoli cell tumours may mimic seminima. A consideration of primary prophylactic retroperitoneal

lymph node dissection should be given to those cases which are unequivocally malignant. Some Sex cord stromal tumours are associated with clinical syndromes. Large cell calcifying Sertoli cell tumours are associated with Peutz-Jeughers syndrome and also Carney's complex. Juvenule granulosa cell tumours may be seen in mosaicism, and gonadoblastomas are associated with intersex conditions. Immunochemistry for these tumours is variable, and a panel of markers may be needed, with an underlying relaince on morphology for their diagnosis. This array of phenotypic and immunochemical diversity may lead to diagnostic challenges.

11.30–12.00 ***Tumours of the Cord and Testicular Adenexae***
Ⓟ Dr VE Reuter
Memorial Sloan-Kettering Cancer Center, New York, USA

▶ 12.00 – 13.00 **Fintry – Level 3**

THE BRITISH DIVISION OF THE INTERNATIONAL ACADEMY OF PATHOLOGY'S KRISTIN HENRY LECTURE
Chair: Prof M Wells, University of Sheffield and President, BDIAP

[S44] ***Bowel Cancer Screening: Extraordinary Conundra for Pathology***
Ⓟ Prof NA Shepherd
Gloucestershire Cellular Pathology Laboratory, Cheltenham, United Kingdom

It is a great honour and privilege, as Past-President of the BDIAP, to give the inaugural Kristin Henry Lecture of the BDIAP at this meeting in Edinburgh. The lecture will address pathological issues of colorectal cancer screening, introduced in England (termed BCSP) in 2006 and we now have complete roll out of the programme, using faecal occult blood testing, such that all patients between the ages of 60 and 70, and many up to 75, are offered screening. There are similar, but not identical, screening programmes in Scotland, Wales, Northern Ireland and the Republic of Ireland. BCSP provides the potential for greatly enhancing our knowledge of the pathology of pre-neoplastic lesions in the colorectum and their management. The major pathological diagnostic and management issues are the biopsy diagnosis of colorectal cancer (which causes particular issues in the UK), the management of pT1/polyp cancers, the assessment of serrated lesions and an extraordinary phenomenon concerning larger adenomatous polyps. Larger adenomatous polyps in the sigmoid colon are prone to mechanical forces such that epithelial misplacement, into the submucosa, is a common feature. Such polyps are likely to bleed and are thus preferentially selected into BCSP. This phenomenon provides extraordinarily disconcerting histological features such that it may be very difficult to differentiate epithelial misplacement from invasive carcinoma. In the UK, we have introduced an "Expert Board" to assess such polyps and to determine whether or not they are malignant. The phenomenon, whereby pathologists are unable to differentiate between a benign condition and a malignant one, is almost unique in UK pathological practice and has certainly provided serious diagnostic debate. The lecture will also discuss research projects, immunohistochemistry, infra-red spectroscopy and three-dimensional reconstruction technology, to see if these can aid the diagnostic process.

▶ 13.00 – 14.00 **Lomond Suite – Level 0**

LUNCH
POSTER VIEWING

▶ 14.00 – 16.00 **Fintry – Level 3**

SYMPOSIUM — *continued*
Update Lectures in Dermatopathology
Chair: Dr T Brenn, University of Edinburgh
Dr E Calonje, St John's Institute of Dermatology, St Thomas' Hospital, London

14.00–14.30 **[S40]** ***Update on Inflammatory Dermatoses***
Ⓟ Dr LA Jamieson
Salford Royal Hospital, Salford, United Kingdom

Baffling to many, the area of inflammatory dermatoses is often left as a "stone unturned" by many pathologists who prefer the comfort of "non-specific chronic dermatitis"! However, once the key reaction patterns are understood and embraced it is possible to delve even deeper into the differential diagnosis and offer the dermatologist an extremely useful working diagnosis and practical differential. I aim to expose useful subtle hints in order to help the general histopathologist, perhaps with a special interest, and dermatopathologist alike. I will discuss newer entities and revisit some old ones with the aid of exposing referral patterns in inflammatory dermatology. I will cover the area of emergency and inpatient dermatology, a vanishingly rare clinical service in the modern NHS as well as links with other sub-specialities. Overall, I aim to impart the listener with a sense of feeling more "comfortable" when faced with a biopsy for inflammatory dermatoses and also a little braver!

14.30–15.00 **Questions**

FRIDAY 21 JUNE — *continued*

CASE PRESENTATIONS IN DERMATOPATHOLOGY

15.00–15.10	**Case 1** Prof WJ Mooi
15.10–15.20	**Case 2** Dr E Calonje
15.20–15.30	**Case 3** Dr P Jansen
15.30–15.40	**Case 4** Dr T Brenn
15.40–15.50	**Case 5** Dr L Jamieson
15.50–16.00	**Questions and Conclusion**

End of Conference

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Abstracts

Posters

P1

Apoplexia Uteri– A Rarely Described Gynaecological Finding at Post Mortem

Ⓟ C Beggan[1]; K Jaber[2]; M Leader[1]

[1]Royal College of Surgeons in Ireland, Dublin, Ireland; [2]State Pathologist Office, Dublin, Ireland

This case report describes a case of apoplexia uteri, a rarely described cause of haemorrhage in the post menopausal endometrium and myometrium associated with terminal stress.
The case is that of a 33 year old female with a background history of hepatorenal syndrome and alcohol usage. She underwent a Coroner's Autopsy where death was confirmed as occurring due to hypoxic brain injury. A discrete focus of endometrial and myometrial haemorrhage was noted displaying the histological features of apoplexia uteri, namely congestion of vascular spaces, and red cell extravasation into endometrial stroma and adjacent myometrium and endometrial cell necrosis. No vasculitis or vascular injury was observed.
Apoplexia uteri is an infrequently reported condition of haemorrhagic necrosis in an atrophic endometrium and myometrium associated with terminal stress. The underlying mechanism is postulated to involve hypo-perfusion and passive hyperaemia and reperfusion injury. Such a history was evidenced in this case by the associated finding of hypoxic brain injury.
Few recent publications are available describing this entity, although it is well recognised in older, mainly German texts. This case describes the pertinent histological features to raise awareness of this condition as a possible cause of haemorrhage in an atrophic endometrium and myometrium in an autopsy examination.

P2

Use of Laboratory Putty in Assessing Variation in Hard Surfaces Within Paved Urban Areas in Relation to Patterned Marks on Bodies

Ⓟ OR Johnson[1]; M Lyall[2]; CP Johnson[2]

[1]University of Birmingham Medical School, Birmingham, United Kingdom; [2]Forensic Pathology Unit, Royal Liverpool University Hospital, Liverpool, United Kingdom

Purpose: Patterned skin marks at autopsy can provide key evidence in identifying an injury that may have been left by footwear. It is also important to consider whether such a mark could be due to the deceased coming into forceful contact with a hard surface at the scene of an incident e.g. by falling. This study aimed to assess a) how surfaces varied within paved urban areas b) the number which were likely to leave defined and/or patterned marks on skin including those which might resemble footwear marks and c) evaluate whether lab putty impression lifting is a practical and effective adjunct to photography in assessing patterned surfaces and injuries in such circumstances.
Methods and results: 18 control "scenes" of approximately 50m2 were assessed for variation in pavement and wall structure with photography and the production of laboratory putty impression lifts and analysed for the purposes above. There were a total of 135 surfaces across the study (range=4-12/scene). 122 (90%) were considered likely to leave distinct marking on skin with forceful contact and 62 (46%) a defined/regular mark similar to a partial footwear injury (mean=3.4/scene). Most of the latter (35) related to grids and 27 to a pavement or wall surface e.g. tiling or brick. Lab putty proved to be a rapid practical way of a) assessing whether a surface would be likely to leave such a mark b) allowing the possibility of subsequent direct comparison of potential pavement surface candidates in the mortuary against a putative patterned body mark and c) providing a permanent evidential record.
Conclusion: Whenever a suspect footwear mark is identified at autopsy, a careful systematic examination of all hard surfaces at the scene of a potential incident is mandatory. We recommend laboratory putty as an excellent tool in characterising the surfaces and facilitating comparison work.

P3

Pyopneumothorax Arising in Rheumatoid Lung Disease

Ⓟ H Buist; N Kirkham

Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom

Although rheumatoid arthritis (RA) is a systemic illness, few patients have rheumatoid lung disease. It presents in a variety of ways including interstitial fibrosis, bronchiolitis obliterans, pleural effusion and rheumatoid nodule formation. The nodules can cavitate, resulting in complications described rarely in the literature such as pneumothorax, pyopneumothorax and bronchopleural fistula. These entities are often recurrent and persistent, requiring frequent repeat intervention.
A case of a 62 year old female with RA is presented. She died unexpectedly following a two day history of vomiting. Previously she had suffered a pneumothorax and was awaiting investigations for ongoing weight loss and dyspnoea. At autopsy, classic features of RA were noted on external examination. There was a large empyema in the right pleural cavity in addition to right middle and lower lobe collapse. The pericardium was thickened and there was a pericardial effusion of clear yellow fluid containing fibrinous material. Subpleural ill defined mass lesions were present bilaterally in the upper lobes. Microscopic examination showed a central zone of fibrinoid necrosis with palisading macrophages in keeping with rheumatoid nodules. The right lung showed patchy pneumonia, bronchiectasis and atelectasis. There was a granulomatous lymphocytic pericarditis. Death was attributed to pleural empyema occurring secondary to rheumatoid lung disease.
The presence of spindle shaped macrophages with fibrinoid necrosis in a pleural biopsy, or the presence of epitheloid cells with giant cells in pleural fluid cytology should make the pathologist consider a rheumatoid pathogenesis. At autopsy, a rheumatoid nodule should be considered in the differential diagnosis of pneumothorax, pleural empyema and mass lesions in the lungs, especially in the context of additional arthritic features or with a clinical history of rheumatoid arthritis.

P4

Sudden Cardiac Death and Body Mass Index

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Sudden cardiac death is a leading cause of death and one of the most common conclusions drawn by UK Coroner's pathologists. Best practice classifies cardiac autopsy results into five cause of death categories based on the degree of certainty which can be attributed to each set of findings. Data consistently finds most causes of sudden cardiac death to be ischaemic with an increasing trend of congestive cardiac failure. Following their description by Davies in 1999 much data was published based on these. Body mass index (BMI) has not traditionally been explored in these publications and indeed since the initial interest, population demographics have changed dramatically. Almost one in four British adults have a raised BMI and this has been increasing sharply in the last ten years. Consequently there is a need to look at data which examine these cases with a focus on BMI. We reviewed 2000 paper autopsy reports in the South West of England from 2012 and identified 440 sudden cardiac deaths. We analysed the data in terms of BMI (underweight, normal, overweight, obese etc.) and cause of death category (Davies criteria categories I - V). We found the overall picture to be largely similar across BMI groups but with some interesting differences. There is an increase in ischaemic causes of death (category I-III) in those with a raised BMI, peaking in the overweight group with category I deaths (coronary artery thrombus). The incidence of congestive cardiac failure (category IV) is variable across all groups but is very low in the underweight group and dramatically increased in obese class III. We found that cases of cardiac death with a morphologically normal heart (category V) were underweight or had a normal BMI. We hope the differences and similarities in cause of death classified by BMI we present will highlight the current and future trends in the types of sudden cardiac deaths encountered by practicing UK autopsy pathologists.

P5

Contemporary Coronial Post Mortem Practice in a Busy City Teaching Hospital Mortuary: Histology – Is it Still Useful?

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Introduction: Coronial post mortem activity can represent a significant part of a pathologist's workload. We examined the post mortem practice of a single consultant working in a large teaching hospital.
Methods: With the permission of HM Coroner, the reports from post mortems performed by a single histopathologist were interrogated with special regard to the use of histology, tissue retention status and inquest attendance. A recent retrospective assessment (2013) was then performed by the original consultant examining whether histology had arguably been potentially avoidable (confirmed a suspected cause of death) or essential (cause of death unknown or mandated for other reasons, e.g. asbestos analysis).
Results: A total of 141 post mortems conducted or supervised (23%) by a single histopathologist in 2009 were studied. Case sources were: community 45%, hospital 44%, A&E 11%, death abroad 1 case. Tissue blocks were taken for histology in 42% of cases (46% community, 49% hospital, 5% A&E). Histological examination was felt to have been potentially avoidable in 41% of instances and essential in 56%. Permission was received for tissue retention in 49% of cases, instructions for disposal in 47% and requests for return in 3%. Inquest attendance was required for 37% of cases, 75% of which had involved histology, 8% toxicology only and 17% neither. Histology was felt to be essential in 62% of histology inquest cases. The most common inquest conclusion was 'natural causes' (50%). In 13 cases, histology was processed 'urgently', avoiding an inquest in 7 cases.
Conclusion: The value of histology in post mortems appears undiminished but it should be used judiciously as it can be associated with time consuming inquest attendance. Urgent processing may avoid the need to open an inquest. Many relatives allow tissue to be retained for scheduled purposes. This material represents a valuable and underused legitimate teaching resource.

P6

Myocardial Infarction and Necrosis in a Paediatric Autopsy Population

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Background: Myocardial necrosis during neonatal life and infancy may be associated with congenital heart disease, coronary artery abnormalities and perinatal asphyxia. In rare cases no underlying cause can be identified. This study investigates infant autopsies showing myocardial necrosis, and describes in detail cases of apparently idiopathic myocardial infarction.
Design: An autopsy database containing detailed anonymised data from every autopsy performed on individuals from birth to 1 year of age undertaken at a tertiary referral centre for paediatric investigation between January 1996 and December 2010. Cases with myocardial necrosis were identified. Necrosis was categorized and findings were related to the clinical history and underlying pathological mechanisms. Three cases of apparently idiopathic neonatal myocardial infarction are described in detail.
Results: Of 1,617 infant autopsies, 187 (11%) showed histological evidence of myocardial necrosis. 29% of these deaths occurred in the first week of life, and 66% within the first 90 days. 69% of cases where location was recorded involved the subendocardial region or papillary muscles (95/137). Congenital heart disease, perinatal asphyxia, coronary artery anomalies and sepsis were the most common associations, accounting for 89% of cases (162/187). Three cases of myocardial infarction were identified with no evidence of other pathologies, structural congenital heart disease, or coronary artery abnormality.
Conclusion: Myocardial necrosis is common in an infant autopsy population. Necrosis occurs in patients at risk of tissue damage in areas of the heart most sensitive to hypoxia. Fatal idiopathic myocardial infarction can occur in the infant age group, but is rare.

P7

Drowning in Infants and Children: Autopsy Experience from a Specialist Centre

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Background: Drownings in infants and children are a significant cause of accidental death. Public health campaigns have encouraged parents to avoid leaving children unattended whilst bathing or near open water sources, in an effort to reduce drowning deaths. Rapid death in drowning may occur as a result of inhalation of water causing hypoxia or changes in blood electrolyte levels, typically resulting in heavy oedematous lungs. Alternatively death may be the result of reflex cardiac arrest or laryngospasm ('dry drowning'), typically resulting in lungs of normal weight. The aim of our study was to investigate the circumstances and autopsy findings in cases of paediatric drowning in our autopsy population.
Design: An autopsy database containing detailed anonymised data from every autopsy performed on individuals from 7 days to 16 years of age undertaken at a tertiary referral centre for paediatric investigation between January 1996 and December 2011. Cases of drowning were identified and the circumstances of death and autopsy findings examined.
Results: 28/2,220 autopsies were drowning/immersion-related (adequate history available in 27). Deaths occurred in baths or swimming pools at home (19/27, 70%), public swimming pools (3, 11%) and open water sources (5, 19%). There was a documented lack of adult supervision in 78% (21/27) of cases. In 20 (74%) there was a survival period of less than 24hrs; histology of the lungs in these cases revealed pulmonary oedema and/or intra-alveolar haemorrhage. Of seven cases with a longer survival period, six showed bronchopneumonia and hypoxic brain injury. Lung weights were greater than expected in 26/27 (on average 70% greater, $P<0.001$).
Conclusion: Most paediatric drownings occur at home with inadequate supervision, suggesting that many of these deaths are preventable. The pulmonary findings in our cases suggest that so-called 'dry-drowning' is a rare occurrence in this population.

P8

Accuracy of View and Grant Approach to Diagnosis of Sudden Adult Deaths: Comparison with Minimally Invasive and Full Autopsy in a Routine Coronial Service

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A reduction in the high autopsy rate in England could be achieved by employing the view and grant (V&G) system, or minimally invasive autopsy (MIA), using postmortem CT with targeted angiography. In this study, we compare the accuracy of V&G with MIA or full autopsy in a series of 120 sudden adult deaths referred to HM Coroner.
A provisional cause of death based on clinical history and external examination (V&G approach) was produced prior to postmortem CT ± angiography, with invasive autopsy only if there was no definite cause of death identified on imaging. The cohort was divided into two halves with postmortem coronary angiography used only in the second set of 60 cases. The confidence of imaging cause of death was classified as definite (no autopsy), probable, possible or unascertained. The V&G cause of death was compared to that based on imaging/autopsy. A major discrepancy was one in which the causes of death involved completely different pathologies/organ systems.
The commonest final cause of death was ischaemic heart disease, diagnosed in 48/120 (40%). Death was unnatural in 16/120 (13%). There was a major discrepancy between V&G and final cause of death in 51/120 (43%) of all cases and 49/104 (47%) of natural deaths. A definite cause of death without autopsy was provided on the basis of CT in 38% of cases without coronary angiography and 70% of cases with angiography. A probable cause of death was identified on imaging in an additional 13 cases. There was 100% agreement between imaging and autopsy causes of death in these, indicating that those cases for which imaging could provide an accurate cause of death without autopsy were correctly identified.
We conclude that the V&G approach is unreliable in identifying the cause of sudden adult death. A two-thirds reduction in the number of invasive Coronial autopsies can be achieved by use of postmortem CT with coronary angiography.

P9

Atypical Lobular Hyperplasia and Lobular Carcinoma in Situ or Lobular Intraepithelial Neoplasia on Core Biopsy: To Split or to Lump

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Introduction: The management of lobular neoplasia found on core biopsy remains controversial. Recent NCCBP guidelines suggest categorising ALH and LCIS as Lobular Intraepithelial Neoplasia (LIN) on core.
Aim: To review our experience of Lobular Neoplasia on core biopsy.
Methods: All core biopsy diagnoses of lobular neoplasia from 2002 to 2012 were retrieved and reviewed, with the clinical and radiological information available at time of initial reporting. Lesions were categorised as ALH, LCIS or Pleomorphic LCIS based on highest grade present. Extent was assessed by number of acini involved. This data was then compared with their paired excision specimens.
Results: Of 70 cases diagnosed, 68 were available for review. Twelve cases were excluded (1 no atypia; 2 focal DCIS; 1 microinvasion; 5 radial scars; 3 papillary lesions) and 15 cases contained PLCIS, leaving 41 cases for this study.
29 of these 41 cases had neither clinically nor radiologically concerning features. Of these 17 contained focal ALH (involvement of 4 or fewer acini). Two of these showed ADH and one a 4mm focus of low grade DCIS on excision whereas 6 contained (35.3%) no further atypia.
9 of the 29 had more extensive ALH. ADH was found on excision in one and an 11mm area of intermediate grade DCIS in a second, while 2 (22.2%) had no further atypia.
Of the 3 with LCIS none upgraded on excision, but all contained residual LCIS.
The 12 remaining cases were clinically or radiologically suspicious. Invasive disease was found on excision in 5 of 7 ALH (71.4%) and 2 of 5 LCIS (40%) cases. Of these the 2 tubular cancers reported were seen on excision of ALH and the only grade 3 carcinoma was associated with LCIS.
Conclusion: Useful detail may be lost by recording ALH and LCIS together as LIN on core biopsy. ALH or LCIS do not explain a clinically or radiologically suspicious lesion and re-biopsy may be appropriate in these cases.

P10

Grading of Breast Cancer on Needle Core Biopsy: Does a Reduction in Mitotic Count Threshold Improve Agreement with Grade of Excisional Specimen?

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Background: Histological grade reported at needle core biopsy (NCB) can underestimate that in the excisional specimen. This observed discrepancy is most often due to an underestimation of mitotic activity in the NCB.
Purpose of the study: To compare histological tumour grade on NCB with that reported on the excision specimen. To assess whether altering the mitotic count threshold on NCB would improve histological grade correlation with the excision specimen.
Methods: The pathology reports and slides from 100 consecutive patients with a NCB diagnosis of invasive breast carcinoma who underwent subsequent wide local excision (WLE) in 2012 were reviewed. The highest mitotic count per 10 high-power fields (diameter 0.55mm) was assessed on NCB. The mitotic count threshold was altered and grade correlation between NCB and WLE was evaluated.
Results: In 77/100 cases there was agreement on histological grade between NCB and WLE. In 15/23 (65%) cases the NCB grade was one lower than that on excision. Of these, 10/15 (67%) were due to a lower mitotic score category on the NCB. Using current appropriate mitotic count thresholds [M1=0-8, M2=9-17, M3>18], NCB correctly categorised 83% of grade 1, 68% of grade 2 and 100% of grade 3 tumours. To try to improve grade 2 agreement, the mitotic count thresholds were changed [M1=0-4, M2=5-17, M3>18]. This led to NCB correctly identifying 83%, 71%, 80% of grade 1, 2, 3 tumours respectively.
Conclusion: We demonstrate good agreement on tumour grade between NCB and WLE. If a discrepancy occurs, the tumour is most commonly upgraded on the excision specimen. The mitotic activity component of the grade is most frequently upgraded. NCB is best at correctly classifying tumours with M1 and M3 scores but less good at identifying those with M2 scores. Altering the mitotic count thresholds on NCB does not improve the correlation of tumour grade between NCB and WLE specimen.

P11

Tissue Microarray Cores vs Whole Sections for the Assessment of Tumour-Stromal Ratio in Rare Cancer Using Male Breast Cancer as an Exemplar

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Tumour-stromal ratio is emerging as an important prognostic indicator in cancer. However, there is considerable methodological heterogeneity between studies, especially in terms of the area of the tissue section selected for study. Tissue microarrays (TMAs) are widely accepted as an efficient tool for in situ tissue analysis. Areas of whole tissue sections are sampled either randomly or in a targeted fashion depending on the intended analysis. A number of validation and feasibility studies have compared the results obtained from whole section analysis to those of TMA cores but results vary considerably and between tissue types.
We aimed to assess the concordance between results from whole sections and TMA cores in male breast cancer, where around 300 cases are diagnosed annually in the UK. Proportion of tumour was measured by point counting virtual tissue sections in 30 male breast cancer cases. All but four whole tissue sections (87%) were compared with two or more TMA cores from the same tissue block. The results were categorised into high (>50%) and low (<50%) proportion of tumour.
There was moderate agreement (κ=0.524) between the results for the whole sections and the average of the TMA core results. There was fair to moderate agreement when the results of only one core were compared (κ=0.211 - 0.524).
Overall, it is best practice to use whole sections for stromal density analysis. Where this is not possible, for instance in rare disease, the reliability of TMA core analysis can be maximised by ensuring appropriate sampling is employed. At least two cores should be analysed and thus techniques should be employed minimise the loss of cores due to folding, damage or other inadequacies.

P12

Does Sentinel Node Biopsy and Simultaneous Axillary Node Sampling Predict Overall Disease Burden in Otherwise Good Prognosis Breast Cancer Patients? A Retrospective Study of Five Years Practise in a Tertiary Referral Centre with Reference to the ACOSOG Z0011 Trial Inclusion Criteria

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Purpose of study: The ACOSOG Z0011 trial demonstrated no survival benefit when otherwise good prognosis breast cancer patients with limited Sentinel Node Biopsy (SNB)-positive disease underwent subsequent axillary lymph node dissection (ALND). During the study period it was standard practice at this institution to supplement SNB with limited axillary node samping (ANS). Patients with positive SNB and/or ANS were then treated with either axillary radiotherapy or axillary lymph node dissection (ALND). This gave the opportunity to map axillary node disease burden in a staged way and explore pathological factors predictive of the extent of axillary node disease burden. We assessed what proportion of patients have ANS-positive nodes in a similar good-prognosis group, to see whether this could predict subsequent ALND disease burden.
Methods: Novel automated data extraction methods were used to extract pathological data from reports of 1394 consecutive patients with invasive breast carcinoma with synchronous SNB and ANS, diagnosed between 2006-2010; >10% of cases were manually checked and reviewed. Those fulfilling the ACOSOG Z0011 inclusion criteria were further analysed for predictors of ALND status.
Results: 220 patients fulfilled the ACOSOG Z0011 inclusion criteria (clinically node negative, ER+, one or two positive sentinel nodes). Seventy received ALND, of which 25 had further positive lymph nodes. ANS identified 33 additional SNB-negative patients with limited nodal disease. The presence of ANS positive nodes in addition to SNB positivity did not predict ALND status (p=0.448); neither did tumour grade (p=0.574), T-stage (p=0.591), nor HER2 status (p=0.415).
Conclusions: Data can be accurately extracted from histopathology reports using this novel system. Supplementing SNB with ANS identifies additional node positive patients, but does not predict the overall burden of nodal disease.

P13

DCIS-like Calcifications without Associated Epithelium in Obliterated Duct Spaces – A Diagnostic Trap for the Unwary!

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Purpose of study: "Burnt out" DCIS was originally described by Muir and Aitkenhead (*Muir R and Aitkenhead C. The healing of intra-duct carcinoma of the mamma. J Path Bact 1934; 38: 117-127*) but has had little mention in modern texts of breast pathology. We describe a series of five cases which illustrates this pathology to raise awareness that this lesion may point to the presence of DCIS.
Methods: We have identified five cases of patients attending breast screening between 2009 and 2012 with coarse mammographic calcifications where initial core biopsy showed coarse calcifications only.
Results: The core biopsies showed coarse calcification only with an impression of duct obliteration but with no epithelial abnormality at multiple levels. In three of the five cases repeat core biopsy of an area initially showing coarse calcification only revealed coarse calcification and high grade DCIS. In two cases repeat core biopsy showed further coarse calcification only and DCIS was only demonstrated on excision. In one of the excisions "burnt out" foci with fibrosis and coarse calcification only could be demonstrated adjacent to viable DCIS and in another a partial lesion was seen but such foci were difficult to find with the bulk of the pathology being viable DCIS.
Conclusions: We recommend that characteristic calcification in core biopsy specimens is investigated further even in the absence of any epithelial abnormality. Although this type of calcification may be seen in benign conditions such as duct ectasia it is uncommon in our experience. In view of the difficulty finding these "burnt out" lesions in our excisions the suggestion by Muir and Aitkenhead that DCIS might burn out in some cases is not a frequent occurrence.

P14

Qualifying an IHC Predictive Biomarker – Her2 Low Expression in Breast Cancer

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The original purpose of the HercepTest was to stratify patients who demonstrate over expression of HER2 by IHC to determine eligibility for treatment with trastuzumab. Subsequently the Herceptest scoring system for HER2 protein overexpression has been modified as a potential predictive IHC biomarker in gastric cancer. In breast cancer there is a group of patients who express HER2 but are determined ineligible for trastuzumab treatment. We have identified this group as a segment of unmet clinical need in which new drugs targeted to the erbB family may be a treatment option.
The aim of this study was to test our new modifications to the HercepTest guidelines to enable semi-quantitative assessment of breast cancers with either no (0), or low HER2 expression (1+ and 2+ (FISH negative)).
Tissues from 710 breast cancer patients previously scored, as 0, 1+ and 2+ using the conventional HercepTest were re-evaluated using our modified criteria. The modified criteria re-categorised the percentage of cell membrane staining observed in tumour cells which resulted in a distribution profile that identified the following subgroups: approximately 22% of cases were defined as negative, 64% were re-classed as 1+ and 14% were in the 2+ category.
Three independent histopathologists found the modified criteria to be a familiar, simple, reproducible scoring system for HER2 protein low expression, which could be readily applied in clinical practice.

P15

p53 Status in Breast Cancer and its Potential Role as a Repressor of Cdc7 Kinase

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TP53 mutations are detected in 20-40% of sporadic breast cancers and in certain sub-types the frequency approaches 100%. Whilst most studies attribute p53 function to transcriptional activation, there is growing evidence that p53 can also affect cellular responses through the repression of gene expression. A proposed target of p53-mediated transcriptional repression is the kinase Cdc7. Cdc7 kinase activates the Mcm2-7 replicative helicase, an essential step in the initiation of DNA synthesis. Therefore, downregulation of Cdc7 kinase by intact p53 would be in keeping with its established role as a tumour suppressor. In this study we assess how Cdc7 protein expression correlates with p53 status and cell cycle phenotype, a recently described and highly accurate marker of proliferation status.
Methods: Archival tissue from 173 patients with breast cancer was immunostained with antibodies against Cdc7 and p53 and the cell cycle phenotype markers Mcm2, geminin and histone-H3. Staining was quantified using a labelling index derived from counting >1000 cells.
Results: Cdc7 expression levels were significantly raised in p53 mutant tumours compared to tumours with intact p53 (12.9% vs 6.3%; $p<0.001$). Furthermore, the p53 mutant/Cdc7 high tumours displayed increased proliferative activity as assessed by cell cycle phenotype, with actively cycling phenotype III tumours significantly over-represented in p53 mutant vs wild type tumours (79.6% vs 49.6%; $p<0.001$).
Conclusion: This study supports the hypothesis that Cdc7 kinase is subject to p53-mediated downregulation and that abrogation of this pathway may play an important role in the tumourigenesis of p53-mutant breast cancers.

P16

The Impact of Hormonal Therapy on the Outcome of Triple Negative Breast Cancers

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Background: Endocrine therapy has a significant effect on improving the outcome of patients with oestrogen (ER) /progesterone (PgR) positive breast cancer. Historically a proportion of patients with oestrogen negative breast cancer were treated with Tamoxifen, either to reduce the risk of contralateral breast cancer or due to uncertainties at the time of the potential for patients with very low or undetectable ER to respond to hormone treatment.
Method: A well-characterized series of 2151 unselected female invasive breast tumours; including 493 of triple negative invasive breast cancers with a long term follow up were investigated in this study to determine whether patients with Triple Negative (TN) tumour had the potential to benefit from adjuvant endocrine therapy in primary breast cancer.
Results: 69(14%) of triple negative breast cancers (TN) were treated with Tamoxifen or Zoladex. As previously shown in TN in general the endocrine treated cohort tumours had poor prognostic characteristics including tumour size > 1.5cm, high histological grade, high mitotic frequency, positivity of basal cytokeratins expression (CK5, CK14 and CK17) and P53 positivity $P<0.0001$. Regardless of histological grade the TN breast cancer patients treated with endocrine therapy showed higher risk of death or of distance metastasis than women treated without endocrine therapy ($P= 0.012$ and $P<0.0001$). In contrast, patients with TN cancer treated with chemotherapy had better BCSS ($P<0.0001$), and DFI ($P<0.0001$) than those with non-TN cancers treated with chemotherapy and TN tumour patients who did not receive chemotherapy.
Conclusion: Patients with TN breast cancers showed no evidence of benefit from endocrine therapy but appear to benefit from adjuvant chemotherapy.

P17

Non-Malignant Breast Lesions at Ile-Ife, Nigeria

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Purpose of the study: The aim was to review the cases of non-malignant breast lesions seen in our hospital within a 2 year period.
Methods : Histological review of all cases of non-malignant breast lesions seen in the year 2011 and 2012 at our hospital was done.
Summary of result: A total of 252 cases of non-malignant breast lesions were seen within the period. The age range was 14-87years (mean 27.8+/- 12.2). 79.8% of the cases were equal to or less than 35years. Fibroadenoma was the most common benign lesion of the breast and accounted for 172cases (68.3%). Fibrocystic disease accounted for 40 cases (15.9%.) .Majority of the fibrocystic disease were non-proliferative lesion, only four cases of moderate ductal hyperplasia were seen . Inflammatory breast lesion accounted for12cases (4.8%), this included breast abscess with mastitis, periductal mastistis and granulomatous mastitis. Lactational changes were seen in four cases, gynaecomastia 6 cases (2.4%). Other tumours seen included Lipoma (3), granular cell tumour (1)and tubular adenoma 4. The right breast was affected in 93cases (36.9%), the left breast 82(32.5) and both breasts in 37cases(14.7%) . In 40(15.9%) cases the side of the breast was not indicated. Bilateral involvement of the breast was common with fibroadenoma.
Conclusion: Non-malignant breast lesion is very common in young in women. Fibroadenoma remains the most common benign lesion and right breast was commonly affected. Involvement of both breasts is also significant.

P18

Cysticercosis of the Breast Mimicking Breast Cancer: A Report of a Case from Ile-Ife, Nigeria

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Introduction:Taenia solium is the causative agent of human cysticercosis .The infection commonly affects the muscle, the central nervous system and the subcutaneous tissues. The involvement of the breast is unusual. To the best of our knowledge, this is the first case from our centre.
Case History: A 54 year old postmenopausal woman, a pretty trader and Jehovah witness. She presented with history of painless right breast lump which was increasing in size. There was history of consumption of pork meat 2 years before presentation. The lump was examined by the Surgeon and a provisional diagnosis of breast cancer was made.
Histology: The breast biopsy showed the presence of cysticerci within a cystic cavity. The wall of which is composed of dense fibrous tissue. Some hooklets and few giant cells are seen with areas of fibrosis and calcification. The background contained heavy infiltration by lymphocytes and eosinophils.
Discussion:Cysticercosis is a condition that occurs when a patient is infected by larvae of Taenia solium acting as an intermediate host instead of definitive. Breast cysticercosis is rare and it represents a difficulty in clinical diagnosis. It should be considered as a differential diagnosis for a lump in the breast particularly if there is a previous history of consumption of pork meat.
Conclusion: It is unusual for Cystericosis to occur in the substance of the breast. Only a few cases have been described in the English literature.

P19

Audit of HER2 Testing in Breast Carcinomas

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Purpose of the study: The guidelines for HER2 testing in UK was published in April 2008. Our aims were to assess the frequency of results and distribution of IHC scores, with comparison to FISH (when performed) as compared to the national guidelines.
Methods: 4357 consecutive cases from January 2011 to December 2012 were retrieved. The IHC scoring was done by two consultants in all the cases. HER2 status of all the cases was first evaluated by HER2 protein (IHC). Equivocal 2+ cases were further evaluated by FISH and cases with borderline copy numbers were further assessed by chromosome 17, to determine whether the amplification of HER2 gene is independent of increases in chromosome 17. Audit of the distribution of IHC scores (0 to 3+) and the comparison between FISH and IHC scores for equivocal (2+) was analyzed.
Summary of results: Of the 4357 cases studied, 1233 were from our hospital and 3124 were referred cases. There were 2876 breast needle core biopsies, 1391 breast excisions and 90 other samples for metastatic carcinomas. We had IHC score 0 in 1464 (33.6%), 1 in 1580 (36.3%), 2 in 851 (19.5%) and 3 in 462 (10.6%) cases. Amongst the IHC score of 2+, FISH was positive in 205, negative in 628 and heterogeneous/insufficient in 18 cases.
Conclusions: IHC scoring methods are often described as semiqantitive or subjective. We had an IHC score of 2+ in 19.5% of our cases as compared to the national audit data of 18% in 2006 and 19% in 2007 audit. Amongst the cases of 2+ by IHC, 24.1% were FISH positive as compared to 24% in 2006 audit and 19% in 2007 audit. IHC score of 3+ was noted in 10.6% of our cases as compared to 13% in 2006 audit and 11% in 2007 audit. The clinical decision making for individual patient is becoming increasingly dependent on the accurate, reliable and timely reports so an ongoing audit of HER2 scores should be performed.

P20

Three Dimensional Reconstruction of Breast Cancer

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Breast cancer is the most common cause of cancer and the second most common cause of cancer related death in women in the UK. Traditional pathological investigation of breast cancer involves analysis of two dimensional (2D) images. This creates a problem in that spatial relationships may be overlooked. Three dimensional (3D) reconstruction has previously been performed in a variety of other tissues. The aim of this pilot study was to evaluate a digital 3D modelling process for breast cancer.
A formalin fixed paraffin embedded block containing an area of breast carcinoma was serially sectioned into 120 sections and mounted onto glass slides. These glass slides were stained with haemotoxylin and eosin (H&E), and whole slides were scanned using digital scanners (Aperio™) creating virtual slides. Specialised automated computer software algorithms allowed for slice-to-slice image registration. A subsection containing the area of interest was selected and re-registered, using an interactive multi-level algorithm built in to the computer software, creating an image stack of the H&E stained structures. Each slice was then annotated, highlighting structures and features within the tumour.
A 3D model of part of the breast carcinoma was created, allowing spatial relationships to be readily observed within the tumour sample. This study has demonstrated the utility of a 3D reconstruction technique to the study of breast cancer. Application of this technique to a larger cohort of breast specimens combined with immunohistochemistry may be help us understand vital structural relationships within breast tumours and learn more about this heterogenous disease.

P21

Prognostic Significance of Deregulated Dicer Expression in Breast Cancer

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Aim: Dicer is a key enzyme in microRNA biogenesis. Aberrant expression of Dicer has been reported in several cancers. While some studies suggest a potential association between Dicer and breast cancer survival, others have not. Previous analyses have assessed Dicer mRNA using microarray hybridisation, reverse transcription-PCR or sequencing. We aimed to investigate the prognostic significance of Dicer protein expression in breast cancer.
Methods: Immunohistochemistry using Dicer antibody (Clonegene, 13D6R) was performed on tissue microarrays of invasive breast carcinoma (IBC) (n=666), DCIS (n=334) and lymph node metastases (n=214). Antibody specificity was confirmed by pre-incubation with competing peptide. Dicer expression was double-scored based on cytoplasmic staining intensity. Negative cases showed absent staining, positive cases showed any staining intensity.
Results: Benign breast epithelium showed strong Dicer staining in the myoepithelial layer. 145/446 (33%) invasive breast carcinomas were positive and 301/446 (67%) were negative. Positive staining was associated with adverse features: ER-, HER2+, high grade and high proliferation rate. Positive staining was also associated with basal biomarkers EGFR and CK14 and with basal-like and HER2 over-expressing subtypes. Positive Dicer expression was negatively correlated with overall survival in univariate analysis (P=0.058) and was an independent prognostic factor for overall survival on multivariate analysis (hazard ratio 2.84). Increased Dicer staining was observed in lymph node metastases compared to primary tumours (P=<0.001). Rates of Dicer expression in DCIS and IBC were comparable.
Conclusion: Deregulated Dicer expression was associated with aggressive tumour characteristics in invasive breast cancer, and was an independent prognostic factor for patient survival. Our findings suggest that Dicer is an important potential prognostic marker in breast cancer.
Acknowledgment: This work was supported by a grant from the Pathological Society.

P22

Characterisation of Expression of MicroRNAs miR-4726 and miR-4728 in HER2-expressing Breast Cancer

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Purpose of the study: MicroRNAS (miRNAs) miR-4726 and miR-4728 have been shown to map to 17q12, the chromosome on which the ERBB2 proto-oncogene is located. These miRNAs were also enriched in immunoprecipitated Ago2 fraction from MCF7 cells. Interestingly, miR-4728 is encoded within an intron of HER2. We determined cellular localisation of miR-4726 and miR-4728 in formalin-fixed paraffin-embedded breast tumour samples and evaluated association of the miRNAs with HER2.
Methods: Nineteen cases of HER2 negative and HER2 positive breast cancers were selected from a breast cancer database. A modified in situ hybridisation method was used to detect miRNA expression, combining the use of LNA oligonucleotide probes with highly specific wash conditions. Staining intensity of miR-4726 and miR-4728 was evaluated in invasive breast cancer (IBC), DCIS and benign epithelial cells.
Summary of results: Moderate to strong cytoplasmic expression of miR-4726 and weak to strong expression of miR-4728 was observed in benign epithelial cells. Regarding miR-4726 staining in IBC, 4/6 tumours were negative; 2/6 showed weak cytoplasmic staining. For miR-4728, 2/4 tumours were negative, 1/4 showed weak cytoplasmic expression and 1/4 showed weak nuclear expression. Of 9 DCIS cases, 2 were negative, 6 showed weak expression and 1 showed focal strong staining. No association with HER2 expression was observed.
Conclusions: Our results provide an insight into the cellular localisation of miR-4726 and miR-4728 in breast tumours. Expression was downregulated in DCIS and IBC compared to benign epithelial cells, suggesting a possible tumour suppressive role for these miRNAs in breast cancer. Greater numbers of cases are currently being evaluated on tissue microarrays.
This research was supported by Path Soc Small Grant SGS 2010 10 08.

P23

Dock4 Expression in Breast Cancer – The Prognostic Significance and Correlation with Histological Parameters

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Introduction: Dock4 is a member of dedicator of cytokinesis (DOCK) family. This cytoplasmic protein functions as a guanine nucleotide exchange factor (GEF) for the small GTPase Rac1 and is involved in cell migration and regulation of adheren junctions between cells. A Dock4 mutation affecting its GEF activity has been reported to promote detachment and invasion of cancer cells. The aim of this study was to analyse Dock4 expression in tumour cells in a cohort of breast cancer specimens (n=405) by using scanned TMA (Tissue Microarray) slides stained with Dock4 antibody and to compare its expression with histological parameters (tumour type, grade, oestrogen receptor(ER) status, Lymph Node (LN) status) and overall survival (OS) at 5 years and 10 years.
Methods: The intensity of Dock4 expression was scored as weak, moderate or strong by using an arbitrary scoring system depending on the colour and the quality of cytoplasmic granules. Due to unavailable OS data, 60 patients were excluded from the analysis (n=345). Dock4 expression could not be assessed in 75 cases (n= 270) either due to no TMA core or no tumour in the available cores. Dock4 was expressed in 270/270 (100%) of tumour specimens. We used Kaplan-Meier for OS and Cox Regression for prognostic significance.
Results: A significant correlation was observed between Dock4 expression and histological tumour type (p=0.002) and grade (p=0.004). No significant correlation was observed between Dock4 expression and ER status (p=0.185) and LN status (p=0.15). There was a non-significant trend towards reduced survival in cases with moderate/strong Dock4 expression.
Conclusion: In our study increased Dock4 expression was observed in ductal carcinoma compared to other histological types. Higher Dock4 expression correlated with high tumour grade. Although not statistically significant, there was a trend towards improved survival in cases with weak Dock4 expression. This warrants further investigation in a larger cohort.

P24

An Unusual Presentation of a Common Malignancy

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Purpose of study: Cutaneous metastases account for 2% of all skin malignancies. Breast carcinoma accounts for the majority of cutaneous metastases in women (exceeding 20%), and is usually seen in the context of a recurrence after wide local excision/mastectomy or as a late manifestation of recurrent disease. Ductal carcinoma is the most common subtype to metastasise to skin, accounting for 80% of cases. Cutaneous metastasis presenting as the first manifestation of breast carcinoma is exceedingly rare. We describe a rare case of lobular breast carcinoma presenting initially as a skin metastasis.
Methods: An 80 year old female presented with a short history of multiple skin lesions on the neck and anterior chest. Clinically, these lesions were thought to be dermatofibromas and one was sampled for histology.
Results: Macroscopically, the surface of the skin ellipse was unremarkable, whilst the dermis was firm and white on sectioning.
Histologically, a grenz zone was present, with the appearances at low power resembling a dermatofibroma. However, the underlying dermis was infiltrated by discohesive cells with scant clear cytoplasm, mildly pleomorphic nuclei and occasionally prominent nucleoli.
The tumour cells were positive for AE1/AE3, CK7, oestrogen and progesterone receptor, while they were negative for S100, CK20, CD45 and CD68. The overall features were in keeping with metastatic carcinoma, favouring a breast origin with lobular features.
The patient had no prior history of breast carcinoma. On clinical examination she was found to have a palpable lump in her outer right breast, in addition to right-sided axillary lymphadenopathy. A biopsy confirmed a diagnosis of lobular carcinoma of the breast (ER, PR positive, HER-2 negative). The patient was started on hormone therapy and is currently well 20 months after her initial diagnosis.
Discussion: Lobular breast cancer presenting as a cutaneous lesion is an extremely rare and unusual occurrence.

P25

Comparison of Predictive Markers in Pre and Post-Neoadjuvant Treated Breast Carcinoma Cases

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Purpose of the study: The Oestrogen receptor (ER), Progesterone receptor (PgR) and HER2 profile of a primary breast carcinoma is essential in determining appropriate treatment. Neoadjuvent chemotherapy is increasingly in use as a therapeutic option however data regarding the effect of neoadjuvant chemotherapy on biomarker profile (ER, PgR, HER2) is limited and conflicting. The aim of this study was to compare the ER, PgR and HER2 profile of primary breast carcinomas pre and post-neoadjuvant chemotherapy.
Methods: ER, PgR and HER2 results were compared for 47 breast carcinoma cases pre and post treatment with neoadjuvant chemotherapy from a single institution in 2011-2012. ER, PgR and HER2 were evaluated by immunohistochemistry (IHC). HER2 cases which were equivocal by IHC (score=2+) were further evaluated by in situ hybridization (Fluorescent (FISH) or Dual DNA in situ hybridization (DISH)). All cases were evaluated by 2 consultant breast histopathologists. Results for pre-treatment core biopsies and post- treatment excision specimens were compared.
Summary of results: ER status changed post neoadjavant treatment in 4.2% of cases. 38 of 47 (80.8%) were ER positive pre-treatment and 36/47 (76.6%) were ER positive post treatment. PgR status changed post treatment in 29.8% of cases. 34 of 47 cases (72.3%) were PgR positive pre-treatment and 22 of 47 cases (46.8%) were PgR negative post-treatment. 1 case which was PgR negative pre-treatment was PgR low positive post-treatment. 15 of 47 cases (31.9%) were HER2 positive pre-treatment. A change in HER2 status post-treatment was observed in 4 cases (8.5%). Of these 2 cases changed from HER2 negative status by IHC to HER2 positive and 2 cases changed from HER2 positive to HER2 negative.
Conclusions: Hormone receptor and HER2 profile of primary breast carcinomas changes in a minority of post neoadjuvant chemotherapy treated cases.

P26

Evaluation of Pre-Operative Mediastinoscopy Lymph Node Sampling in Non-Small Cell Lung Cancer

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Background: Mediastinoscopy is the current gold standard for mediastinal staging of non-small cell lung cancer (NSCLC). There are no internationally accepted recommendations regarding which lymph node stations should be biopsied, or how rigorously the tissue obtained should be examined histologically, in order to detect metastases.
Purpose of the study: To assess the accuracy of detecting metastatic carcinoma in pre-operative mediastinoscopy lymph node biopsies.
Methods: All patients who underwent formal resection for NSCLC, in a single centre, between 1996 and 2006 were identified. Patients who had a negative mediastinoscopy but a final resection lymph node stage of N2 or N3 were selected. In these cases, mediastinoscopy lymph node biopsies were reviewed and further examined at multiple levels and using pancytokeratin immunohistochemistry (IHC).
Results: During the study period, 89/802 patients had a negative mediastinoscopy but final resection stage of N2/N3. Of these, 41/89 patients (the study group) had positive resection lymph nodes in stations that were accessible to biopsy at mediastinoscopy (stns 1,2,3,4,7). The most common site of metastatic carcinoma at resection was station 7, but only 33% of nodes sampled at mediastinoscopy were from station 7. Within the study group, 11 patients (27%) did not have the metastatic station sampled at mediastinoscopy. In the remaining 30 patients, examination at multiple levels detected 2 metastases, one of which in retrospect was present in the initial section. The pancytokeratin IHC detected isolated tumour cells in another 2 cases.
Conclusion: Pre-operative mediastinal staging in NSCLC can be improved by ensuring adequate sampling of lymph node stations and especially station 7. Examination of multiple levels may increase the detection of metastases (although a significant burden of technical work is created). The role of IHC remains unclear.

P27

Characterisation of Asinine Pulmonary Fibrosis and Similarities to an Emerging Human Interstitial Lung Disease

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Purpose of the study: Pleuroparenchymal Fibroelastosis (PPFE) is an emerging, idiopathic and likely under diagnosed pulmonary disease entity. Key features include an upper zone predominance of pleural fibrosis with intra-alveolar fibrosis and elastosis. The objective of our study was to examine ex vivo lung tissue from a cohort of aged donkeys with a high prevalence (37%) of fibrosing interstitial lung disease termed Asinine Pulmonary Fibrosis (APF). APF is a debilitating and untreatable syndrome of donkeys that is poorly understood and rarely documented. We hypothesise that some cases of APF share several key gross and histopathological features of PPFE and propose that both conditions could be a consequence of recurrent respiratory infections.
Materials and Methods: Whole asinine lungs were collected from 30 aged donkeys at routine necropsy at two UK donkey sanctuaries between June 2009 and January 2013. Nineteen 'APF' donkeys had evidence of pulmonary fibrosis on gross examination while 11 'control' animals had grossly normal lungs. Histological and HRCT features were categorised as 'consistent with' or 'inconsistent with' PPFE using a system described previously in the literature.
Results: Ten of 19 APF lungs were categorised as 'consistent with' PPFE on both histology and HRCT characteristics. All 10 lungs demonstrated predominantly dorsal pleural and subpleural fibrosis extending along inter-lobular septae. Intra-alveolar fibrosis with septal elastosis was a consistent feature.
Conclusions: This study is the first to combine HRCT and histological data to characterise and document pathological features of APF. We conclude that the majority of APF cases share key pathological features with human PPFE. Further study of APF may yield valuable information to help elucidate the aetiopathogenesis of this emerging human disease.

P28

Use of Digital Whole Slide Scanning and Automated Image Analysis to Assess Bleomycin Induced Interstitial Fibrosis of the Lung in a Rodent Model: An Objective Analysis of the Efficacy of Potential Therapies

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BACKGROUND: Pulmonary fibrosis (PF) is characterised by increased fibroblast proliferation and collagen deposition in lung interstitium. Bleomycin (BLM)-challenged rodents are commonly used for studying pathogenesis and treatment of PF. Traditionally drug effects on PF are assessed by microscopic review of lung sections by pathologists which is often time-consuming and subjective. The aim of this investigation was to identify whether quantitative analysis of changes in fibrotic parameters would identify statistically significant changes following administration of potential drugs to BLM challenged rats, thus assessing the usefulness of quantitative tissue image analysis to evaluate drug efficacy.
METHODS: Four cohorts of male Sprague Dawley rats were administered with BLM on Day 0. Treatment was initiated on Day 0 with pirfenidone and on Day 15 with pirfenidone, imatinib mesylate or prednisolone, until the end of protocol. Cohorts were sacrificed on Days 20, 30 and 40. Lungs sections were stained with H&E and Masson's Trichome. Scanned whole slide tissue sections were analysed by commercial image analysis software to analyse PF. Statistical analysis of data was performed using student's t-test.
RESULTS: We observed a significant increase in interstitial lung fibrosis with BLM by Day 40 ($p<0.05$). Objective changes were identified in morphological lung parameters following treatment. A reduction in collagen deposition was seen with imatinib mesylate on Day 30 (6.6% decrease; $p=0.714$), but this did not reach significance
CONCLUSION: Digital whole slide scanning coupled with automated image analysis is a powerful and effective tool to objectively quantify changes in PF. Use of these methods allows scientific investigators to further refine their preclinical models to enable their use to identify novel treatments for pulmonary fibrosis, and test them against current standard of care treatment protocols.

P29

Posterior Mediastinal Haemangioma: A Case Report

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Purpose: Case report of cavernous haemangioma in the posterior mediastinum.
Methods: Paraspinal posterior mediastinal tumour was submitted to our department for analysis. Patient was a 60 year old man who presented with upper back pain. Radiological features had suggested a neurogenic tumour at T8, which is the commonest lesion of the posterior mediastinum. Tumour was extradural but extended back to the neural exit foramina.
Results: Histological features were of a lobulated vascular proliferation without atypia, consistent with a cavernous haemangioma. Immunohistochemistry supported this diagnosis.
Conclusions: Haemangiomas are uncommon mediastinal tumours, with an incidence of less than 0.5% of mediastinal masses. Posterior mediastinal haemangiomas are relatively rare compared to the more common anterior mediastinal location. The majority of cases occur in patients under the age of 35 years. Most cases are discovered incidentally on chest x-ray. This cases is very unusual in terms of tumour site, age of patient and symptomatology.

P30

Lysosomal Activities and Cellular Homeostasis in Epithelial Tumours of Salivary Glands: An Immunohistochemical Investigation

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This investigation aims to explore lysosomal activities with relation to intracellular homeostasis, histological type and cellular phenotype in salivary neoplasia.
Paraffin-embedded, surgical specimens from 84 benign and malignant epithelial salivary tumours / adjacent glands were investigated by immunohistochemistry for CD63 antigen (a lysosomal membranous protein) and HSP27 (a member of the Heat Shock Protein family with roles in intracellular homeostasis).
Diffuse cytoplasmic CD63 immunoreactivity was seen in serous cells of acinic cell carcinoma; and mucous cells of mucoepidermoid carcinoma, pleomorphic adenoma (PSA) and Warthin tumour. Apical rims of CD63 immunoreactivity were seen in nondescript luminal cells of PSA, acinic cell carcinoma and polymorphous low-grade adenocarcinoma (PLGA). HSP27 immunoreactivity was seen in non-luminal cells of PSA; basal cells of oncocytic tumours; epidermoid cells of PSA and mucoepidermoid carcinoma; and cells outlining aggregates and lining pseudolumina of adenoid cystic carcinoma. PLGA often lacked HSP27 immunoreactivity. CD63 and HSP27 are not co-expressed in cells of epithelial salivary tumours. Expression of CD63 is preferentially associated with differentiated and luminal tumour cells, which probably reflects lysosomal processing of secretory granules and absorption of luminal material respectively. Expression of HSP27 is preferentially associated with non-luminal tumour cells and could reflect remodelling of cytoskeleton. HSP27 immunohistochemistry may be useful in the histopathological differential diagnosis between PLGA and adenoid cystic carcinoma.

P31

Identification and Turnover of Cells in Mucous Extravasation Cysts of the Minor Salivary Glands: An Immunohistochemical Investigation

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The presence of macrophages in these cysts has been established, but little is known about subsets and turnover of stromal cells in the cystic lining. The present investigation attempts to remedy this and increase understanding of events in obstructive, cystic, salivary disease.
Archival material from 45 mucous extravasation cysts, which had been routinely processed for histology, was investigated with the use of immunohistochemistry for subsets of interstitial / defence cells (CD34, SMA, CD68, factor XIIIa, CD117) and cell-cycle antigens (Ki67).
Widespread or focal meshworks of CD34(+) and SMA(+), capillary-sized vessels variously involved the lining of all cysts. While sheaths of CD34(+) fibroblasts sub-adjacent to the lining were seen in 87% of the cysts, about 1 out of 10 cysts showed spindled, SMA(+) myofibroblasts adjacent to the lumen. High numbers of CD68(+) and XIIIa(+), vacuolated or granular macrophages, occasionally multinuclear, were present in the cystic lining and lumen. Dendritic XIIIa(+) cells or CD117(+) mast cells were inconspicuous. The Ki67 index was low.
The results suggest that absorption and repair in mucous extravasation cysts are not simultaneous and vary in site, extent and rate. Absorption is intense and effected by macrophages involved in heterophagy. Angiogenesis contributes to repair. The growing cyst often effects re-arrangement of pre-existing CD34(+) fibroblasts, to sheath the lining. Adluminal myofibroblastic reaction, possibly in response to increased luminal pressure, is rare. Dendrocytes and mast cells are of little or no pathogenetic significance. Mucous extravasation cysts are low-turnover, absorptive granulomata the cell populations of which are influenced by the microenvironment.

P32

Suspicious Ulcer on the Tongue of a 7 Year-Old Male

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Introduction: Traumatic Ulcerative Granuloma with Stromal Eosinophilia (TUGSE) is an uncommon, self limiting ulcerative lesion of the oral mucosa which is known to mimic malignancy both clinically and histologically. Aetiology is unclear but tongue is the typical site and patients show a bimodal age distribution with peaks in infancy and middle age.
Clinical presentation: A 7 year old male with mild asthma presented with a 10 day rapidly enlarging 1x1.2cm ulcerative lesion on the ventral tongue and left cervical lymphadenopathy. There was no history of trauma. The tongue lesion was asymptomatic with elevated, indurated, erythematous borders and a sloughy centre. After six days, the lesion was unchanged and therefore biopsied to rule out malignancy.
Histopathology: Biopsy showed fibrinous ulcer slough with a deep inflammatory infiltrate including frequent eosinophils and plump pale histiocytes extending into skeletal muscle. The histiocytes were CD1a positive and S100 negative by immunohistochemistry. After consultation with haematopathology to exclude lymphoma and Langerhans cell histiocytosis, a diagnosis of TUGSE was made and close clinical review was advised.
Follow up: Review at two weeks revealed initial healing, followed by complete resolution of the lesion and associated lymphadenopathy at five months.
Conclusion: The sometimes dramatic clinical presentation of TUGSE may be concerning for oral malignancy and Langerhans cell histiocytosis and lymphoma may feature in the histological differential diagnosis. Importantly, the lesion is self limiting and rarely reoccurs. This case highlights the need for clinicians and pathologists to be aware of this condition in order for timely, accurate diagnosis and avoidance of unnecessary treatment with high morbidity.

P33

PAX9 Expression in Oral Cancer and Potentially Malignant Disorders of the Oral Cavity

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Purpose of the study: Oral cancer (OC) is a lethal disease and a global healthcare problem. Significantly, there are clinically recognisable oral precursor lesions that precede the development of cancer, called potentially malignant disorders (PMDs). Early detection of OC is known to improve patient outcomes. Predicting which PMDs will inevitably progress to cancer, using molecular biomarkers, would facilitate appropriate treatment decisions. PAX9 is a transcription factor that regulates epithelial differentiation and is thought to act as a tumour-suppressor; for example, PAX9 is progressively lost during oesophageal carcinogenesis. The role of PAX9 in OC formation is unknown.
Methods: This study, supported by a Pathological Society grant, examined PAX9 expression in biopsies from patients with PMDs and OCs. PAX9 expression was determined using immunohistochemistry. 199 oral mucosal biopsies, including normal oral mucosa, PMDs and OCs were stained. Image analysis was used to quantify the staining. These data were correlated with patient demographics, epithelial dysplasia grade and clinical outcome.
Summary of results: Compared to normal tissue, PAX9 expression was down-regulated in OCs, PMDs of all histological grades and morphologically normal epithelium adjacent to PMDs ($p<0.05$). However, PMDs with higher levels of PAX9 were more likely to transform to OC; 90% of PMDs with >40% positive nuclei progressed to OC.
Conclusions: PAX9 down-regulation in PMDs and OCs is consistent with its documented role as a tumour suppressor. Paradoxically, whilst the majority of PMDs showed low PAX9 expression, elevated PAX9 expression was associated with transformation to cancer. Further work is being carried out to establish the functional significance of PAX9 deregulation in oral carcinogenesis.

P34

Sino-Nasal Tract Myoepithelial Carcinoma Ex-Plemorphic Adenoma – A Case Report and Review of the Literature

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Background: Salivary gland type adenocarcinoma of the sino-nasal tract are unusual, of which adenoid cystic carcinoma is the most common type. However there are only isolated case reports of carcinoma ex-pleomorphic adenoma in the sino-nasal tract. The rarity of this tumour means the diagnosis is often not raised by pathologists, especially if the underlying pleomorphic adenoma is not recognised.
Case Report : A 32 year old patient present with left nasal obstruction of more than one year associated with intermittent bleeding and occasional epiphora. On examination the left nostril and left post nasal space was completely occluded by a polyp, with no further polyps in the right nasal cavity. Radiology showed complete obliteration of the left maxillary antrum, with further opacification of the left ethmoid sinus. The nasal airway was also obscured, punctuate calcification, which extended into the nasopharynx. A biopsy was taken, comprising fragments of partially smooth-surfaced and partially papillomatous friable light brown/ yellow tissue measuring 80x15mm. Histology (including specialist review) subsequently showed a multinodular tumour with dense hyalinised and fibrous areas, more cellular areas and a mucinous background. The cellular areas appeared to have a dual population of myoepithelial and epithelial cells (confirmed with immunohistochemistry) with pleomorphism and high mitotic index, raising the most likely diagnosis of a myoepthelial carcinoma. The more fibrotic areas had small ducts with myoepithelial cells and a low mitotic index, and represented residual pleomorphic adenoma.
A comprehensive review of the literature will also be performed with discussion of the clinical presentation, pathology and differential diagnosis.

P35

Is the SH2 Domain of Cten Essential for Cell Motility?

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Cten is a known oncogene in colorectal cancer. It is the smallest member of tensin gene family and has a role in enhancing cell motility. It is classically located at focal adhesions although, it has also been seen to localise to nucleus in metastatic deposits of tumours. Cten is a fascinating protein because of its interaction with integrins and the presence of a Src Homology 2 (SH2) domain. This suggests a role in communication with extra cellular matrix proteins and translating their signals through its interaction with other tyrosine phosphorylated proteins via the SH2 domain.
Cten increases cell motility in colorectal cancer cell lines, although the role of the SH2 domain in mediating this process is unknown. In order to investigate this, site directed mutagenesis was used to introduce a mutation in an important Arginine residue (at site 474) in the SH2 domain of Cten. Both Cten-GFP and SH2 mutant Cten-GFP were forcefully transfected in two colorectal cell lines HCT116 and RKO (both lacking Cten). The effect of forced expression was evaluated by performing transwell migration, wound healing assay.
It was seen that indeed there is a decrease in motility when transfection with SH2 mutant Cten-GFP was compared to control Cten-GFP ($p<0.05$). On western blotting, it was noticed that ILK and FAK levels were also decrease and N-cadherin and E-cadherin levels were also affected showing an epithelial mesenchymal transition (EMT switch) with Cten-GFP but not with SH2 mutant Cten-GFP. Wound healing assays showed a similar loss of cell motility with the SH2 mutant Cten-GFP.
It is concluded that Cten's effect of enhancing cell motility is in part modulated through its SH2 domain. This leads to interaction with other proteins involved in signal transduction such as integrin linked kinase (ILK) and focal adhesions kinase (FAK).

P36

Damage Associate Molecular Patterns (DAMPs) Inhibit Cell Motility in the Colon

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DAMPs are Damage Associated Molecular Patterns (DAMPs) represent cellular contents released into the surrounding micro-environment as cells undergo necrosis. DAMPs are detected by surrounding viable cells and are believed to modulate a wide range of cellular responses including migration and proliferation. CD24 has been recently identified as a putative receptor for DAMPs and has been shown to be up-regulated in inflammatory bowel disease and in colonic neoplasia — two conditions in which an increase in DAMPs may be expected.
The current study aimed to investigate the possible effect of DAMPs on colonic epithelial cells. Initially four different colorectal cancer (CRC) cell lines (two positive and two negative for CD24 expression) were stimulated with DAMPs and tested for effect on cell proliferation and cell motility. The DAMPs were prepared by repeat freeze-thaw cycles and stimulation was with DAMPs prepared from autologous cells. DAMPs exposure resulted in no effect on cellular proliferation assay in any of the cell lines. However, exposure to DAMPs resulted in significant reduction in cell motility in all cell lines as assessed by both transwell migration ($p<0.01$) and the wound healing assay ($p<0.004$). Furthermore, the effect seemed to be both through general inhibition of cell motility and inhibition of chemotaxis. In order to test the role of CD24 as a receptor for DAMPs and a mediator of inhibited cell motility, we knocked-down CD24 in cell line which was positive for CD24 expression. This had no effect on the response of the cell line to DAMP exposure.
We conclude that DAMPs appeared to inhibit both directional and non directional cancer cell motility but showed not effect on cellular proliferation. The inhibitory effect of DAMPs is not mediated through CD24.

P37

Quantitative Proteomic Profiling of Human Sarcoma Using Isobaric Labelling Coupled to LC MS/MS

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Sarcomas are rare forms of cancer that can form in connective tissue, such as muscle, bone, nerves, cartilage, blood vessels and fat. Although rare, the outcome for patients is poor, with surgery and post-operative radiotherapy the standard treatment for patients. A better understanding of the molecular pathology of these diseases may allow for the development of improved strategies for their treatment. Genomics has provided detailed knowledge of genetic abnormalities in sarcomas but provides no information on levels or localisation of targetable proteins expressed by these tumours. To begin to define the proteome of sarcoma and to atempt to identify novel targets and biomarkers expressed in different forms of high grade sarcoma we have carried out an initial study using Tandem Mass Tag (TMT) isobaric labelling coupled to liquid chromatography-tandem mass spectrometry (LC-MS/MS) of a panel of different sarcomas. We identified 1568 proteins that could be quantified and we found that a loose trend in dysregulated proteins exists between the 3 sarcomas studied, with 749 proteins >2 fold up-regulated and 88 <0.5 fold down-regulated in all 3 sarcomas. We further validated 4 proteins deemed to be potential drug targets and demonstrated by qRT-PCR and immunohistochemistry that CD44, CD63, CLIC1 and CLIC4 are all up-regulated in sarcoma.

P38

The Effects of Novel Carbonic Anhydrase Inhibitors on the Proliferation and Invasion of Breast and Ovarian Cancer Cells

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The hyperproliferation of cells within a tumour causes the formation of regions of hypoxia and a build-up of metabolic waste, which is compounded by the aberrant tumour vasculature, and leads to the formation of distinct regions within a tumour: a necrotic core surrounded by a hypoxic peri-necrotic area. Cancer cells within the hypoxic area rely on glycolysis to produce energy, leading to the production of lactic acid, which causes extracellular acidosis. To survive in this acidic environment, hypoxic cancer cells have increased expression of HIF-1 (hypoxia inducible factor-1) regulated enzymes such as carbonic anhydrase IX (CAIX). The aim of this study was to assess the effects of novel carbonic anhydrase inhibitors (CAIs) on the proliferation, migration and invasion of breast (MDA-MB-231) and ovarian (SKOV-3) cancer cell lines through the use of SRB (sulphorhodamine) assays, wound healing assays, and 3D invasion assays. High concentrations of the inhibitors were found to inhibit the proliferation and migration of both the MDA-MB-231 and SKOV-3 cell lines. High concentrations of the CAIs were also found to decrease the amount of invasion that occurred in MDA-MB-231 spheroids, while low concentrations of inhibitor caused increased invasion; the analysis of the effects of the CAIs on the invasion of SKOV-3 cells was not possible due to the failure of the ovarian cancer cells to form proper spheroids. The ability of the novel CAIs to prevent invasion was then reproduced in ER+ and triple negative breast tumour explants derived from human patients. Overall, the results of this project highlight the potential of these novel CAIs as candidates for antimetastatic therapy.

P39

Testing for KRAS and BRAF in Colorectal Cancer? A Comparison of Three Methods

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Purpose of the study: The widespread use of targeted therapies has generated the need for accurate and cost-effective methods of mutation detection. Several platforms are currently being used in molecular pathology services for KRAS and BRAF testing in colorectal cancer. Our centre currently offers KRAS and BRAF testing of these tumours using pyrosequencing. We wished to investigate the utility of two alternative testing platforms.

Methods: 64 colorectal tumour samples formalin fixed paraffin embedded with greater than 20% tumour content, were analysed for KRAS codon 12 and 13, and codon 61 mutations and BRAF V600E mutations using pyrosequencing. The results were compared to those of two new platforms; the COBAS 4800 System (Roche Diagnostics), which is based on real-time PCR, and the Evidence Investigator (Randox) which uses multiplex biochip technology.

Summary of results: Similar KRAS mutation results were obtained for 63 tumours when using pyrosequencing and COBAS (98.4% concordance rate). However, a false positive result, a p.Gly60Gly silent mutation, confirmed by sequencing was obtained by COBAS. False positive and false negative KRAS results were obtained when comparing Randox with pyrosequencing (89% concordance rate). There was 100% concordance for BRAF testing using all three platforms.

Conclusions: Our results show good concordance for KRAS and BRAF testing using the three methods described. However, false positive and negative KRAS results should not be underestimated as these patients would be denied or be given unnecessary treatment. We conclude that pyrosequencing is a reliable and cost-effective method to test for KRAS and BRAF mutations.

P40

HER2 Testing In FFPE Breast Tumours Using Droplet Digital PCR

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The benefit to patients of HER2 testing all breast cancer cases is clear and well documented. However, the financial and time pressures that this places on histology departments are quite considerable. Our pathology service tests over 1700 breast tumours per year for HER2 status, using a recommended ISH technique, adding over £130K to the annual reagent bill, as well as the cost of consultant time required to analyse each slide as it is produced.

We have conducted preliminary investigations into the feasibility of using a droplet digital PCR (ddPCR) method for HER2 analysis. This technique is able to count the number of HER2 copies in a given sample relative to RNaseP, the reference gene of choice in many gene copy number studies. A result is produced with little or no time required from a histopathology consultant. We tested 27 FFPE breast tumours, approximately half were core biopsies and half were resections, all of which had previously been assessed with SISH and evaluated by experienced histopathologists.

Our initial data is extremely encouraging with 27/27 samples producing an expected clinical answer; amplified (11 samples) or non-amplified (16 samples). The data indicates that an assessment will be at its most robust if the samples are assessed in duplicate or even triplicate. Whilst the assay may have a drawback in that there is no histological assessment of the sample, the lack of required consultant time, the low cost per sample of the assay as well as this interesting early data suggests that this technique should be more fully investigated as an alternative means for routine assessment of HER2 status.

P41

Founder Effect Analysis Of Disease Haplotypes In DFNB23/ USH1F Linked Pakistani Families

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Usher syndromes are a group of autosomal recessive disorders characterized by moderate to profound sensorineural hearing loss and progressive visual loss from retinitis pigmentosa. Clinically they are classified into three types on the basis of phenotypes. Within each clinical group molecular heterogeneity exists and people with indistinguishable phenotypes have mutations in different genes. Protocadherin-15 (PCDH15) is one of the five genes identified as being mutated in Usher 1 syndrome and defines Usher syndrome type 1F (USH1F). Mutation in this gene also cause nonsyndromic deafness DFNB23. A total of 25 families were collected in which pattern of inheritance was autosomal recessive and were screened for locus DFNB23 by using fluorescently labeled markers D10S2529, D10S546, and D10S2522. Three families were found to be linked with DFNB23. Haplotypes of these families were compared with 12 previously linked families obtained from CEMB repository. Seven families divided into two groups shared same haplotypes while in other eight families, no correlation was found between the haplotypes. Variability of haplotypes among families indicate presence of different type of mutations and families with same haplotypes may have same founder. These results will lead to better understanding of hearing impairment caused by mutations in PCDH15 and will help in identification of carriers and genetic counselling.

P42

A System for Requesting and Electronically Recording Generic Authorisation (consent) for use of Surplus Tissue for Medical Education and Research: One Centre's Experience as Part of the Cancer Research UK Stratified Medicine Programme

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Purpose: To outline our experience of requesting and electronically recording authorisation (consent) from patients to use their surplus tissue in medical education and research. The patients described are participating in Cancer Research UK's Stratified Medicine Programme (SMP). **Methods**: The SMP aims to profile somatic cancer gene mutations in 9000 cancers from across the UK between 2011 to 2013. Eight centres, including our own, are submitting cancer tissue and matching blood samples. **Results**: Sample identification, collection and submission are organised via the Bio-Repository which is embedded in the Pathology Department. The Bio-Repository aims to give all patients the opportunity to donate their surplus tissue. Authorisation processes are therefore generic rather than study-specific. Before their hospital visit all patients are sent an information sheet. Most patients awaiting elective surgery attend a pre-operative assessment clinic where their wishes regarding surplus tissue are recorded in their electronic record. Thereafter research nurses identify appropriate cases and request consent from any patients not already approached. Patients can withdraw their authorisation at any time. For patients contributing to the SMP, letters of thanks are sent. To date, 1005 patients have been approached to enter the SMP and 986 (98%) have provided authorisation. Only one patient has withdrawn. **Conclusions**: This system enables the patient's wishes regarding the use of surplus tissue to be easily identified and updated during their journey within the NHS. Almost all patients are keen for their tissue to be so used. Broad, enduring authorization avoids the need for consenting for individual studies, which saves time and should facilitate recruitment. **Acknowledgements**: funding for SMP from Cancer Research UK, AstraZeneca, Pfizer, Roche, Bristol-Myers Squibb & Oracle Health Sciences; local funders include Cancer Research UK via ECMC & NHS.

P43

Surplus Blood Samples can be Routinely Collected for Research Purposes: One Centre's Experience as Part of the Cancer Research UK Stratified Medicine Programme

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Purpose: To outline our approach to and experience of routinely identifying and collecting surplus blood samples for research. The patients described are participating in Cancer Research UK's Stratified Medicine Programme (SMP). **Methods**: The SMP aims to profile somatic cancer gene mutations in 9000 cancers from across the UK between 2011 to 2013. Eight centres, including our own, are submitting cancer tissue, as tissue sections, and matching blood samples for DNA analysis. Samples are organised via the Bio-Repository which is embedded in the Pathology Dept. **Results**: Until recently, for such a study, blood samples would have been requested, authorised and withdrawn individually from each patient. In our centre there is a system for requesting and electronically recording generic authorisation (consent) for use of surplus tissue. A system has also been developed to identify and collect surplus blood from routine Full Blood Count (FBC) samples. Only 88µL of a typical 4ml EDTA sample is tested. Usually over 3.8ml is surplus, stored in a 4°C fridge for 3-7 days then discarded. Instead, Bio-Repository staff now keep a list of patients potentially eligible for SMP and liaise with the ten Haematology Depts in our Health Board area to identify and collect recent blood samples: most were post-operative. Breast cancer patients usually have only pre-operative blood samples which are more difficult to identify in time. To date, 935 patients have entered the SMP from our centre. Matching surplus blood samples have been obtained from 877 (94%); those missing are from patients with breast cancer or from other health board areas. **Conclusions**: Surplus blood is an excellent resource for research: its collection is feasible within a system of generic consent and with appropriate staffing. **Acknowledgements**: SMP funding from Cancer Research UK, AstraZeneca, Pfizer, Roche, Bristol-Myers Squibb & Oracle Health Sciences; local funders include Cancer Research UK via ECMC & NHS.

P44

Primary Sinonasal Adenoid Cystic Carcinoma Presenting with Skin Metastases Both Carrying the t(6;9)(q22-23;p23-24) Chromosomal Translocation. A New Diagnostic Biomarker for Adenoid Cystic Carcinoma?

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Introduction - Metastatic deposits of adenoid cystic carcinoma (ACC) are known to occur mainly in the lung, bone, liver and brain. Cutaneous metastases are very rare, usually confined to the head and neck area and discovered as synchronous disease to the primary salivary gland ACC. To the best of our knowledge this is the first case of ACC manifesting itself as recurrent cutaneous metastasis to the skin 7 and 5 years before the primary paranasal ACC was diagnosed. There is recent evidence that ACC harbour a specific chromosomal translocation t(6;9) leading to fusion gene MYB-NFIB and overexpression of oncogene MYB on immunohistochemistry. We speculated that molecular analysis of t(6;9) could be useful to confirm primary and metastatic ACC in this case.
Case report - 89 year old woman presented with recent falls and dysphasia. MRI revealed multiple lytic lesions in the skull and left maxillary sinus. The patient has two skin lesions removed from her left forearm 7and 5 years previously.
Materials and methods - Tumour tissue from left maxillary sinus, left forearm were tested for t(6;9) chromosomal translocation and immunohistochemistry.
Results - The t (6;9) translocation was demonstrated in both paranasal and skin tumours.
Discussion - In our study we have demonstrated this translocation was present in both primary ACC of paranasal sinus and in the skin deposits thus confirming the primary and metastatic ACC. This report illustrates the role of MYB-NFIB fusion transcript as a novel diagnostic biomarker in primary and metastatic ACC.

P45

Evaluating Stress Biomarkers in the Cuprizone Model of Multiple Sclerosis

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The cuprizone model of multiple sclerosis (Blakemore, 1973) is a well established model of toxic demyelination of the central nervous system. In this model young adult mice are fed low doses (0.2%) of cuprizone over a number of weeks. Cuprizone is a copper chelator that consistently leads to demyelination within cortical grey matter and a number of white matter tracts including the corpus callosum. Recent studies suggest that oxidative stress and inflammatory mechanisms are key players in the demyelination process.

Recent studies have assessed the ability of a new generation of genetically engineered toxicity- stress reporter mouse models to monitor and localise cuprizone-induced demyelination. These models utilise molecular reporters which are attached to the regulatory sequences of key stress sensor genes that are activated by a wide variety of chemical toxins and carcinogens. Upon activation of the stress-gene, one of these reporters, the biologically inactive beta-chain of human chorionic gonadotrophin, is excreted into the blood and subsequently the urine, while the second reporter remains localised to the cells in which the sensor gene is activated. Any chemical or pathological condition that causes toxicity will result in a real-time "signal of toxicity" that can be monitored by urine analysis for the excretable reporter. The site of toxic insult can then be identified by staining brain sections for the in situ reporter. We have demonstrated in our dual-reporter mouse model, which utilize SOD2 stress-related promoters, that histological analysis confirms demyelination of the corpus callosum following cuprisone treatment. Interestingly, significant changes in expression of our stress reporter occur at 5 weeks of treatment which corresponds with the period of maximal demyelination (Franco-Pons et al, 2007). Our model represents an in vivo method of studying demyelination.

P46

Protein Extraction from Formalin-fixed Paraffin-embedded Material: Unlocking the Door to Biomarker Discovery

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Background: Comparative proteomics allows comparison of the protein content of two tissues (e.g. disease and control). Differences in protein composition represent potential biomarkers for the condition of interest which can be confirmed using other methods such as tandem mass spectrometry. This allows rapid translation of protein differences into clinically-applicable tests. The use of archival formalin-fixed paraffin-embedded tissue would allow application of the technique in diseases with a low incidence. To be used in proteomic analysis, protein must be successfully removed from paraffin blocks, rehydrated and the effects of formalin fixation reversed, before standard proteomic processing and analysis. This has been successfully achieved by means of commercially-available kits, but these are prohibitively expensive for large studies.
Aim: To develop a technique from first principles enabling successful removal of protein from archival blocks for use in proteomic analysis.
Method: 1. Removal of tissue cores from archived blocks. 2. Five washes in xylene to remove paraffin. 3. Rehydration by immersion in decreasing concentrations of ethanol (100%, 95%, 90%, 80%, 70%, 0%). 4. Incubation at 60°C for 2 hours in 50mM NaHCO3 containing 2% ASB-14 to reverse some of the crosslinking cause by formalin-fixation. 5. Mechanical Homogenisation. 6. Standard proteomic analysis.
Results: Between 50 and 277 proteins were identified from archival pooled post mortem kidney and heart samples. These hit numbers are generally comparable with previously reported extractions from formalin-fixed paraffin-embedded tissue.
Conclusions: Protein extraction from formalin-fixed, paraffin-embedded samples is possible using simple, inexpensive techniques, allowing the use of archival specimens for proteomics and biomarker discovery.

P47

Automated Cellient^{TM} Cytoblocks – Better, Stronger, Faster?

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Purpose of the study: Cytoblocks are an important adjunct in cytopathology to provide additional morphologic detail and a platform for immunocytochemistry (ICC). The automated Cellient (^{TM}) system produces cytoblocks (CCBs) in 45 minutes using a vacuum assisted methanol based fixation protocol in comparison to traditional cytoblocks (TCBs) which use overnight formalin fixation. The aim of this study was: 1.To compare the CCB and TCB methods in terms of cellularity, morphology and immunoreactivity 2.To assess the potential to add formalin fixation to the CCB method for ICC studies to allow direct comparison with routinely used formalin fixed tissue controls.
Methods: 40 cytology samples (32 malignant, 8 benign) were included. Each sample was evenly divided to produce cytoblocks using A) TCB method B) CCB method (methanol fixation) and C)CCB method using formalin fixed material. H&E sections were assessed for cellularity and morphology (using scoring criteria for nuclear membrane, chromatin and nucleolation). ICC was assessed on 14 cases using a panel of antibodies. A further process method used formalin fixation of unstained CCB sections during the ICC process. 3 additional CCB samples of variable cellularity were serially sectioned to determine the optimal sectioning depth and number of sections possible. Scoring was performed by 2 independent, blinded reviewers.
Results: For malignant cases, morphology was significantly superior with CCBs compared to TCBs ($p<0.001$). All methods yielded sections of comparable cellularity. ICC was excellent in all groups and the addition of formalin, either to the CCB method or on-slide during the ICC process did not influence the quality of ICC staining. Serial sectioning through CCBs showed optimum cellularity at 30-40um with minimum 27 sections possible.
Conclusions: 1. Methanol fixed CCBs provide significantly superior morphology to TCBs. 2. Cellularity is comparable but not superior between TCBs and CCBs with maximum CCB cellularity at 30-40um and minimum 27 sections posible. 3. Turnaround time of 45 minutes allows same day ICC for urgent cases whilst preserving superior cytological morphology. 4. Ability to formalin fix CCB sections during the ICC process allows the use of standard control material and protocols for ICC without any compromise to results.

P48

Bone Histology Requests for People with Fractured Neck of Femur

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Background: Bone histology samples are frequently sent for people with fractured neck of femurs to screen for underlying malignancies, but the quality of the requests can be vague. It is not always clear if a specific pathology is suspected and if so why, making it difficult to provide a clinically relevant report.
Objectives: To assess if bone histology requests are being completed with sufficient clinical and radiological information.
Method: A retrospective audit of histology from 200 operations was performed to identify bone samples from patients with neck of femur fractures. The histology requests for these patients were reviewed, as were the electronic patient records which contained information on co-morbidities.
Results: Forty-three patients were identified. The reason for histology was "?pathological fracture" in 53%, whilst metastases from a known primary were suspected in 37%. The remaining 10% were suspected metabolic bone disease or infection. Only one case provided sufficient clinical detail, and 66% provided partially sufficient clinical information, for example, "24 year old female ?pathological". 63% of requests did not state whether or not the patient had a known malignancy. No request contained sufficient radiological information, but two alluded to suspicious features without elaborating upon them e.g. "unusual bone on x-ray". Furthermore, review of electronic records showed significant known medical history was not included on 30% of request forms, including five malignancies and five cases of osteoporosis.
Conclusion: Request forms frequently omit useful clinical and radiological features; their inclusion would aid the pathologist to put their findings in context and select additional stains if necessary.

P49

Assessing the Quality of Colorectal Cancer Reporting by an Advanced Practitioner Healthcare Scientist

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Purpose of the study: The workforce in Histopathology departments is changing in response to increasing workload and efficiency pressures. The role of the Advanced Practitioner Healthcare Scientist is evolving, driven by qualifications in specimen dissection, the Modernising Scientific Careers agenda, and an RCPath sponsored reporting pilot project for Healthcare Scientists, based on ST1 training. The purpose of this study is to assess the quality of microscopy by an Advanced Practitioner Healthcare Scientist.
Methods: 36 colorectal cancer resections were dissected and reviewed by the Advanced Practitioner between March 2012 and February 2013. Minimum dataset items were recorded independently and then correlated with the findings of the Consultant Histopathologist at joint review before issuing of the final report.
Summary of results: The mean time taken for each dissection was 70 minutes (range 30-240). A mean of 4.4 blocks of tumour were sampled per case (range 3-11). 32 out of 36 cases (88.9%) were correctly TN staged. Of the 4 incorrectly staged, 2 were upstaged and 2 were downstaged. Assessment of extramural vascular invasion by the Advanced Practitioner was accurate in 28 out of 36 cases (77.8%). The mean number of lymph nodes retrieved per specimen was 28 (range 8-76). There was a discrepancy in lymph node metastasis assessment in 2 out of 36 cases (5.6%), resulting in one incidence of upstaging and one of downstaging.
Conclusions: Advanced Practitioners who participate in colorectal cancer dissections should be encouraged to take part in the microscopic reporting of these specimens. These results show a high level of concordance with the final pathologists report, but also indicate areas for future education.

P50

Sudden Adult Death on Cruise Ships

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Commercial cruises are a rapidly growing industry with over 80 million individuals embarking on cruises each year and it is estimated one passenger dies every 4–6 weeks on a single ship. Currently, despite this, no cruise company maintains an adequate record of these deaths nor of the causes, which presents a significant knowledge gap in a growing industry with an ageing clientele. Southampton is a major port on the British south coast. As such, all deaths occurring on-board passenger cruise ships docking in this city are referred to H.M. Coroner for Southampton and New Forest. 53 deaths, in which a post mortem examination took place, were reviewed. Deaths below 18 years of age and those who were admitted to hospital prior to death were excluded. Most deaths were male, and over 60 years with two or more known co-morbidities at the time of boarding. 46% of deaths were attributed to cardiovascular disease. 14% died as a result of infection or infectious exacerbations of chronic respiratory conditions. The remaining 40% of cases were the result of accident, suicide and hepatobilliary disease. Not surprisingly, the prominent cause of death was cardiovascular in nature, with ischaemic heart disease accounting for 20%. Deaths due to infections of the respiratory tract contributed to a large proportion of death, despite most reports focusing on the apparent prevalence of gastrointestinal infection morbidity and mortality. Suicide and significant natural disease was found amongst a small proportion of crew members.

P51

Asbestos Exposure and Post Mortem Practice

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Asbestos related disease is a common encounter in the post mortem room, with possible compensation if death has occurred prematurely due to occupational exposure. All post mortem examinations with a history of asbestos exposure were reviewed and audited in accordance with the Royal College of Pathologists best practice guidance for such deaths. Retrospective data from a three year period for post mortem examinations undertaken at a teaching hospital, in which there was a suspicion of occupational asbestos exposure, was analysed. 103 cases where "asbestos exposure" was suggested were identified and 102 were male. In 44 cases (42.7%), asbestos or asbestos related disease was included within the cause of death. A further 5 cases confirmed asbestos bodies with light microscopy, but it was not thought to be significant in the cause of death. 36.9% of cases showed no apparent fibrogenic dust (only one case was sent for mineral fibre analysis). 15.5% had no histology taken. Therefore, only 48.5% of examinations followed the Royal College best practice guidance. For those cases where no asbestos bodies were seen, or no samples were taken, there was little macroscopic evidence to suggest asbestos related disease to the severity of affecting quality of life. However, the only definitive method of measuring exposure is to undertake mineral fibre analysis. We recommend that the guidelines are followed in order to ensure a quality service is delivered in a time when the post mortem examination is being placed under such high scrutiny.

P52

Audit of Thyroid Fine Needle Aspiration Cytology Samples Reported as Insufficient for Diagnostic Purposes

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In our department, there were perceived to be a large number of thyroid fine needle aspiration cytology (FNA) samples which contained insufficient material for accurate diagnosis. Immediate thyroid FNA adequacy assessment is recommended in the Royal College of Pathologists (RCPath) cytopathology tissue pathway (2010), which is not currently practiced as part of our local service.
Objectives: (1) To identify the proportion of FNAs reported as "insufficient". (2) To establish the delay in diagnosis due to repeat sampling. From July 2009 to July 2012 850 thyroid FNAs were processed through the department, from 744 patients. 169 samples were reported as "insufficient," of which 21 had at least one further "insufficient" FNA. Cases were sorted as to whether the final diagnosis was subsequently made on cytology or histology. Other cases had either radiological follow-up, inconclusive investigations or no further investigations. 20% of thyroid FNAs were reported as "insufficient" (169 of 850). 45% of "insufficient" cases did not have further cytology or histology and of these, half had benign radiological or clinical findings. 24% of cases had a mean delayed diagnosis on repeat FNA of 96 days (standard deviation 109). 19% of cases were diagnosed on subsequent thyroid tissue histology with a mean delay of 148 days (standard deviation 119). 12% of cases had at least one further repeat FNA which was "insufficient" and currently no further pathology investigations. There are a high proportion of thyroid FNAs which are presently reported as "insufficient" for diagnosis. This results in diagnostic delay, as well as repeat sampling being time-consuming, costly and unsatisfactory for the patient. There are general recommendations from the RCPath and the British Association for Cytopathology regarding the FNA cytology service and we are evaluating local implementation in order to address the current thyroid FNA "insufficient" rate.

P53

Double Reporting in Histopathology: A Local Evalution of Practice

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The recent RCPath publication *"Double Reporting in Histopathology"* provides guidance on cases that should be double reported. However, most pathologists utilise the opinions of colleagues regularly in day to day practice. This study evaluated the frequency of and attitudes to "double reporting". A retrospective review of 38,000 cases in a large teaching hospital evaluated the frequency of second opinion for each consultant, comparing this with duration of consultant experience and area of specialist practice. A qualitative survey of double reporting practice was also carried out. Double reporting was recorded on the laboratory IT system in 1900 cases (5%) and was more common with consultants of less than 5 years experience than consultants with more than 20 years experience. There was a higher proportion of double-reported cases in breast, respiratory and dermatopathology than other diagnostic areas. Double reporting occured in 4 common settings – a "negative" biopsy, an unexpected finding, unusual histological appearances and uncommon diagnoses. The increased use of double reporting by less experienced consultants is not surprising, it is possible that this has always been the case. However, shorter training and less independent trainee reporting than in previous years may be relevant. Consultant re-training as part of departmental reconfiguration accounts for the increased proportion of double reporting in breast and respiratory pathology. In skin cases, the increase is substantially due to RCPath guidance on melanocytic lesions. Double reporting is a crucial part of consultant practice – how it is used and documented requires formal consideration with regard to revalidation.

P54

An Audit on Hydatidiform Moles in an Irish Hospital

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Hydatidiform moles are defined as 'abnormal conceptions with excessive placental and little or no foetal development'. Complete Moles (CM) are usually due to endoreduplication after nonospermic fertilisation of an anucleate Oocyte. Partial Moles (PM) most frequently result from dispermic fertilisation of a nucleate Oocyte. Complications of MP include Persistant Trophoblastic Disease (PTD), where the mole invades into or through the uterine wall, which can lead to haemorrhage and metastasis to other organs. Choriocarcinoma occurs in 2-3% of MP, particularly CM. Both PTD and Choriocarcinoma are highly responsive to chemotherapy when diagnosed at an early stage.

In our Audit, we compared the number of MP to the total number of documented pregnancies over a 2 year period. We found the incidence of MP was 1.5/1000 pregnancies, similar to the UK (1-3/1000) and worldwide (0.5-2.5/1000). Moles occurring as part of a twin pregnancy are reported as rare worldwide (1:100,000), however we found 2 cases of concurrent twin and MP. None of the women in our study developed Choriocarcinoma.

Increased ultrasound monitoring has resulted in earlier detection of MP. However 8 out of 11 cases were not clinically suspicious for molar pregnancy, highlighting the importance of submitting all POCs for histological examination.

Early CM often lack the classical features of later CM, posing diagnostic challenge. On review, 2 out of the 7 PM in the study were reclassified as early CM based on morphological features. Both were persistent and required further D&C. 1 PM was confirmed by FISH/P57KIP2. A previous study found up to 50% of early CM were misdiagnosed as PM, suggesting that immunohistochemistry and genotyping may be of benefit in cases where morphology is ambiguous.

P55

An Audit of Prostate Biopsy Reporting Suitable for Revalidation

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The five-year revalidation cycle requires pathologists to participate in audit that fulfils GMC criteria. We present an audit that can be carried out in any department that routinely reports prostate biopsies.

Prostate needle biopsies reported by 2 pathologists (A and B) between April 2011 and February 2013 were identified from the pathology records of C&V UHB. The distribution of important diagnostic categories, the distribution of Gleason sum scores, the frequency of detection of perineural invasion (PNI) and extraprostatic extension (EPE) was determined for the individual pathologists.

1049 sets of prostate biopsies were reported by the 2 pathologists. The overall diagnostic categories were inadequate: 1 (0.1%); benign: 306 (29%); high-grade PIN: 108 (10.2%); suspicious for carcinoma: 45 (4.2%); and adenocarcinoma: 589 (55.8%). Among the cases of prostate cancer, PNI was identified in 209 (35.5%) and EPE in 48 (8.2%). The Gleason sum scores were 6: 248 (42%), 7: 232 (39%), 8 +: 105 (19%).

There was no significant difference between the two pathologists in the frequency of various diagnostic categories, distribution of Gleason sum scores or in the frequency of PNI reported. However, the detection rate of EPE was significantly different (4.1% by A vs. 10.6% by B, Student's T Test, P=0.004). The frequency of detection of carcinoma, grade distribution, and perineural invasion is within the ranges previously reported; the frequency of "suspicious for carcinoma" is well below the recommended upper threshold (10%).

The audit conforms to GMC requirements as it focuses on individual performance, can be compared to published data and recommended thresholds, and provides information that can assist in both reflection on, and improvement in practice. Following this audit the 2 pathologists will review their criteria for the diagnosis EPE and pathologist A will be more alert to the possibility of EPE.

P56

Postradiation Angiosarcoma of The Small Intestine: A Case Report

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INTRODUCTION: Postradiation angiosarcoma is a high-grade sarcoma presenting mainly in the skin and subcutaneous tissue. Postradiation angiosarcoma of the small bowel is a very rare entity, with less than 15 cases reported in the English literature.

CASE DESCRIPTION: We report the case of a postradiation angiosarcoma of the small intestine in a 92 year-old woman, 12 years after pelvic radiotherapy for a Dukes's C colonic cancer. The patient presented with symptoms of intestinal obstruction. A computer tomography study of the abdomen revealed dilated small bowel loops and multiple masses in the liver. At exploratory laparotomy parts of the small bowel looking fibrosed/strictured and of questionable viability were excised. There was no suspicion of malignancy at the time of the resection. Macroscopically, the small bowel specimen showed focal thickening and haemorrhage in the wall. Microscopically, the small bowel was infiltrated by a poorly differentiated tumour with a solid spindle cell appearance, apparently arising in the submucosa and invading through muscularis propria to the serosa. In areas of better differentiation there was recognizable vascular channel formation within the tumour. The diagnosis of angiosarcoma was confirmed immunohistochemically by tumour cell expression of vimentin, CD31 and CD34.

DISCUSSION: Although angiosarcomas of the small bowel are extremely rare tumours, this diagnosis should be entertained for any poorly differentiated neoplasm arising in a previously irradiated site. They can be mistaken for a gastrointestinal stromal tumour, other sarcomas, a malignant melanoma or a poorly differentiated carcinoma. Immunohistochemical stains are mandatory to establish a diagnosis.

P57

Assessment of Trends in Lymph Node Yield in Colorectal Cancer

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The presence of lymph node metastasis is a key prognostic factor in colorectal cancer and lymph node yield is an important parameter in assessing the quality of histopathology reporting of colorectal cancer excision specimens. It is important to identify all lymph nodes in colorectal cancer excision specimens and this is re-emphasised in the recent Healthcare Improvement Scotland quality performance indicators for colorectal cancer which re-states this guidance with a target of at least 12 lymph nodes being examined in at least 80% of specimens.

This study assesses the trend in lymph node evaluation over time in a single institution and assesses current performance in relation to this quality performance indicator. It compares the lymph node yield of a contemporary dataset compiled from the histopathology reports of 2178 patients who underwent surgery for primary colorectal cancer between 2005 and 2012 with that of a historic dataset compiled from the histopathology reports of 1038 patients who underwent surgery at 5 yearly intervals from 1975 to 2000.

There was an increase in lymph node evaluation over time with 100% of patients from the contemporary dataset having a lymph node count documented compared to 34% of patients from the historic dataset. The number of lymph nodes examined also increased with time. The mean lymph node yield was 5.41 in 1995 compared to 21.38 in 2012. In 2012 92.9% of all cases had at least 12 lymph nodes examined and for those cases which did not receive neoadjuvant therapy the mean lymph node yield was 22.02 with 94.3% of those cases having at least 12 lymph nodes examined.

In conclusion the data indicates that this centre is exceeding the quality performance indicator for lymph node yield.

P58

Primary Gastric Melanoma: A Case Report

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Introduction: Primary gastric melanomas are extremely rare with fewer than 17 case reports in literature. It is an under diagnosed entity due to its non-specific signs and symptoms. A high clinical suspicion and specific immunohistochemistry is necessary to reach a conclusive diagnosis.

Case report: A 59 year old gentleman presented with an eight week history of central epigastric pain and malaena. On examination he had epigastric tenderness and laboratory investigations revealed a haemoglobin of 5.8 g/dl .

Computed tomography revealed thickening of the lesser curvature of stomach with a 15mm lesser sac node and bilateral pulmonary nodules suspicious of metastasis. Upper GI endoscopy showed a large ulcerated gastric lesion in the upper body of the stomach.

Histology of the biopsy from this lesion showed a poorly differentiated tumour composed of spindle and epithelioid cells which were positive for S100, HMB45, Melan A and vimentin and were negative for CK7, CK20, CEA, TTF1, CD117, CD34, Desmin, SMA, CK and EMA. This confirmed the diagnosis of malignant melanoma.

The patient denied history of any prior skin lesions. There were no suspicious lesions identified on clinical examination. The patient was referred to oncology but died 12 months after the diagnosis.

Discussion: The clinical manifestation of gastric melanomas is similar to those of other gastric tumours. CT, endoscopy and histopathology play a key role in diagnosis. Criteria for the diagnosis of primary gastric melanoma include an absence of a concurrent lesion and a lack of history of a cutaneous melanoma.

Conclusion: Primary gastric melanomas are extremely rare. Amelanotic melanomas or poorly differentiated tumors can be easily missed unless appropriate immunohistochemistry is performed. Early detection and surgical intervention is critical for improved survival, although the overall prognosis remains poor.

P59

Pathology Trainees (and EVG) can Improve the Quality of Colorectal Cancer Reporting: An Audit Following Change in Practice

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Aim: We audited our colorectal cancer reporting to assess the impact of a departmental change in practice from predominantly consultant to predominantly trainee delivered trimming of colorectal cancer specimens.

Method: Colorectal cancer resection reports from the 5 months prior to and 5 months following the change in trimming practice were identified. These were audited against standards in the Royal College of Pathologists Dataset (for lymph nodes harvest, rates of lymphovascular invasion and peritoneal surface involvement) and the Healthcare Improvement Scotland Cancer Quality Performance Indicators (for percentage of cases with <12 lymph nodes identified).

Results: The proportion of cases trimmed by consultants reduced from 77.8% to 31.1% following the change in practice. The mean number of lymph nodes identified per case was 18.1. Trainees in years 2 to 4 of training found the highest average number of nodes per case at 19.2 and found <12 nodes in 11% of cases. Year 1 trainees and consultants averaged 18.1 nodes per case and found <12 nodes in 22.5% and 14.3% of cases respectively. ST5 trainees found 16.6 nodes per case with <12 nodes found in 23% of cases. LVI was found in 35.3% of cases. The LVI rates for consultants requesting an Elastic Van Gieson stain (EVG) more frequently (in over 40% of cases) was 42.8%, compared to 29.7% for consultants using EVG less frequently. Serosal surface involvement was reported in 29.9% of colonic and 20.3% of rectal cases.

Conclusion: The results demonstrate that our department is achieving national targets for colorectal cancer reporting. Increased trainee trimming has improved the quality of colorectal cancer reporting. It is interesting to speculate why pathology trainees at an earlier stage of training achieved better lymph node harvests than more senior trainees and consultants in this audit. More frequent use of EVG is associated with increased detection of LVI.

P60

A Study of Her-2 Expression in Oesophageal and Gastric Adenocarcinoma

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Purpose of the Study: Her-2 is overexpressed in 13-27% of gastric cancers and treatment with a monoclonal antibody against the human epidermal growth factor receptor (Her2) can offer a survival benefit. The aim of this study was to determine the rate of Her-2 expression in gastric and oesophageal adenocarcinoma at our institution.

Methods: Cases of oesophageal and gastric adenocarcinoma were selected from October 2010 to January 2013 at our hospital, including diagnostic biopsies and resections. Immunoperoxidase staining with an anti-Her2/neu monoclonal antibody 4b5 (Roche) was performed in each case. Results were evaluated by two histopathologists using the following criteria: None or 1+ staining was considered negative and 3+ as positive. 2+ staining was an indication for in situ hybridisation for Her-2 (S-ISH). The rate of overexpression was analysed in relation to the Siewert type, tumour subtype (intestinal versus diffuse) and grade (G2 versus G3).

Results: 110 cases were identified, including 40 resections and 70 biopsies. Her-2 overexpression was identified in 29% (12/42), 13% (4/30) and 15.6% (6/38) of Siewert I, II, III tumours, respectively. Her-2 expression heterogeneity was identified in 5 of 110 cases (4.5%). Grade 2 tumours of intestinal type had the highest incidence of Her-2 expression (28%, 13/46), followed by grade 3 intestinal type (17%, 7/42) and grade 3 mixed type (25%, 1/4). None of the 18 G3 diffuse type adenocarcinomas overexpressed Her-2.

Conclusions: This study correlates with some of existing literature regarding the incidence of Her-2 expression. The greatest incidence of Her-2 overexpression was identified in Siewert type I oesophageal adenocarcinoma and adenocarcinomas of intestinal type.

P61

Dual Immunohistochemical Staining in the Detection of Extramural Vascular Invasion in Colorectal Carcinomas

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Although not part of the TNM staging of colorectal carcinomas, extramural vascular invasion is an independent prognostic factor. It has an association with increased risk of visceral metastasis including liver metastasis and a decreased overall survival time. It also correlates with an increased local recurrence rate, and its presence may influence the decision over adjuvant therapy.
The 2007 dataset for colorectal carcinomas published by The Royal College of Pathologists states that the standard for the identification of extramural vascular invasion detection should be at least 25%. It is suggested that examining the section to multiple levels and using elastin stains may facilitate this process.
In our department, dual staining with desmin and AE1/AE3 is preferred over the use of EVG as the AE1/AE3 (red staining) highlights the tumour cells and desmin (brown staining) shows the smooth muscle within the vessel wall. It helps clarify situations where EVG may be unclear, such as when there is a full tumour plug within a damaged vein. Other departments have been known to use CD31 or CD34 along with AE1/AE3 to detect endothelial cells but desmin has the advantage where the endothelial cells are compressed, lost or stripped away.
We have found this technique useful in deciphering venous invasion in gynaecological and urological malignancies also, but the majority of our cases have been in colorectal carcinomas.

P62

Adenocarcinoma with Dystrophic Calcification Causing Stricture of the Oesophagus

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Dystrophic calcification is a rare finding in the oesophagus which has not often been reported in the literature. This phenomenon occurs when necrotic cells are not promptly destroyed and reabsorbed, attracting calcium salts and other minerals, which then become calcified. Although dystrophic calcification can arise due to benign conditions, in this case it was found in association with oesophageal adenocarcinoma. We report a case of a 76 year old female with problems of a persistent stricture at the distal oesophagus. Initial biopsies showed no histological evidence of malignancy, however, repeat oesophageal biopsies several months later revealed abundant dystrophic calcification together with foci of a well differentiated adenocarcinoma. An oesophagectomy was performed and histological examination of the specimen reported a moderately differentiated adenocarcinoma.
The findings highlight the importance of having an awareness of the potential causes of this type of calcification and to consider the possibility of malignancy when reporting these biopsies.

P63

Colorectal Serrated Polyps and the 2010 WHO Classification: a One Institution Retrospective Case Review Study

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Background: 2010 WHO Classification defines serrated lesions (SL) as hyperplastic polyp (HP), sessile serrated adenoma with or without dysplasia (SSAC+, SSAC-), traditional serrated adenoma (TSA), serrated polyposis (SP) and serrated carcinoma (SC). Since SL morphology have been long argued, SL differential diagnosis can be still difficult.
Materials and methods: 2 GI-tract dedicated pathologists reviewed, according to 2010 WHO Classification, all lesions originally reported as serrated adenoma with or without dysplasia, serrated and mixed serrated polyp between 2005 and 2010; polypectomies with at least one HP diagnosis of the same period have been also reviewed, to find eventually misdiagnosed serrated adenomas.
Summary of Results: 267 lesions with an original serrated adenoma/polyp diagnosis have been reclassified as follows: 68 (25.5%) SSAC-, 10 (3.7%) SSAC+, 7 (2.6%) TSA, 6 (2.2%) cloacogenic polyps (CP), 68 (25.5%) LG tubular adenoma, 55 (20,6%) HP, 1 (0.4%) HG tubular adenoma, 1 (0,4%) DALM; in 23 cases tissue artefacts do not allow a definitive diagnosis; 28 polyps had a controversial diagnosis, demanding further investigations. Polypectomies (1850 lesions), with at least one HP diagnosis, review revealed 8 SSAC-, 1 TSA, 4 CP and 3 polyps needing further investigations (all cases initially diagnosed as HP). Overall SL (not-HP) prevalence was 1.25%.
Conclusions: In our experience erroneous diagnosis of LG tubular adenoma as SSA is the most common pitfall; HP and CP can be also wrongly reported as SSA. Conversely serrated adenomas are rarely misdiagnosed as HP. SL (not-HP) low prevalence and morphologic features can make difficult an accurate diagnosis, nevertheless, the faster progression of the serrated adenoma/carcinoma pathway makes crucial SL detection and additional investigations (immunohistochemistry, molecular analysis) should be performed in controversial cases in daily histopathological practice.

P64

Audit of Interobsever Variability in Diagnosing High Grade Dysplasia in Colorectal Polyps/biopsies from the Bowel Cancer Screening Programme

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PURPOSE: The aim of this study was to audit the interobserver variability in the assessment of high grade dysplasia in colorectal adenomas/biopsies from BCSP in our department.
BACKGROUND: Reporting the degree of dysplasia (low or high) is one of the requirements in the proforma for BCSP reporting. High grade dysplasia is diagnosed on architecture, supplemented by an appropriate cytology. Hence, its presence is nearly always suspected by the appearance under low power of complex architectural abnormalities rather than cytological abnormality alone.
METHODS: A total of 53 cases of BCSP reported and coded as high grade dysplasia in our department were all assessed again by the authors for the degree of dysplasia. The cases were categorized into three categories: 1) high grade dysplasia in an adenoma confirmed/agreed 2) high grade dysplasia in superficial non adenoma biopsies suspicious of adenocarcinoma (no muscularis mucosa) and 3) low grade dysplasia in an adenoma.
RESULTS: High grade dysplasia were confirmed and agreed in 41 out of 53 cases (77%) and of these 9 cases were superficial biopsies suspicious of adenocarcinoma (17%). 60% of the cases were high grade dysplasia in an adenoma. 12 of the 53 cases were downgraded to low grade dysplasia (23%).
CONCLUSION: The presence of high grade dysplasia does not alter the patients risk category according to the adenoma surveillance guidelines by NHSBCSP. However, a reproducibility of the degree of dysplasia is required for accurate assessment and management. There is over-reporting of high grade dysplasia in 23% of cases in this study.
RECOMMENDATION: Re-audit the reporting of high grade dysplasia on larger number of cases and after reducing the number of reporting pathologists (mainly those with special interest in GI pathology). All pathologists should participate in BCSP EQA and at least attend one GI pathology meeting annually.

P65

Metastatic Intramucosal Colorectal Adenocarcinoma – A Case to Support Review of Current British Concepts (and Staging) of Early Colorectal Cancer

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British pathologists do not recognise an intramucosal stage for colorectal adenocarcinoma, in contrast to the latest (7th TNM edition) for oesophagogastric cancers, where early cancers are divided into T1a (mucosal) and T1b (submucosal). The rationale for this difference is that the colorectum was historically reported not to contain mucosal lymphatics, or that mucosal lymphatics were unable to carry cancer cells. Recent publications, however, have thrown doubt over this long-standing dogma. D240-positive lymphatics have been identified in colon in the setting of inflammation and/or neoplasia, and another recent paper has identified lymph node metastases in "Tis" cancers. This case describes a rectosigmoid tubulovillous adenoma containing adenocarcinoma confined to lamina propria and muscularis mucosae containing a dyscohesive signet ring cell component. Subsequent excisions (and residual adenoma serially examined in its entirety) failed to demonstrate any submucosal stromal invasion, but tumour venous thrombus was observed in continuity with residual recurrent adenoma. The patient developed multiple mesenteric and distant metastases and died from the disease. The original adenoma, residual adenoma in the resection specimen and the intravascular carcinoma all showed the same KRAS codon 13 mutation. In conclusion, it would make practical and biological sense for upper and lower GI cancers to be equivalently staged. Metastases from intramucosal carcinoma is rare in upper GI cancers, and likely yet rarer in the colorectum. Rare cases such as this, we hope will lead to the recognition of the concept of colorectal intramucosal adenocarcinoma, and enable the development of clear MDT diagnostic and management guidelines.

P66

Evaluating the Use of Immunohistochemistry to Characterise Liver Metastases

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The liver is a common site for both metastatic and primary malignancy. Liver biopsy is a commonly used tool to investigate liver lesions. Often there is clinical uncertainty surrounding the nature and origin of the tumour. Tumour morphology and immunohistochemistry (IHC) play a vital role in confirming the primary source of a tumour. Recent advances in the management of metastatic carcinoma make the phenotyping of these lesions increasingly important. This study has examined the use of IHC in characterising liver tumours.

All malignant liver specimens received in a single department of pathology during 2011 were analysed, including core biopsies, resections, and frozen sections. A panel of IHC markers comprising TTF1, CK7, CK20, CDX2, AE1/AE3, PSA, CAM5.2, and ER was used to characterise adenocarcinomas. The use of markers for other tumour types was dictated by morphology and clinical suspicion. For each specimen the following data was recorded: patient age and sex, type and size of specimen, clinician impression, immunophenotype, and histological diagnosis.

During 2011, 208 liver specimens were received. 80 cases containing malignant disease were included. Mean patient age was 66.5 years and 60% were male. The majority of tumours were adenocarcinomas. The primary source of adenocarcinoma was localised to the colorectum in 54% of cases, and pancreatobiliary/upper GI in 18%. 13% of adenocarcinoma cases were localised to other sites, and 15% were equivocal.

The number of malignant liver specimens is increasing with the majority of specimens comprising metastatic adenocarcinoma. By using appropriate targeted IHC the primary tumour was characterised in 92% of cases. Within the subgroup of adenocarcinomas, 85% were localised accurately. Precise localisation of disease is improving, however there is still a need for markers which can further localise tumours to the pancreatobiliary/upper GI tract.

P67

Accuracy of Frozen Section in the Diagnosis of Liver Mass Lesions

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INTRODUCTION: Surgeons frequently utilise frozen sections as a tool to gain intraoperative information. The use of frozen sections has certain benefits as well as limitations which vary according to the situation. However, it is a generally thought to be a reliable method for the diagnosis of liver lesions.

AIMS: The aim of this study is to evaluate the diagnostic accuracy and reliability of intraoperative frozen section diagnosis of liver lesions thought to be malignant tumours and if possible to determine the cause of any errors.

METHODS: We identified 131 consecutive hepatic frozen sections from 127 patients from the laboratory archive over a six year period from 2004 to 2012. The frozen section reports were compared with the final paraffin section reports. All cases with any discrepancy between the 2 reports were reviewed.

RESULTS: The final histological diagnosis was divided into positive (53%) and negative (47%) for malignancy. In three cases (2%), diagnosis was deferred to paraffin section. One false positive and two false negative diagnoses were identified giving a positive predictive value of 98.3% and a negative predictive value of 97.2%. The discrepant cases were further analysed to ascertain the nature of diagnostic difficulties, which included one case of pathological misinterpretation, one case of sampling error, and one case with technical imperfections.

CONCLUSION: The data are in accordance with those of similar studies in other sites, and confirm that the frozen section is a highly accurate and reliable method for intraoperative diagnosis of suspected liver lesions.

P68

Epidermoid Cyst of Testis: 3 Cases of Testicular Mass with Normal Tumour Markers

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Epidermoid cyst is a rare and non-teratomatous benign tumour of the testis. It cannot be differentiated reliably from the far more common malignant testicular mass on a clinical basis. Testicular epidermoid cysts are of two types, occurring through one of two possible lineages proposed; those of monodermal teratoma origin and those of invaginated mesothelial origin. Intratubular germ cell neoplasia is not reported in association with true testicular epidermoid cysts, which are defined, mainly by the absence of scarring and absence of any dermal appendages and sebaceous glands.

We here by report three cases of epidermoid cyst of testis in young boys aged 11, 14 and 18. In all three cases the clinical information on the form mentioned testicular mass with negative tumour markers. The histological examination showed a fibrous cyst capsule lined by well-differentiated squamous epithelium that surrounded a cavity of laminated keratin. Negative immunohistochemistry ruled out intratubular germ cell neoplasia in these cases. The absence of mesodermal and endodermal components distinguished this from dermoid cyst or teratomas. Radical orchiectomy has been extensively carried out earlier but some authors have lately encouraged testis-sparing surgery in adults.

P69

Epithelial and Stromal Tenascin-C Expression is Associated with Poor Prognostic Features in Egyptian Urinary Bladder Carcinoma

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Background: Urinary bladder carcinoma (UBC) is the third most prevalent cancer in Egypt, accounting for 12.22% of all cancer cases after breast carcinoma and leukaemia. Tenascin-c (TN-C) is a member of the matricellular protein family. Little data are available on the prognostic significance of TN-C in UBC. The aim of this study was to evaluate immunohistochemical staining of TN-C in UBC and correlate it with prognostic clinicopathological features.
Material and methods: This study included 65 cases divided into 15 cases of normal urinary bladder biopsies and 50 cases of UBC including 25 cases of urothelial carcinoma (UC), 21 cases of squamous cell carcinoma (SCC) and 4 cases of adenocarcinoma (ADC)
Results: TN-C expression was not observed in normal bladder urothelium or underlying stroma. In contrast, 59% of the studied total malignant cases showed TN-C expression in malignant cells and 28% in tumour stroma. TN-C expression was observed in malignant cells of all ADC cases, 76% of UC and 29% of SCC cases. SCC cases showed lower H score values in malignant cells as compared to UC and ADC cases (P= 0.000 and 0.016 respectively). TN-C positivity in tumour cells was associated with older age, metastasis to lymph node and higher pT stage. TN-C expression in stroma cells was associated with higher mitotic index in tumour cells.
Conclusion: Tenascin-c may have a role in the development and progression of UBC and could be used as a tool for differentiation between high grade UC and SCC in the difficult cases.
Key words: Tenascin-c, urothelial carcinoma, squamous cell carcinoma and adenocarcinoma

P70

Prostatic Adenocarcinoma versus Urothelial Carcinoma among Egyptian Patients: an Immunohistochemical Study

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Background and Purpose: Urothelial carcinoma (UC) and prostatic adenocarcinoma (PAC) commonly occur in elderly and share common carcinogenic factors. Simultaneous occurrence of PAC and UC within the prostate is not uncommon. Moreover, invasion of PAC into the urinary bladder wall could pose a diagnostic challenge with UC and other primary urinary bladder tumors. This study aimed at differentiation between PAC and UC using histochemical and immunohistochemical (IHC) panels.
Material and Methods: This study was carried out on formalin-fixed paraffin-embedded tissue sections representative of 21 PAC cases, 26 UC cases, in addition to nodular prostatic hyperplasia and chronic cystitis, nine cases each, used as controls. IHC using specific antibodies against p63, CK7, CK10 and PSA was performed. Moreover, for differentiation between neutral and acetic mucosubstances, combined alcian blue-PAS (AB-PAS) technique was used, while mercury bromophenol blue method was employed in detecting total proteins.
Summary of Results: Statistically significant differences were observed between PAC and UC regarding the expression of p63, CK7, and PSA; where 100% of UC cases were p63+ and CK7+ and PSA- ($p < 0.000$). CK10 positivity was observed in 52.4% of PAC cases, yet all UC cases showed negative expression ($p < 0.000$). The incidence of acid mucins was statistically different between UC and PAC ($P<0.000$).
Conclusions: Therefore, p63 and CK7 could be considered as markers of urothelial differentiation. Moreover, the IHC panel of p63, CK7, CK10 & PSA, and the histochemical AB-PAS stain can be used in the differential diagnosis, along with other markers, in morphologically difficult cases particularly in poorly differentiated PAC and high grade urinary bladder UC.

P71

Can Free PSA/total PSA Ratio Predict the Outcome of Prostate Biopsy?

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Aim: Correlation of free PSA/total PSA ratio(%) with benign and malignant cases of prostate and it's role in predicting the Gleason score in TRUS biopsies done at our district general hospital.
Material and Methods: A retrospective study was done where clinical and pathological results of all the TRUS guided prostate core biopsies from 01.01.2013 to 25.02.2013 were retrieved. From the data available we got the information regarding the total number of TRUS biopsies (benign and malignant) with free PSA/total PSA ratio provided and then correlated these with the outcome of the biopsy results. The malignant cases were then tabulated in two categories, one with the free PSA/total PSA ratio of <19% and other group with ratio>19%. Our findings were then compared to the results found in other studies available.
Results: We had a total number of 81 prostate TRUS biopsies. Out of these 34 (42%) were malignant and 47 (58%) benign. Free PSA/total PSA ratio was available in 15 (44.1%) of the malignant and 22 (46.8%) of the benign cases.
In the malignant group 11 of the 15 cases (73.3%) had free PSA/total PSA ratio of <19% and all had Gleason's score > 7 (100%). The other 4 (26.7%) had free PSA/total PSA ratio of >19% out of which only 1 case had Gleason score of >7, rest 3 had score <7. All 4 cases with perineural invasion belonged to the low free PSA % group.
In the benign group 14 of 22 cases (63.6%) had free PSA/total PSA ratio of <19% and 8 of 22 cases (36.4%) had free PSA/total PSA ratio of >19%.
Conclusions: Our study shows, a low F/T PSA does not correlate positively with presence of malignancy (73.3% in malignant cases and 63.6% in benign cases). However, the ratio did have a role in predicting the Gleason's score (100% with low F/T PSA).

P72

Glomerulopathy Associated with Myeloproliferative Neoplasms

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Myeloproliferative neoplasms (MPN) are clonal haematopoetic stem cell disorders characterized by expansion of one or more of the myeloid lineages (granulocytic, erythroid, megakaryocytic or mastocytic) that occur usually in the elderly. The renal involvement associated with MPN has been a rarely diagnosed complication and may have been hidden within some "nonspecific" diagnostic category like vascular nephrosclerosis or focal segmental glomerulosclerosis (FSGS).
We wish to present two such cases associated with polycythaemia vera (PV) and essential thrombocythaemia (ET) both occurring in men. Indications for biopsy were proteinuria and slowly progressive chronic renal insufficiency. In histology, there was a mixture of mesangial sclerosis and segmental hypercellularity. In one case, there were intracapillary thrombocytes and features of chronic thrombotic microangiopathy (TMA). On follow-up the patient's renal insufficiency persisted but their proteinuria slightly improved.
MPN-related glomerulopathy enlarges the spectrum of renal diseases associated with hematological neoplasms. This condition is rare and probably an under diagnosed complication of some myeloproliferative neoplasm and we believe that a greater awareness of this disease among the nephropathologists and the clinicians would help to determine its overall incidence and may contribute to finding a suitable therapy.

P73

Glomerulosclerosis in the Absence of Arteriolar Hyalinosis: an *In-Vivo* Model for Chronic Calcineurin Inhibitor Nephrotoxicity in Non-Renal Conditions

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Purpose of the study: Chronic calcineurin inhibitor (CNI) nephrotoxicity, caused by ciclosporin (CsA) or tacrolimus (Tac), is demonstrated on renal biopsy by arteriolar hyalinosis (AH) and subsequent glomerulosclerosis (GS). We have observed GS without AH in renal biopsies taken from children treated with a CNI for minimal change nephropathy (MCN). We hypothesise that GS is an independent marker of CNI nephrotoxicity.
Methods: We analysed biopsies taken over a 15 year period from a pathology database in children whose primary diagnosis was nephrotic syndrome secondary to minimal change nephropathy (MCN). Other causes of nephrotic syndrome were excluded as they could confound for GS.
Summary of results: Of the 109 biopsies which met inclusion criteria, 83 were taken preCNI therapy and 26 were taken postCNI therapy; of which 4 demonstrated AH and 22 did not. The difference in median %GS between the preCNI (0%) and postCNI without AH (7.12%) groups was significant (p=0.001). %GS was significantly associated with duration of CNI therapy (n=26, R=0.28, p<0.001) but not with MCN duration (n=60, R=0.008, p=0.81). Paired analysis of biopsies revealed significant progression in mean %GS between preCNI and postCNI biopsies (n=13; 9 on CsA; 4 on Tac; Δ%GS=+11.9%; p=0.006). Average CNI plasma levels were not significantly associated with GS for CsA (n=14, R=0.37, p=0.29) or Tac (n=5, R=0.13, p=0.55).
Conclusions: MCN in children is not associated with GS, but when such children are treated with a CNI, GS occurs independently of AH and correlates with duration of therapy. The progressive GS occurring in children treated with a CNI represents an *in-vivo* model for CNI nephrotoxicity in non-renal conditions. We suggest the need for regular assessment for nephrotoxicity in such children.

P74

Causes of Error in Urine Cytology: a Retrospective Single Centre Study

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Diagnostic "errors" in urine cytology are of two types: interpretive (tumour cells present but not reported, or benign cells misinterpreted as malignant) and sampling (tumour cells not present in the sample). It has been proposed that diagnostic accuracy can be improved by use of "experts" and by reducing use of the "atypical" diagnostic category. In this study, we determined the relative frequency of errors between pathologists, and the type of error (interpretative vs sampling) in 778 patients attending a one-stop haematuria clinic.
After a follow-up of 21-66 months, 156/778 (20%) patients were diagnosed with urothelial carcinoma (UC) on histology. Urine cytology reports were categorized 1 benign, 2 atypia probably benign, 3 atypia of uncertain significance, 4 suspicious, 5 malignant. A final diagnosis of UC was made in 9%, 21%, 50%, 74% and 86% for categories 1-5. There were diagnostic errors in 72 patients, defined as cytology category 1/2 with a final diagnosis of UC (n=57) or category 4/5 with a final benign diagnosis (n=15). Slides were available for review in 62/72. Six pathologists reported at least 20 specimens each (mean 125, range 39-210), a total of 749 cases, 53 of which had diagnostic errors. These slides were reviewed by a single pathologist (who had issued 210 of the original reports), blinded to the final diagnosis and initial report. The mean % of reported specimens with diagnostic errors was 8.1% (range 4.5-12.8%) for the 6 pathologists. One pathologist had a significantly higher error rate than a colleague (10/90 vs 10/210 p=<0.05) but had issued fewer category 3 reports (10% vs 14% of total). On review, the diagnoses were changed from category 1/2 to category 4 in only two cases (4%) and to category 3 in 11 cases (17%).
We conclude that most misdiagnoses are sampling errors. Atypia of uncertain significance is associated with UC in 50% of patients and is a useful diagnostic category. Increased use of categories 1/2 and 4/5 increases the proportion of diagnostic errors.

P75

Reproducibility of Assessment of Extraprostatic Extension in Radical Prostatectomy Specimens

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A key decision when reporting radical prostatectomy specimens is whether extraprostatic extension (EPE) of tumour is present, resulting in a stage of pT3a rather than pT2 (organ confined tumour). Patients with pT3a tumours are considered for entry into trials of adjuvant therapy. Guidance on assessing EPE is provided in the RCPath dataset for prostatic carcinoma. In this study we assess the reproducibility of diagnosis of EPE using the RCPath guidelines.
Three specialist uropathologists staged 20 consecutive radical prostatectomy specimens from the archives in a UK teaching hospital which had been originally scored as pT2 or pT3a. Scoring was blinded to the original report and the other pathologists' scores. Criteria for assessing EPE were involvement of periprostatic fat, tumour involving large nerve bundles in the region of the neurovascular bundles or tumour beyond the normal contour of the prostate involving connective tissue looser than prostatic stroma.
Fourteen of 20 cases had originally been staged as pT2 and 6 as pT3a. There was complete agreement between the 3 pathologists in 12/20 (60%) cases - 9 stage pT2 and 3 stage pT3a. In the 8 cases where there was disagreement, 4 cases were staged as pT2 by 2/3 of the pathologists and 4 were staged as pT3a by 2/3 of the pathologists. The kappa score for interobserver agreement was 0.47 (moderate). Sources of discrepancy were differences in definition of "normal contour" of the prostate in a gland distorted by tumour, when neurovascular bundles become extraprostatic and when fibromuscular stroma is beyond the extent of non-neoplastic glands.
Use of the RCPath guidelines results in only moderate interobserver agreement for assessment of extraprostatic extension of carcinoma in radical prostatectomy specimens, with lack of consensus in 40% of cases. Assessment of EPE has important implications for patient management and there is a need for more precise guidance.

P76

Review of a Referral Practice Reveals the Areas of Diagnostic Difficulty in Renal Tumour Diagnosis

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In order to identify those areas of diagnostic difficulty in renal carcinoma we conducted a review of a multi-modality referral practice. The University of Dundee laboratory uses a combination of morphology, immunocytochemistry, FISH and molecular genetics to support the diagnsis of referred renal tumours. We reviewed 158 consecutive referrals to the laboratory from the UK and Ireland, international referrals were excluded because of incomplete clinical data. There were 5 main diagnostic problems identified. The most common specific problem was the distinction between chromophobe carcinoma and oncocytoma 41 case (28.8%), followed by rare renal tumours 32 cases (20.3%), translocation RCC 24 cases (15.2%) possible collecting duct carcinoma 18 cases (11.4%) while diagnostic uncertainty of varied types constituted the remaining 39 cases (24.7%). Amongst the chromophobe oncocytoma cases the eventual diagnosis was chromophobe carcinoma 20 cases, oncocytoma 11 cases hybrid tumour 3 cases and Birt Hogg Dube syndrome 2 cases. Nine of 24 referrals proved to be translocation associated RCC and 8 of 20 referrals as possible collecting duct carcinomas were eventually confirmed as such. The multi-modality approach allowed a diagnosis of 10 inherited RCC, 6 cases of BHD, 3 cases of hereditary leiomyomatosis with RCC syndrome and one case of succinate dehydrogenase B associated RCC, with important clinical implications for outcome and genetic counselling. Seven cases (4.4%) remained unclassifiable. The combined use of morphology, IHC and genetic methodology resolves the majority of diagnostic difficulty in RCC. Our case review reveals that the distinction between chromphobe and oncocytoma along with recognition of translocation associated RCC and collecting duct carcinoma are the main diagnostic dilemmas in this area of practice.

P77

Paraganglioma of Urinary Bladder: A Clinicopathologic Case Series from a Tertiary Oncology Care Centre

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Purpose of the study: Paraganglioma (PG) of the urinary bladder is a rare neuroendocrine neoplasm, accounting for < 0.1% of all bladder tumours. Distinction from urothelial carcinoma is imperative as management and prognosis vary markedly.
Methods: All cases of PG of urinary bladder diagnosed at our institute from 2002-2012 were retrieved and diagnosis confirmed in accordance with WHO classification. Clinical and treatment details were obtained from hospital medical records.
Summary of Results: Fourteen cases of PG of urinary bladder including 5 consult cases were analysed. These included 11 transurethral resections, 2 partial cystectomies and 1 radical cystectomy. Two out of the 5 consult cases had been submitted with a diagnosis of urothelial carcinoma and 1 with that of a rhabdomyosarcoma. Age ranged from 15-84 years (mean, 43 years) with a male to female ratio of 1:2.5. Presenting symptoms were haematuria, dysuria and flank pain; only 1 case had antecedent hypertension. Histologically, typical 'zellballen' (79%), diffuse (21%) and ribbon-like (7%) growth patterns amidst a richly vascularised stroma were seen. Muscularis propria invasion and necrosis was present in 72% and 21%, respectively. Substantial cautery artifacts led to misdiagnosis in the 3 erroneous cases. Tumour cells were positive for chromogranin, synaptophysin; sustentacular cells were S-100 positive. Follow up was available in 6 patients; median follow-up was 29 months (8-120 months). One patient developed distant metastasis in cervical lymph node 10 years after diagnosis; remaining were alive without evidence of disease.
Conclusions: PG of the urinary bladder is rare and may be misdiagnosed as urothelial carcinoma, especially owing to cautery artifacts. A high index of suspicion and supportive immunohistochemical studies assist in making a correct diagnosis. Late metastases necessitate a long term follow-up.

P78

The 4EBP1/EIF4E Axis In Clinically Confined Clear Cell Renal Cell Carcinoma

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4-EBP1 and eIF4E represent the two main terminal effector molecules of the mTOR pathway, an important therapeutic target in metastatic renal cell carcinoma (RCC). 4EBP1 normally prevents the translation of key onco-proteins such as c-myc and cyclin D by holding eIF4E in an inactive state. In growing tumours this confirmation is reversed upon phosphorylation of 4-EBP1 (p4EBP1).
We examined the importance of 4-EBP1 and eIF4E in tumours resected from 151 patients with clinically confined, clear cell RCC. We found the over-expression of eIF4E strongly correlated with the presence of p4-EBP1 (p=0.005) in these tumours. This co-expression was not associated with any conventional histological parameters, although a strong trend with high tumour grade was observed (p=0.057).
Kaplan-Meier survival analysis showed patients whose tumours co-expressed both p4-EBP1 and eIF4E had significantly reduced disease-free survival than patients whose tumours expressed either or none of the biomarkers (3.29 vrs 6.17 years; p=0.0001). Multivariate analysis also determined the combined p4EBP1 and eIF4E to be a powerful and independent prognostic biomarker (HR=4.7; p=0.001) that was more significant that tumour grade and tumour stage.
We propose that p4EBP1 and the over-expression of eIF4E co-operate to drive early relapse in RCC and that their assessment will be of use in staging schemes that incorporate biomarkers to improve prognostication. Finally, the ratio of 4EBP1 and eIF4E is gaining acceptance as an important determinant of response to mTOR inhibitors. Therefore our current results will have implications for patient selection with molecular targeted therapies in the adjuvant setting.

P79

How Should the Length of Prostate Cancer in Needle Cores be Measured?

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The length of tumour in a needle biopsy core correlates with the tumour volume in subsequent radical prostatectomy (RP) specimens. However there is no agreed way to measure tumour length in a core. There are good theoretical reasons for using the dimension between the outer margins of tumour in the core involved — the whole tumour length (WTL); although some pathologists are reluctant to report two small separate foci as a single long length and prefer to sum the lengths of separate foci- the sum tumour length (STL).
The aim of the study is to determine the measurement which best correlates with tumour size and hence gives the most appropriate information to clinicians. 81 of a series of 530 RPs had a single core positive in prior protocol biopsies. The length of tumour was measured in the positive core by both WTL and STL methods. The tumour volume in the RPs was calculated by a simple method (3 dimensions multiplied X 0.4). The predictive power of the respective length measurements for significant tumours (defined as tumours >0.5ml volume) was tested by receiver operating characteristic (ROC).
There was a difference between the two measurements of at least 1.0mm in 12 cases. Measurements by both methods correlated strongly with the tumour volume; the correlation of volume with WTL was more significant than the STL, p=0.002 vrs p= 0.008 (Spearmans) respectively. On ROC analysis the area under the curve was 0.58 for the STL and 0.64 for WTL. The WTL curve differed significantly from 0.5 (p=0.033) but STL did not (p=0.21). WTL is a simpler method and correlates better with tumour volume; it is thus recommended as the method used to report tumour length in prostate cores, this length should also be used when calculating percentage involvement of cores by tumour.

P80

Staging Laparotomy Should we Sample Macroscopically "Normal" Omentum?

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Purpose of the study: Omentectomy is part of surgical staging for ovarian and endometrial malignancies. Recommendations from the RCPath and CAP are similar i.e. 1-2 representative blocks of macroscopic tumour after measurement of the largest nodule and in cases of macroscopically "normal" omentum 4-6 blocks (RCPath) and 5 -10 blocks (CAP). There is little evidence to support this. We decided to retrospectively audit pathologists' examination of macroscopically "normal" omentum to influence prospective sampling with an evidence base.
Methods: We studied 167 serial gynaecology specimens that included omentectomy from June 2012-January 2013. 22 were excluded. Cases were analysed based on the macroscopic and microscopic omentum appearances described in the pathology report. We recorded if the case was cut up by a histopathology trainee or a consultant in gynaecological pathology and the size of omentum submitted. There is no recommended size of omentectomy for adequate surgical staging, this was reflected in the variable sizes of omentectomy specimens submitted.
Summary of Results: Of 145 cases analysed, 45 were cut up by trainees and 100 by specialists. 4% of cases cut up by consultants contained microscopic tumour when no focal lesions were identified, 2 of which were interval debulking surgical procedures. Missed microscopic deposits were related to serous ovarian borderline neoplasms with peritoneal implants and ovarian high grade serous carcinoma. 23% cases were uterine primary malignancies and 74% were primary ovarian tumours. The size of omentum sampled varied from 4.5 to 110 cm in maximum dimension, the mean was 31 cm.
Conclusions: We conclude that for macroscopically abnormal omentum a representative block of tumour is appropriate. When the omentum is macroscopically "normal" we propose a sampling strategy which is adaptive to the ovarian pathology.

P81

Ectopic Vaginal Prostatic-type Tissue (Skene's Glands) in a 3 month-old Female

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The purpose of this study is to demonstrate a case of misplaced Skene's glands in a 3-month-old female, a diagnosis that hasn't yet been reported in a prepubertal female.
Methods used involved haematoxyllin-eosin staining and an immunohistochemical analysis on formalin-fixed, paraffin embedded tissue.
A 3-month-old female patient presented with a polyp measuring 7 mm located in the posterior wall of lower vagina. There was no history of in utero exposure to diethylstilbestrol or other medications. On histology, the polyp was lined by stratified squamous epithelium. Polyp stalk contained multiple well-demarcated glandular and tubular elements with focal cribriform architecture, covered by epithelium exhibiting oval, regular nuclei with no atypia or mitoses. The glands were surrounded by several outer layers of cells somewhat resembling basal cells of the prostate, surrounded by neutrophils. On immunohistochemistry, the glands were positive for progesterone receptors (PR) and pancytokeratin, negative for prostate-specific antigen and estrogen receptors (ER). The outer cell layer was positive for estrogen receptors, CD10, pancytokeratin, p63 and 34βE12 cytokeratin. The histologic pattern and positivity to ER, PR and CD10 in the layer surrounding the glands raised concern for endometriosis, which, albeit rare, has been reported in prepubertal females. However, the shape of the glands and presence of oval nuclei, coupled with a positive outer layer reaction to p63 and 34βE12 argued against endometriosis. The overall resemblance of the lesion to previously reported cases of ectopic prostatic tissue in the lower female genital tract rendered the diagnosis of misplaced Skene's glands.
In conclusion, we report a case of misplaced Skene's glands resembling other previously reported cases of ectopic prostatic-type tissue in the lower female genital tract, which until now have never been reported in a prepubertal female.

P82

Malignant Potential of in-situ Serous Carcinoma of the Cervix

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Primary serous carcinomas of the cervix are rare. The few cases reported are associated with high risk HPV and most reported cases tested were negative for p53. We report on a case of primary in-situ serous carcinoma of the cervix which was negative for high risk HPV but which was positive for p53 with a metastatic deposit to one ovary.
A 37-year old lapsed cervical screening attender presented with contact bleeding and per vaginal discharge. An opportunistic smear revealed abnormal glandular cells. Colposcopic examination and cervical punch biopsy revealed low grade CIN, with no representation of glandular tissue. No further investigations were performed and a cervical smear was repeated in 6 months. This showed glandular dyskaryosis ?adenocarcinoma . Repeat Colposcopy was normal. A diagnostic loop biopsy showed high grade in-situ serous carcinoma. Fragments of similar glands were also seen in the endometrial curettings, but it was difficult to be certain at this point if the serous neoplasm originated in the cervix or endometrium. A subsequent radical hysterectomy showed that the epicentre of the lesion was in the endocervix. The endometrium was benign and un-involved. Both tubes and ovaries were completely sampled. There was a small 5mm subcapsular deposit of a tumour in the right ovary similar in appearance to that in the cervix. This was positive for p16 and p53 but negative for WT-1 and oestrogen receptor. In-situ hybridisation for high risk HPV was also negative.
Primary serous carcinomas of the cervix is rare and diagnosis in our case was made after exclusion from more common primary sites. Interpretation of invasion is difficult in such cases and we feel that shedding of exfoliated surface tumour cells and spread through endometrial cavity and fallopian tube lumen confer malignant potential of even apparent in-situ lesions. Furthermore, we highlight potential problems using HPV triage and primary HPV testing in cervical screening.

P83

Primary Cloacogenic Adenocarcinoma of the Female Genital Tract — a Potential Diagnostic Pitfall

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Adenocarcinomas of enteric type are rare in the female genital tract. We report on a case arising between the urethra and vagina and would like to raise awareness of this entity to avoid diagnostic pitfalls resulting in delayed diagnosis and treatment.
A 66 year old lady who presented with urinary obstruction was found to have an urethro-vaginal fistula associated with a polypoid lesion on the anterior vaginal wall. Biopsies of the lesion showed 'enteric-type' glandular mucosa with dysplasia and possible invasion. Gross examination of the exenteration specimen showed a lesion more extensive and diffuse than originally estimated, extending to the base of the urinary bladder and reaching up to the pubic symphysis. It is difficult to determine the exact site of origin; we feel that the area between the vagina and urethra is the most likely site of origin as the majority of benign appearing rests were located at this site. The tumour showed a spectrum of changes ranging from benign intestinal type epithelium on the surface to areas showing a villoglandular architecture and complex dysplastic glands with diffuse invasion of the underlying stroma by small round glands lined by epithelial cells with mucinous and sometimes clear cytoplasm. Mucin lakes containing detached mucinous epithelium are also seen dissecting the stroma. Prominent vessel space invasion and perineural invasion were also seen. The benign and neoplastic showed strong positivity with CDX2 and CK20. They were focally positive for CK7 and CEA and negative with p16, CA125 and oestrogen receptor. Ki67 shows proliferative hot spots in the more dysplastic areas.
The tumour was more extensive than first estimated. Although several biopsies were performed from the 'vaginal polyp', these were misleading due to sampling of surface benign areas reminiscent of metaplastic change rather than true neoplasia. We would like to raise awareness of this entity to facilitate timely accurate diagnosis and treatment.

P84

Characterisation of Phosphorylated Checkpoint Kinase 1 as a Poor Prognostic Biomarker in Serous Ovarian Cancer

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Due to limited studies on the use of biomarkers to overcome ovarian cancer platinum resistance, we set out to characterise checkpoint kinases 1 and 2 (Chk1 and Chk2) in a cohort of ovarian cancers and paired platinum sensitivity serous ovarian cancer cell lines.
Chk1 and Chk2 proteins were measured in a cohort of 128 pre-treatment ovarian cancer lysates using reverse phase protein arrays. A validation cohort of 468 ovarian cancers used automated quantitative immunofluorescence image analysis. Chk1/2 inhibitor AZD7762 and cisplatin treatments of paired serous ovarian cancer cell lines were used to assess Chk1 and Chk2 function in the platinum-induced DNA damage response.
High phosphorylated-Chk1 at Serine 317 (p-Chk1) levels was associated with poor overall survival (corrected P=0.03). In multivariate analysis with other significant factors, high p-Chk1 tumours had a relative risk of 3.0 (95% CI 1.1 — 8.0, P=0.03). The DNA damage marker p-H2AX (Ser139) was highly expressed in the high p-Chk1 tumour group (P=0.008). In the larger cohort, high cytoplasmic p-Chk1 was associated with poor overall survival (corrected P = 0.02). Within the serous ovarian cancer subgroup, cytoplasmic and nuclear p-Chk1 were associated with poor overall survival (P=0.029 and P=0.043, respectively). In the cell line model, a sublethal AZD7762 concentration sensitised both platinum sensitive and resistant serous ovarian cancer cell lines to cisplatin by inducing apoptosis, inhibiting intra-S phase arrest, and increasing double stranded DNA breaks.
This is the first study to identify p-Chk1 as an independent prognostic ovarian cancer biomarker and supports Chk1 as a therapeutic target in platinum-resistant serous ovarian cancer.

P85

Not all Optically Clear Vacuoles Indicate Fat and Hence Uterine Perforation in an Endometrial Biopsy – Pseudolipomatosis a Well Described but Little Known Pitfall

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Background: Pseudolipomatosis is an artefact more commonly described in gastrointestinal specimens. The term refers to the presence of optically clear vacuoles which mimic fat within biopsies. Pseudolipomatosis is thought to artifactually contaminate specimens as a result of suction technique or due to chemicals used in the sterilization of surgical instruments .Pseudolipomatosis has also been described in skin specimens and less commonly in gynaecological biopsies. It has been classified as type A or B, according to the variation in size of the vacuoles observed.
Case report: We describe the case of an endometrial Pipelle biopsy from a 45 year old which showed optically clear vacuoles and was initially reported as containing fat . The possibility of an uterine perforation was raised and the report was urgently communicated with the gynecologist. The gynecologist however pointed out that this would be extremely unlikely from this Pipelle biopsy which was performed without curettage. A Sudan black stain modified for paraffin embedded material was then performed and the histology reassessed. It was concluded that the vacuoles seen on initial histological assessment are best interpreted as an artefact, and a supplementary report was then issued with clinico-pathological correlation.
Conclusion: Pseudolipomatosis is a well described but little known pitfall in endometrial biopsies. Clinico-pathological correlation and an awareness of this terminology would avoid over interpretation of fat within endometrial biopsies. This would eliminate the stress involved in raising the possibility of uterine perforation to all parties concerned.

P86

Squamous Cell Carcinoma and Cervical Intraepithelial Neoplasia in Routinely Removed Endocervical Polyps – A Seven Year Review

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Purpose of Study: Endocervical polyps, commonly encountered in routine pathology practice, can harbour sinister pathologic findings. The reported rate of squamous cervical intraepithelial neoplasia (CIN) or carcinoma ranges from 0.1%-0.7%. We report the incidence of CIN and invasive carcinoma arising in endocervical polyps in our institution and discuss the issues that arise when such diagnoses are made.
Methods: 5183 reports coded "cervix" were reviewed over a seven year period generating 126 endocervical polyps. Parameters recorded included age, symptoms, prior smear cytology, previous biopsies, polyp size and presence/absence of dysplasia/malignancy.
Summary of Results: One case of invasive squamous cell carcinoma was identified in a 15mm polyp from a 57 year-old post-menopausal woman (0.7%). There were three cases of CIN II/III and one case of CIN I. The overall rate of dysplasia/malignancy was 3.9%. Of these five cases, three had recent smears - the CIN I case had a negative smear, one CIN III case was classified as borderline change: high-grade dyskaryosis not excluded and the invasive carcinoma case was reported as severe dyskaryosis.
Discussion: Our series reveals a higher rate of CIN compared to similar studies but our number of polyps is small. Despite this, our series does include one case of invasive squamous cell carcinoma arising in a polyp. A review of published English literature yielded only four reported cases of invasive squamous cell carcinoma arising in endocervical polyps. This study also highlights the limitations encountered when reporting invasive carcinoma in a polyp including accurate measurement of depth and horizontal extent, determining the status of excision margins and pathologic staging.
Conclusions: Squamous dysplasia/malignancy can rarely occur in endocervical polyps justifying their routine excision.

P87

Pathological Assessment of Lymphadenopathy: An Audit of a Haematopathology Service over Two Years

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Persistent, unexplained or clinically atypical lymphadenopathy requires pathological assessment. This audit reviewed 104 clinically atypical or suspicious lymph nodes which were assessed pathologically. Lymph node excision accounted for 46 cases, 22 had FNA,18 cases had FNA with tissue fragments and 18 cases had a core biopsy. Accurate diagnosis with FNA was possible in 5 cases (25%), in 6 cases (29%) if tissue fragments were provided, in 10 cases (56%) with core biopsies and in 43 cases (94%) with excisions.
In 26 cases lymphoma was diagnosed. A malignant diagnosis was made via lymph node excision in 19 cases, core biopsy in 5, and on material from FNA with tissue fragments in 2 cases. Malignancy was never diagnosed using FNA alone, reflecting the insufficiency of material for immunohistochemistry, or spreading or drying artefacts or the lack of flow cytometry in our institution.
In the follow up of the non malignant cases, one patient was subsequently diagnosed as a high grade B cell lymphoma indicating a false negative rate of approx 4%.
Accuracy rates in the literature regarding lymph node assessment by FNA range from 7-87%. Pathologists and clinicians should be aware of the limitations of FNA analysis of atypical adenopathy especially if facilities such as flow cytometry or molecular analysis are not available.. Clinicians should not be falsely reassured by a negative FNA report if the node is clinically suspicious.

P88

Chronic Lymphocytic Lymphoma with Transformation to Acute Lymphoblastic Lymphoma: a Case Report and Review of the Literature

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Introduction: Chronic Lymphocytic Lymphoma/Leukemia (CLL) is a low grade lymphoproliferative disorder which is usually stable over many years. A small proportion of cases transform to a high grade lymphoma, most commonly Diffuse Large B Cell Lymphoma (Richter syndrome). We describe a rare case of B Cell Acute Lymphoblastic Lymphoma (ALL) arising in a patient with CLL, discuss the clinicopathologic features and review the literature on this uncommon occurrence.
Case History: A 52 year old asymptomatic male was diagnosed with CLL following detection of lymphocytosis on routine bloods. Bone marrow aspirate, trephine biopsy and flow cytometry confirmed a clonal population of small lymphocytes with condensed chromatin and scant cytoplasm, which were positive for B cell markers CD20 and CD79a with co-expression of CD5 and CD23. 18 months later, repeat bone marrow trephine revealed persistent evidence of CLL accompanied by an extensive blast infiltrate, which stained positively with B cell markers as well as TdT and CD10. The morphological and immunophenotypic findings were consistent with B cell ALL arising in a background of CLL.
Discussion: The literature on ALL occurring in patients with CLL is limited to isolated case reports with less than 10 cases documented. The underlying mechanisms remain unclear. Knowlegde of this rare type of aggressive transformation that may occur in patients with CLL is essential for all those involved in the diagnosis of haematological malignancies to ensure accurate diagnosis and appropriate treatment.

P89

An Unusual Case of HIV-associated Burkitt's Lymphoma with Mandibular and Tooth Socket Involvement

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Burkitt lymphoma (BL) is a high grade B-cell lymphoma originally described by Dennis Burkitt in equatorial Africa. Later, Epstein and colleagues identified the role of the Epstein-Barr virus (EBV) in the pathogenesis of BL. There are three clinical subtypes of BL: endemic, sporadic and immunodeficiency associated. BL represents 3-4% of all lymphomas and commonly affects children, representing 40% of all childhood head and neck lymphomas.

Endemic BL is seen in central and sub-Saharan Africa with a peak incidence of 4-7 years and predominantly involves the jaws and facial bones. Sporadic BL is seen throughout the world and affects children and young adults. Jaw involvement is less common in sporadic BL; the majority of patients present with an abdominal mass. In immunodeficiency-associated BL the disease is commonly presents with nodal and bone marrow involvement. EBV is present in almost all cases of endemic BL; an EBV association is seen in 30% of sporadic BL cases and in 25-40% of immunodeficiency-associated BL cases.

A 47 year old male with no previous history presented with axillary swelling and was diagnosed with HIV infection and BL. Within 2 weeks of diagnosis he developed a submandibular swelling and had to undergo dental extractions. Histologically the tooth sockets showed infiltration by EBV-positive BL (as seen in the axillary node biopsy). This clinical pattern of disease was unusual and resembled that seen in children with endemic BL. Although it is rare for immunodeficiency-associated BL to show jaw and dental involvement, orofacial manifestations of the disease may be one of the first clinical findings.

P90

Retroperitoneal Hyaline-vascular Castleman's Disease Mimicking Intra-abdominal Sarcoma

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Background: Castleman's disease (CD) is an uncommon lymphoproliferative disorder and is especially rare in the retroperitoneum.

Case Report: A 37- year old female was referred by her GP with history of a recent increase in size of an intra-abdominal mass. The mass was first detected in 2001 as incidental finding on CT scan following a car accident. An open biopsy from the right para-aortic lesion in December 2012 was reported as reactive lymphoid tissue. Since 2001 the patient had been followed up with routine CT scans at her local hospital. Although essentially asymptomatic, she had suffered from occasional bouts of vomiting and right-sided abdominal pain. On this admission clinical examination revealed a palpable mass in the right upper quadrant and CT scan showed a well-encapsulated 6 x 5.5 cm mass abutting the IVC and anterior to the right kidney. The mass was pushing the head of pancreas and duodenum forwards and showed a heterogeneous internal texture with some peripheral calcification. The patient was discussed at the abdominal sarcoma MDT meeting and underwent excision of the mass; the presumed diagnosis was a low-grade mesenchymal tumour. The specimen was a well-circumscribed haemorrhagic mass weighing 130g and measuring up to 80mm in diameter. Histology showed the characteristic features of hyaline-vascular Castleman's disease and no evidence of malignancy. The patient has remained asymptomatic and has been referred to the haematology team for follow-up.

Conclusion: Although retroperitoneal CD is rare, it does fall into the differential diagnosis of retroperitoneal tumours. Histology is required for a definitive diagnosis.

P91

Morcellated Spleens – Lessons From Beetroot Soup

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Splenectomies following either spontaneous or traumatic rupture receive scant attention in Histopathology departments. We report our five year experience of a consecutive series of 64 splenectomies.

Patients & Methods - 38 emergency splenectomies were identified in our departmental archives over the 2008-2012 period. Of these, there were 9 cases of spontaneous rupture, 12 traumatic ruptures, 7 splenectomies due to iatrogenic injury and 10 intra-operative splenectomies done to gain surgical access. During this period, we also identified 26 elective splenectomies done for a specific pathology. 38 emergency splenectomies submitted to the Histopathology department were in varying states of morcellation ranging from beetroot soup to partly disintegrated specimens. The number of blocks submitted for microscopy ranged from 3-15 in both emergency and elective splenectomies.

Results - Histology showed 1 splenic marginal zone lymphoma, 1 mantle cell lymphoma, 1 angiosarcoma, 1 cavernous haemangioma and 1 case of extramedullary haematopoiesis in 9 splenectomies submitted for spontaneous rupture. There was no previous clinical suspicion of a haematological disorder or robust history of splenomegaly. The 26 elective splenectomies included 10 B-cell lymphomas, 7 idiopathic thrombocytopenic purpura, 4 haemolytic anaemia, 2 extramedullary haematopoiesis related to chronic myleoproliferative disease, 2 congestive splenomegaly due to portal hypertension and 1 case of abscess.

Conclusions - Encountering an unexpected sinister histology is not uncommon in Histopathology practice. Morcellated spleens may get scant attention and ominous diagnoses can be missed. Interestingly, both elective and emergency splenectomy cases saw a similar range of sampling between 3-15 blocks. Our series demonstrates that morcellated spleens can harbour an unexpected pathology and these specimens should be properly attended to and meticulously examined.

P92

Correlation Between Lymph Node Aspirate and Biopsy in the Diagnosis of Lymphoid Malignancies

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Aim: In this retrospective study, we examined the correlation between fine needle aspirate (FNA) and lymph node biopsy in the diagnosis of haematolymphoid malignancies.

Material and Methods: We analyzed the cytology and histology reports of 74 cases of clinically suspected lymphoma that had a definitive or suspicious fine needle aspirate diagnosis of lymphoma at our centre between 2005 and 2012. All cases had subsequent excisional biopsies with lymphoma cases sub-classified according to the WHO classification.

Results: 45 patients were males and 29 were females. The median age at presentation was 65 years. Cervical lymphadenopathy was the most common presentation. 49 (65%) cases had a definitive diagnosis of lymphoma on FNA and which were confirmed on biopsy. 21 (28%) cases had a suspicious morphology on FNA; and on subsequent biopsies a definitive diagnosis of lymphoma was made. Four cases had suspicious FNA diagnosis of lymphoma but excisional biopsies revealed a different diagnosis, including reactive lympahadenopathy, tuberculosis, neurosphilis, and myeloid sarcoma. Ancillary studies (immunocytochemistry and or flow cytometry) have been carried out on 52 cases which contributed towards a correct diagnosis in 77% of cases, while the remaining 23% being inconclusive.

Conclusion: FNA is a reliable tool in the initial diagnosis of lymphoma, mainly when combined with immunocytochemistry and flow cytometry. However, it should be borne in mind that unusual reactive conditions and less common haematolymphoid malignancies can mimic common lymphomas and therefore, excisonal biopsy should be encouraged for a definitive diagnosis and further classification of lymphoma.

P93

Follicular Lymphoma Insitu: A Study of 4 Cases

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Introduction: Follicular lymphoma insitu (FLIS) is a rare entity with a prevalence of only 2.3 %. Here we discuss four cases of FLIS with their clinical presentation.
Material and Methods: Clinical histories were retrieved from the medical records. Histopathology specimens were blocked appropriately and stained with H&E. Immunohistochemistry was performed in all 4 cases and molecular/ PCR analysis was performed in 2 cases.
Results: The age range was 62-72 years, comprising two males and two females. Clinically, lymphoma was suspected only in one case. On histopathological examination, one case showed Diffuse Large B cell lymphoma (DLBCL) of the small bowel with a minor component of Follicular Lymphoma (10%). The mesenteric lymph nodes removed as part of the resection showed features of Follicular lymphoma grade 1 and FLIS. The remaining three cases showed only FLIS.
Discussion: FLIS has a very low rate of progression to clinically significant Follicular Lymphoma (FL). Currently there is no evidence for starting any therapy for "in situ" lymphoma, and a "wait-and-see policy" is strongly suggested. The patient with concurrent DLBCL received chemotherapy and is under remission 13 months after surgery. Out of the two patients who had an incidental diagnosis of FLIS, one also had colorectal adenocarcinoma and the other had a pancreatic carcinoma. For both of them the survival was more related to the primary malignancy rather than the incidental findings of FLIS. The patient who had clinical suspicion of lymphoma underwent bone marrow biopsy which was negative.

P94

A Histopathologic Analysis of Non-Viral Infectious and Tropical Diseases at a Tertiary Health Institution in South Western Nigeria.

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Introduction: Africa suffers significant population losses each year from infectious and parasitic diseases. Infectious and parasitic diseases rank second among the top killer of the world according to WHO report. The objective of this study is to present the pattern, age, sex and site distribution as well as histopathology features of non-viral infectious and tropical diseases as seen in our facility. This study also aim at documenting the top five most common parasitic diseases in our centre based on tissue biopsies.
Materials and Methods: This was a retrospective review of the surgical registers in the Department of Morbid Anatomy & Forensic Medicine, Obafemi Awolowo University Teaching Hospitals Complex Ile-Ife, Nigeria, for cases of non-viral infectious and parasitic diseases. The study period was from January 1, 1990 to December 31, 2010 .The cases seen were analyzed using SPSS version 15.
Results: A total of 164 cases were diagnosed histologically during the study period. About 41.5 %(68 cases) of the cases were tuberculosis. The top five common diseases were tuberculosis(41.5%),salmonella typhi (18.3%),schistosomiasis (15.2%), onchocerchiasis (6.7%), histoplasmosis (5.5%) and leprosy (5.5%).The ages ranged from 1-85 years (mean of 27.69) with the peak in patients 20-29 year age group and Male :Female ratio of 1.47:1.The commonest site was the lymph node and tuberculosis accounted for the majority at this site. Unusual sites such as ovary, pericardium and breast were also documented.
Conclusions: Non-viral infectious and tropical diseases are major policy issue that transcends national boundaries. Tuberculosis remains the commonest non-viral infectious and diseases in our centre.

P95

A Second Malignant Neoplasm: A Rare Case of Paediatric Insular Thyroid Carcinoma following Chemo-radiotherapy

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Childhood thyroid neoplasms are uncommon and second malignant neoplasms are typically of follicular or papillary subtype. We present the first literature reported paediatric case of insular thyroid carcinoma post chemo-radiotherapy treatment for bilateral anaplastic Wilms' tumour.
12 year old euthyroid girl had an incidentally detected right thyroid lobe nodule whilst reinsertion of her neck permacath access. She had been previously treated for bilateral Wilms' tumour at age 3, with left nephrectomy/chemotherapy. Right-sided relapse, 6 months later, was treated with second-line chemotherapy, consolidated with high-dose melphalan, autologous transplant and right flank radiotherapy 25.2Gy in 14 fractions. Long-term remission from a further relapse was achieved with right nephrectomy/adjuvant chemotherapy.
Fine needle aspiration demonstrated atypical neoplastic cells however it was unclear whether this represented primary or metastatic disease.
A subsequent right hemithyroidectomy revealed a 27x18x18mm encapsulated nodular tumour composed of large solid nests (insulae) and anastomosing islands. Tumour cells showed round nuclei, nuclear pleomorphism, stippled chromatin, conspicuous mitoses with expression of TTF-1 and thyroglobulin. Foci of necrosis, vascular and capsular invasion were seen. These microscopic features were of a poorly differentiated "insular" thyroid carcinoma.
This is the first described case of insular carcinoma arising in this clinical setting and carries an intermediate prognosis between follicular/papillary and anaplastic subtypes.
There is an increasingly recognised risk of secondary malignancy in long-term survivors of childhood malignancy. The mechanism of alkylating agents, radiotherapy, underlying genetics predisposing to secondary malignancy is being studied. Future cancer treatments should incorporate strategies to screen and reduce risk of second malignant neoplasms.

P96

Post Mortem Examinations in Cases of Stillbirth: Is PM Microbiology Useful?

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Introduction: Although infant mortality rates have dropped, stillbirth rates have not declined to the same extent. The cause of stillbirth is incompletely understood and the PM rate is low; more than half of cases remain unexplained. Regional variation in PM practice exists.
Aims: To examine whether the RCPath's guidelines for microbiology investigation in stillbirth is justifiable. The current recommendation is; a routine lung swab, blood culture +/- other sampling dependent upon the clinical history and macro findings.
Methods: We audited histology and microbiology from stillbirth PM cases over a 12 month period (n=48). Bacteria grown at PM were classified into pathogenic and non-pathogenic organisms and correlated with histological evidence of infection at PM.
Results: Microbiology was taken in 31/48 (65%) of cases, in accordance with RCPath guidelines. In 17 cases where microbiology was not taken, 5 (29%) had histological evidence of chorioamnionitis. 11/31 (35%) cases were sterile, 8/31 (25%) grew non-pathogenic bacteria and 12/31(39%) grew pathogenic bacteria. Of these pathogenic isolates, 7 were E.Coli, 5 were Group B Streptococci and 1 was Staphylococcus aureus (of which 4 cases showed histological evidence of chorioamnionitis.)
Conclusion: E.coli, Group B Streptococci and Staphylococcus aureus are potentially significant pathogens, and may be important contributory factors in stillbirth. In view of the percentage of cases which grew a pathogenic organism, we suggest bacteriology should be performed in most cases. Microbiology plays a useful part aiding interpretation of histological evidence of infection at PM. Further research is required to improve our understanding of the cause of stillbirths and specifically how significant positive cultures should be interpreted in the light of absent histological features of infection. We recommend close liaison with the microbiology team in such cases and possibly toxin analysis.

P97

Influenza A (H1N1) Infection as a Trigger of Fatal Bronchial Asthma

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Background: Clinical studies have reported that children with asthma have increased susceptibility to infection with H1N1 Influenza A, and infection with H1N1 Influenza A can reveal underlying asthma by inducing a severe asthma attack in atopic children without previous history of asthma. Influenza-related deaths in asthmatics are usually due to development of secondary bronchopneumonia. We present a child dying of acute asthma, without bronchopneumonia, in the context of H1N1 Influenza A infection.
Case Report: A 2-year old girl with a 3 month history of repeated hospital attendances with respiratory tract symptoms and febrile convulsions suffered fevers in the week before death but was otherwise well. She was put to bed, apparently well, and found dead the next morning. Autopsy demonstrated an otherwise normal child whose lungs showed features of acute asthma with prominent mucus plugging and eosinophilic infiltration of airway walls. Chronic changes were also present (goblet cell hyperplasia, smooth muscle hyperplasia and thickening of bronchial basement membranes). There was no bronchopneumonia. The presence of coexisting H1N1 infection was confirmed by Polymerase Chain Reaction.
Conclusion: This case supports data suggesting that H1N1 Influenza A infection can trigger severe asthma attacks in previously undiagnosed children and demonstrates that deaths may occur in children with H1N1 Influenza A infection as a result of acute asthma, even in the absence of bacterial superinfection.

P98

The Prognostic Impact of MGMT Expression on Low-grade Gangliogliomas

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Ganglioglioma (GG) is an uncommon brain parenchymal neoplasm. Although most cases have indolent clinical behaviour, a subgroup of GGs does recur, especially in patients with unresectable disease. O6-methylguanine DNA methyltransferase (MGMT) is a DNA repair protein that removes mutagenic and cytotoxic adducts from O6-guanine in DNA. Lack of MGMT protein expression immunohistochemically is related to drug responses in patients of malignant glioma treated with alkylating agents. Furthermore, MGMT promoter methylation has also been investigated as an independent favourable prognostic factor for glioblastoma. The primary management is surgical resection for GGs and grossly total resection is recommended. Despite infrequent use of chemotherapy for low-grade GGs, it was still introduced to a subset of patients, especially who had unresectable disease.
We render clinicopathologic features of nine cases of low-grade GGs to further elucidate the relationship between the status of the MGMT protein expression and the prognosis. This series included four men and five women with a mean age of 21.6 years at the first surgery. The mean postoperative follow-up period was 6 years. Only two patients had recurrent disease after 1.7 and 3.2 years of the first surgery. Immunohistochemically, 11.1% exhibits 3+ nuclear staining for MGMT protein, 11.1% exhibited 2+ staining, 33.3% exhibited 1+ staining, and 44.4% exhibited 0 staining. Tumours with more intensive MGMT protein expression (2+~3+ immunostaining) tended to recur more frequently ($p < 0.05$), corresponding to the worse prognostic predictive value of intensive MGMT staining.

P99

Atypical Fibroxanthoma and Pleomorphic Dermal Sarcoma with Pseudoangiomatous Features: a Histologic and Immunohistochemical Mimic of Cutaneous Angiosarcoma

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Atypical fibroxanthoma (AFX) and pleomorphic dermal sarcoma (PDS) may show pseudoangiomatous features making separation from cutaneous angiosarcoma challenging. Accurate diagnosis is necessary in view of the implication on behaviour and treatment.
Eleven AFX and three PDS with pseudoangiomatous features were retrieved from departmental and consultation files. H&E-stained sections and immunohistochemistry for markers of endothelial differentiation, including CD31, CD34, Fli-1 and ERG, were evaluated. Clinical and follow-up data were obtained.
The tumours presented as exophytic nodules on sun-damaged skin of the head and neck of elderly males (age range: 69-88). Histologically, they were composed of pleomorphic epithelioid and spindle cells in varying amounts, forming solid sheets and fascicles. All cases showed pseudoangiomatous features in the form of blood-filled, pseudovascular spaces with areas of haemorrhage and hemosiderin deposition, comprising 20%-80% of the tumour. While AFX were confined to the dermis with a pushing growth pattern, PDS were diffusely infiltrative invading deep subcutis and underlying fascia. There was no evidence of necrosis or perineural or lymphovascular invasion. By immunohistochemistry, focal expression of CD31 was seen in four AFX (36%) and one PDS (33%). Seven AFX (64%) showed weak expression of Fli-1. All PDS (100%) showed nuclear staining of Fli-1. No expression of CD34 and ERG was observed. Follow-up, available in 10 patients (median: 43 months), showed no evidence of recurrence, metastasis or disease related mortality. AFX and PDS with pseudoangiomatous features closely resemble poorly differentiated cutaneous angiosarcoma histologically. They arise in the same clinical setting and may share expression of the endothelial markers Fli-1 and CD31. Negativity for CD34 and ERG, in particular, are important distinguishing features allowing accurate distinction.

P100

Impact of Immunohistochemistry on Turnaround Times in Reporting Biopsies of Non-melanoma Skin Cancer

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Non-melanoma skin cancer is common in the older members of our society and is mainly a consequence of long term sun exposure. These cancers carry a low risk of metastasis but may progress to invade into surrounding tissues if not completely excised.
The RCPath standard for histopathological reporting of these biopsy specimens is that a report should be produced within 7 days in 90% of cases.
In this retrospective audit of data from the laboratory information system the turnaround time from receipt of the specimen to the time of reporting was analysed.
Immunohistochemistry (IHC) is an additional method sometimes used to aid in differential diagnosis. The utility of immunohistochemistry in aiding differential diagnosis, and its effect on turnaround time, was also analysed.
The standard for histopathological reporting was achieved for both types of cancer. In the majority of cases the use of immunohistochemistry lead to some further delay in producing the report, but reports were still produced within 7 days.
In a small number of cases reports were not produced within 7 days. The majority of these reports were produced by a single pathologist suggesting that individual variation in practice may have contributed to lengthened turnaround times to a greater degree than the time needed to perform additional immunohistochemistry.
IHC is only rarely used in routine diagnostic practice (5% of SCCs and 1 % of BCCs). IHC defines a small number of tumours showing basosquamous differentiation that had not been recognised on H&E.

P101

Ber EP4 in the Differential Diagnosis of Non-melanoma Skin Cancer

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Non-melanoma skin cancer is common in the older members of our society and is mainly a consequence of long term sun exposure. These cancers carry a low risk of metastasis but may progress to invade into surrounding tissues if not completely excised. The major diagnostic categories are squamous cell (SCC) and basal cell carcinoma (BCC). A further category of basosquamous carcinoma (BSCC) is less commonly recognised and its classification is confusing.

Ber EP4 has been used as a dependable marker in differential diagnosis, typically being strongly positive in most basal cell carcinomas, less strongly positive in cytoplasm and often showing membrane-positivity in basosquamous carcinoma, and negative in squamous cell carcinomas. In an audit of six months in 2012 95 SCCs and 277 BCCs were reported. Ber EP4 staining was carried out in 5% of SCCs and 1% of BCCs. As a result of Ber EP4 positivity 5 cases originally reported as SCC were reclassified as BSCC.

To see if greater use of Ber EP4 would identify more BSCCs a random selection of 19 SCCs with a pushing margin and 19 SCCs with an infiltrative margin were stained with Ber EP4. As a result 2 BSCCs were identified, 1 from each group (5%).

The clinical management of BSCCs is the same as for SCCs. Routine use of Ber EP4 as an adjunct to H&E diagnosis used to identify BSCC may identify a small number of BSCCs that had not been recognised on H&E, but as the clinical management of BSCCs and SCCs is the same this does not appear to have an economic justification. Ber EP4 does still have a role in the differential diagnosis of unusual cases.

P102

Malignant Melanoma Minimum Reporting Dataset: Is Cork University Hospital Compliant?

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Purpose of the Study: Analyse completeness of histopathological reporting of malignant melanomas at our institution.

Methods: A computer-based search was performed, retrieving cases reported as "malignant melanoma" between January to March 2012. Primary tumours only were included, with wider excisions and metastatic deposits disregarded for the purposes of this audit. Histopathological reports were then compared to the Royal College of Pathologists' Minimum Dataset. Parameters required included the following: Breslow thickness, Clark level, Ulceration, LVI, perineural infiltration, tumour lymphocytes, microsatellites, regression, mitoses, coexisting naevus, margin status, pathological stage.

Results: 49 primary melanomas were found, including 20 invasive tumours and 29 in situ tumours. Invasive tumour reports were fully compliant for all parameters, except Clark level and tumour regression, which were 90% and 75% compliant respectively. In situ tumour reports were broadly compliant for all relevant parameters, except pathological staging as pTis (13.8% compliant).

Conclusion: Tumour reports are satisfactorily completed in the majority of invasive malignant melanoma cases, but reporting of tumour regression should be improved, especially as this may have significance as regards possible later metastatic potential. In situ melanomas are not routinely staged pTis, and this will require further attention. A reaudit is recommended at a later date.

P103

Comparison of Bone Histology Samples Obtained from Solid Samples with Reamings

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Background: Bone histology samples are frequently sent for people with fractured neck of femurs to screen for underlaying malignancies. Samples often take the form of solid samples, such as bone fragments or femoral heads, or reamings from femoral canal preparation. It has previously been hypothesised that reamings are less useful than solid samples as the tissue may be damaged during the process of extracting it from the femur.

Objectives: To assess if there was a difference in the number of inconclusive results, or concordance of suspected and tissue diagnoses between these two groups.

Method: A retrospective audit of histology from 200 operations was performed to identify bone samples from patients with neck of femur fractures. The histology results for these patients were reviewed.

Results: Forty-three samples were identified; 19 reamings, 24 solid samples. Of the reamed samples definitive diagnoses were made in 32%, no pathologial process was identified in 58%, and the results were inconclusive in 11%. Of the solid samples 21% gave a tissue diagnosis, 75% identified no pathological process, and 4% were inconclusive. 26% of the reamed samples provided tissue diagnosis consistent with that suspected, it was 17% in the solid sample group.

Conclusion: Although the sample size is small, there is no significant difference between the two sampling techniques in terms of the results obtained, or their concordance with suspected diagnosis. This suggests that either techniques can be employed when seeking a tissue diagnosis.

P104

Is Intervertebral Disc Degeneration Linked to Anatomical Changes in the Vertebral Disc End Plate?

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Background: Discogenic back pain (DBP) affects 80% of people, costs £12.3B/annum, and causes considerable morbidity. A better understanding of DBP could significantly impact on health care. It has been hypothesised that a reduction in nutrients to intervertebral disc (IVD) cells secondary to thickening of the bone end plate (EP) of adjacent vertebral bodies causes the cellular dysfunction leading to IVD degeneration (IVDD), the IVD disorder associated with DBP. Nutrition of the avascular IVD relies on nutrient diffusion via terminal capillary buds and marrow spaces of the EP. This is the first histological study to examine this hypothesis.

Methods: Image analysis was conducted on 226 EP from 51 patients and EP thickness correlated with age, sex and extent of IVDD. 80 EP were then used to measure mean and minimum diffusion distances and blood vessel/marrow space length (% length of diffusion) and thereby derive the "diffusion index (D/A)". These were correlated, using linear regression analyses and Mann-Whitney testing, with IVDD.

Results: Showed: Mean EP thickness decreases insignificantly with age; No relationship between EP thickness and degeneration; No correlation between EP thickness and diffusion distance; but significant correlations between D/A and % length of diffusion, and mean diffusion distance.

Conclusion: This study does not support the hypothesis implicating EP thickness and diffusion distance in IVD degeneration. Thus, disordered nutrition predisposes to IVD cell dysfunction it is not related to an anatomical disturbance of EP vascularisation.

P105

Anti-calponin 1 Antibodies Highlight Intracytoplasmic Inclusions of Infantile Digital Fibromatosis

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Aims: Infantile digital fibromatosis (IDF) presents as a nodule occurring almost exclusively on the digits of infants and young children with potential for recurrence. The lesion is a proliferation of fibroblasts demonstrating pathognomonic intracytoplasmic inclusions. A diagnosis of IDF is challenging due to the low frequency of occurrence. Accurate diagnosis is however important as the lesion can cause joint deformity and lead to functional impairment. We used a panel of myogenic markers by standardised immunohistochemical stains to assess the nature of the tumour and inclusions as well as aid detection of the inclusions for diagnosis.
Methods: Eight cases of IDF were reviewed alongside a range of "non-inclusion" pediatric fibromatosis and exposed to a panel of immunohistochemical stains using a fully automated immunostainer.
Results: The cytoplasm of the lesional cells expressed calponin 1 (8/8 cases), calponin 2 (8/8 cases), calponin 3 (8/8 cases), a-smooth muscle actin (8/8) and desmin (8/8). There was no immunoreactivity with caldesmon (0/8). The inclusions reveal "ground glass" (punch-out) pattern with all the aforementioned stains except calponin 1. The tumour inclusions show strong immunoreactivity for calponin 1 (8/8) rendering them unmissable.
Conclusions: The cytoplasm of IDF cells shows positive immunoreactivity for calponin 1 which also clearly highlights the pathognomonic intracytoplasmic inclusions illustrating that calponin 1 is a useful marker for identifying the intracytoplasmic inclusions of IDF and may aid in understanding their composition. Cytoplasmic positivity allows the shape, size and extent of the tumour to be readily appreciated allowing discrimination from adjacent normal tissue and facilitating comment on the adequacy of excision.

P106

Osteoarthritis (OA) and Obesity – Are the Co-Culprits?

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Osteoarthritis (OA) is a multifactorial degenerative joint disease leading to patient's disability. Obesity is one of the growing problems of western civilization as well. In the past it has been pointed that obesity as comorbidity with OA can have a huge impact on OA progression. Proteins produced by adipose tissue such as adipokines may play destructive or protective role in cartilage degradation. A molecular analysis of adipokines gene expression was conducted between patients undergoing knee replacement surgery with attention to the role of obesity in OA pathogenesis. The human chondrocytes were isolated from (a) lean, patients with BMI score at 25 and (b) patients with BMI score more than 35 during routine knee replacement surgery. The semi-quantitative PCR was performed to see the expression of confirmed adipocyte related genes. The preliminary data shows that in 2D culture of chondrocytes, the genes such as ADIPOR1 and ADIPOR2 did not show any change in gene expression. On the other hand two adipocyte related genes such as visfatin and PPARG was down regulated in obese OA patient compared to lean group. However, in the synovium the transcript level of adiponectin was found to be significantly down-regulated in obese patient. The differential expression of adiponectin and other adipose tissue related genes in the osteoarticular tissues of obese and lean groups may suggests distinct mechanism of interaction with molecules such as cytokines, and metalloproteases and ADAMTSs. So, further investigation on the mechanisms of these molecular markers can help us to analyze the role of adipokines in progression of Osteoarthritis.

P107

High Expression of IL13RA2 in Osteoarthritis and Its association with Matrix Metalloproteinases

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Osteoarthritis is an idiopathic disease which is characterized by degeneration of articular cartilage that leads to fibrillation, fissures, gross ulceration and finally disappearance of the full thickness of articular cartilage. Proinflammatory cytokines are believed to play a pivotal role in the initiation and development of osteoarthritis. In the present study we have studied the expression of IL13RA2 in chondrocytes isolated from normal and OA human knee joints. IL13RA2 is a subunit of the interleukin 13 receptor complex which is closely related to IL13RA1. IL13RA2 binds IL13 with high affinity but lacks cytoplasm domain, and generally does not appear to function as a signal mediator- A decoy receptor. Five different cartilage tissues were taken from two groups, viz, normal and OA patient. The RT PCR result suggests that IL13RA2 is over expressed in the chondrocytes of OA group compared to normal chondrocytes. The transcript of levels of IL4R receptor was also found to be increased in OA cells compared to normal chondrocytes. We next determined whether Il13ra2 gene silencing through in vitro administration of human IL13RA2 specific siRNA blocks the expression of IL13RA2, IL4R and other related chondrocytes specific genes in the OA cells. The human IL13RA2 siRNA inhibits expression of IL-13Ra2 after stimulation with IL-13, IL4. The stimulations of OA cells by IL1α and TNF-a, induce the expression of IL13RA2. Further we assessed that the transcript levels of MMP13, Opiod receptor, ADMTS5 were unchanged in OA cells after silencing IL13RA2 but stimulation of IL13 and IL4 in control OA cells, downregulated the expression of MMP13, Opiod receptor, and ADMTS5. Though similar pattern of IL13RA2 has been seen in murine and canine chondrocytes, further studies on signalling will advance our understanding on IL13 mediated Osteoarthritis.

P108

CD7 Immunoreactivity in Ewing's Sarcoma/Primitive Neuroectodermal Tumour

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Purpose of the study: Ewing's sarcoma/primitive neuroectodermal tumours are round cell sarcomas demonstrating varying degrees of neuroectodermal differentiation. They most commonly occur in males below the age of twenty arising both in bone and soft tissues. They show membranous staining with CD99, vimentin and neural markers and a proportion of cases show dot positivity for cytokeratin. Approximately 85% of cases demonstrate translocation t(11;22). Our aim was to demonstrate CD7 immunoreactivity in a proportion of Ewing's sarcomas.
Methods: 23 Ewing's sarcomas were identified. Tumour rich blocks were identified on haematoxylin and eosin stained sections and Immunohistochemistry for CD7 was performed. Two independent pathologists assessed the pattern and quantified the percentage of tumour cells showing CD7 positive staining using a four point scale: Negative, <25%, 25-75% or >75% of tumour cells positive. The cases which demonstrated scattered positive cells were subsequently stained with CD45 to rule out cross-reactivity with CD7 positive T lymphocytes.
Summary of results: 7 out of the 23 cases showed granular cytoplasmic tumour cell expression of CD7. Most positive cases showed 25-75% staining in tumour cells while one case showed >75% of tumour cells. Furthermore two other cases showed <25% staining.
Conclusion: This study demonstrates CD7 immunoreactivity in a number of cases of Ewing's sarcoma/PNET. This is the first description of this finding. Further work would be necessary to investigate and explain these results.

P109

Congenital Infantile Fibrosarcoma – A Series of 5 Cases

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Introduction: Congenital Infantile Fibrosarcoma (CIF) is a rapidly growing malignant neoplasm of infants, typically involving extremities or the head/neck region. We report a series of 5 cases from Our Lady's Children's Hospital, Crumlin (OLCHC), Ireland's largest paediatric hospital providing the majority of tertiary care for over 130,600 children annually
Methods: 5 CIF cases diagnosed between 2001-2011 were retrieved from the OLCHC database. Histology and immunohistochemistry were reviewed. Clinical details including follow-up were obtained. RT-PCR assay for ETV6-NTRK3 fusion transcripts were performed on all cases.
Results: All cases occured in males, aged 2 days to 2 months. Clinical presentations varied, including 2 rapidly growing cutaneous masses, an oral mass, a neck mass and an ileal perforation. Interestingly, the 2 cutaneous lesions clinically mimicked Kaposiform Haemangioendothelioma (KHE), a vascular tumour of intermediate malignant potential, presenting in infancy and displaying a rapid growth phase. Despite substantial clinical similarities, the clinical course and treatment of these two lesions differ widely. ETV6-NTRK3 fusion transcripts were identified in all cases. At 6 months follow-up, 4 patients responded well to treatment and 1 patient developed pulmonary metastasis.
Conclusion: CIF presenting as a rapidly growing, ulcerating mass can be life-threatening and requires timely appropriate therapy. The cutaneous tumours which represent 40% of CIFs in this series clinically masqueraded as KHE making it is clear that clinical diagnosis poses significant challenges. Molecular studies play a vital role in the diagnosis of a tumour with no characteristic immunoprofile.

P110

Massive Localised Lymphoedema of the Morbidly Obese - A Diagnostic Challenge of the Modern Age

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Introduction: Massive localized lymphoedema(MLL) is a rare reactive pseudotumour strongly associated with obesity, first described by Farshid and Weiss in 1998. Only approximately 30 cases have been reported in the literature.
Case History: A 66 year old, morbidly obese lady presented with a pendulous enlarging right medial thigh swelling over a 5 year period. The clinical impression was that of a soft tissue sarcoma. A biopsy was performed initially, which showed adipose tissue interspersed by loose fibroconnective septa containing atypical fibroblasts with surrounding increased vascularity. Atypical adipocytes or lipoblasts were not seen. Histology of the resected specimen mirrored the appearance of the biopsy allowing better appreciation of the interstitial oedema and vascular proliferation at the interface between fat and fibroconnective tissue. In addition, the overlying skin showed evidence of chronic lymphoedema (epidermal thickening, lymphangiectasia, dermal fibrosis with inflammation). A diagnosis of well differentiated liposarcoma (WDL) was considered but following intradepartmental consultation a diagnosis of MLL was rendered. At MDM, review of the radiological features concurred with the pathological diagnosis. The patient is well with no evidence of recurrence at 3 months follow-up.
Discussion: MLL can cause significant diagnostic difficulty and is often misdiagnosed as WDL, clinically and histologically. The clinical setting of MLL is distinctive and additional specific histological features including chronic lymphoedema of overlying skin, interface vascular proliferation and oedema can assist in making a correct diagnosis. Recurrences are common. However, the overall prognosis is excellent.
Conclusion: Recognition of this entity in the appropriate clinical setting by both clinicians and pathologists should avert the misdiagnosis of a WDL.

P111

This abstract has been withdrawn

P112

Audit of Needle Core Biopsies of Soft Tissue and Bone Sarcomas

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The Sarcoma Diagnostic and Treatment service received pathology referrals for over 200 sarcoma patients in 2012, of which approximately 50% were for patients who had biopsies in our hospital. The aims of this audit were to review the efficiency of the diagnostic needle core biopsy pathology service over a 3 year period, the turnaround times and the proportion of inadequate biopsies.
All needle biopsies performed in 2010-2012 for the orthopaedic oncology service were reviewed. Target turnaround times were derived from the sarcoma histopathology dataset of the Royal College of Pathologists, with the expectation that 80% of soft tissue specimens should be reported within 7 calendar days and 80% of bone specimens should be reported within 10 days.
Out of 277 needle biopsies, 174 were soft tissue, 86 were bone and 17 were insufficient biopsies. 180 (65%) of the adequate specimens carried a malignant diagnosis. The median turnaround time was 5 days. For soft tissue needle biopsies, 70% had a final report within 7 days and 93% within 13 days. For bone needle biopsies, 82% were reported within 10 days. The main reasons for prolonged turnaround times was immunohistochemistry, molecular studies and second opinion. The inadequate specimens mostly contained non-diagnostic necrotic material or haematoma.
The turnaround times for orthopaedic needle core biopsies are slightly longer than the target for soft tissue samples, but are clinically acceptable as initial reports are available for the weekly MDT meeting. A re-audit is planned following refinements to the immunohistochemistry service that should reduce perceived delays.

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