



# Ghent Pathology 2011

10 – 13 MAY

6<sup>th</sup> Joint Meeting of the British Division of  
the International Academy of Pathology  
and the Pathological Society  
of Great Britain & Ireland



Hosted by  
The Department of Pathology, University of Ghent, Belgium

Venue  
Het Pand, University of Ghent, Onderbergen 1, 9000 Ghent

Companion Session  
Association of Clinical Electron Microscopists



**CONTENTS**

Programme quick reference pages..... 3

Scientific sessions information..... 7

CPD..... 9

Fees and Registration..... 10

General arrangements..... 11

Future meetings..... 12

Detailed programme

    Tuesday 10 May..... 13

    Wednesday 11 May..... 20

    Thursday 12 May..... 32

        Association of Clinical Electron Microscopists Meeting..... 37  
        *See separate programme for the Association of Clinical Electron Microscopists*

    Friday 13 May..... 42

Acknowledgements (Trade Exhibition / Sponsors)..... 46

Abstract reviewers..... 48

Poster Abstracts..... 49

Index of presenters and abstract numbers..... 70

**Programme acknowledgements**

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**12.00** [Reception]  
**Registration and Coffee**

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**12.45–13.00** [Room Rafter – Storey]

**Welcome address**

Chair: Prof C Cuvelier, University of Ghent

Speaker: P. van Cauwenberge, Rector of Ghent University

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**13.00–17.00** [Room Sacriste – Storey]

**Slide Seminar Competition – Case Viewing: *Tumours of the Skeleton: Test Your Knowledge up to The Bare Bone***

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**13.00–15.30** [Room Rafter – Storey]

**Symposium: *Advances in Gynaecological Pathology***

**13.00–15.30** [Room Rector Vermeylen – Second Floor]

**Oral Presentations**

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**15.30–16.00** [Kapittelzaal – Storey]

**Coffee**

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**16.00–18.00** [Room Rector Vermeylen – Second Floor]

**Satellite Symposium (*Sponsored by Roche*) — *Targetted Therapies: An update on the Her1 and Her2 Stories***

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**18.00–20.00** [Pacification Room · Town Hall · Ghent]

**Welcome Reception – *Hosted by the Lord Mayor***

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**08.00** [Reception]  
**Registration and Coffee**

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**09.00–17.00** [Room Sacriste – Storey]  
**Slide Seminar Competition – Case Viewing: *Tumours of the Skeleton: Test Your Knowledge up to The Bare Bone***

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**09.00–12.00** [Room Rafter – Storey]  
**Symposium: *The Pathologist as Part of the Puzzle in Diagnosing Inflammatory Disorders***

**09.00–12.00** [Room Rector Vermeylen – Second Floor]  
**Oral Presentations**

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**10.30–11.00** [Kapittelzaal – Storey]  
**Coffee**

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**12.00–13.00** [Room Rafter – Storey]  
**Keynote Lecture (Sponsored by: *Ferring Pharmaceuticals*)**  
Prof D Elewaut, Ghent: *Mechanisms Regulating Combined Gut and Joint Inflammation in Spondyloarthritis*

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**13.00–14.00** [Kapittelzaal – Storey]  
**Lunch**

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**14.00–15.00** [Corridor]  
**Poster Viewing and Trade Stands**

**13.30–14.30** [Room Priorzaal – First Floor]  
**Trainees' Session – Meet The Experts**  
Prof I Salmon, Brussels: *Diagnostic Dilemmas in Thyroid Pathology*

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**14.00–15.00** [Corridor]  
**Chairman's Poster Rounds**

14.30–15.00  
Coffee will be served during rounds

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**15.00–17.00** [Room Rafter – Storey]  
**Symposium: *Lung Pathology Updated***

**15.00–17.00** [Room Rector Vermeylen – Second Floor]  
**Oral Presentations**

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**17.30–18.30** [Aula - Ghent University] — *Note: separate venue*  
**Public Lecture**  
Prof P Piot, London: *Old and New Challenges in Global Health*

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**19.00–20.30** [Het Pand Museum]  
**Guided Tour of Museum of History of Medicine**  
*followed by Reception*

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**08.00** [Reception]  
**Registration and Coffee**

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**09.00–17.00** [Room Sacriste – Storey]  
**Slide Seminar Competition – Case Viewing: *Tumours of the Skeleton: Test Your Knowledge up to The Bare Bone***

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**09.00–12.00** [Room Rafter – Storey]  
**Symposium: *Clinicopathological and Molecular Advances in Benign and Malignant Liver Tumours***

**09.00–12.00** [Room Rector Vermeylen]  
**Oral Presentations**

**09.10–17.00** [Room Priorzaal – First Floor]  
**Association of Clinical Electron Microscopists Meeting**  
*See separate programme*

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**10.30–11.00** [Kapittelzaal – Storey]  
**Coffee**

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**12.00–13.00** [Room Rafter – Storey]  
**Pathological Society's 30<sup>th</sup> CL Oakley Lecture**  
Dr A Jubb, Oxford: *Predicting Benefit from Anti-Angiogenic Therapies*

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**13.00–14.00** [Kapittelzaal – Storey]  
**Lunch**

**13.30–14.30** [Room Rafter – Storey]  
**Pathological Society's Annual Business Meeting**

**13.15–14.15** [Room Rector Vermeylen – Second Floor]  
**Trainees' Session – Meet The Experts**  
Prof S Pinder, London: *Preneoplastic Lesions of the Breast*

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**14.00–15.00** [Corridor]  
**Poster Viewing and Trade Stands**

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**14.15–15.00** [Corridor]  
**Chairman's Poster Rounds**

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**15.00–17.00** [Room Rafter – Storey]  
**Plenary Oral Presentations**

**09.10–17.00** [Room Priorzaal – First Floor]  
**Association of Clinical Electron Microscopists Meeting**  
*continued*

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**16.00–16.30** [Kapittelzaal – Storey]  
**Coffee**

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**17.00–18.00** [Room Rafter]  
**Pathological Society's 9<sup>th</sup> Doniach Lecture**  
Prof F Bosman, Lausanne: *Colorectal Cancer: of Dukes and Genes*

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**19.00–22.30** [Augustine Monastery]  
**Conference Dinner**

**08.15** [Reception]  
**Registration and Coffee**

**09.00–12.00** [Room Refter – Storey]  
**Symposium: *Recent Evolutions in  
Endocrine Pathology***

**08.30–10.50** [Room Rector Vermeylen  
– Second Floor]  
**Trainees' Symposium on  
Urological Neoplasia**

**09.00–09.50** [Room Priorzaal – First Floor]  
**Slide Seminar Competition  
Discussion: *Test Your Knowledge up  
to The Bare Bone***

10.30–11.00 [Kapittelzaal – Storey]  
Coffee

10.50–11.00 [Kapittelzaal – Storey]  
Coffee

**09.50–12.00** [Room Priorzaal – First Floor]  
**Slide Seminar Session: *Soft Tissue  
Tumours***

10.30–11.00 [Kapittelzaal – Storey]  
Coffee

**12.00–13.00** [Room Refter – Storey]  
**BDIAP George Cunningham Lecture**

Prof CA Cuvelier, Ghent: *The Terminal Ileum, Follicle Associated Epithelium and M Cells: How They Manage to Keep Our Gut Going Right or Wrong*

**13.00** [Kapittelzaal – Storey]  
**Lunch** (*take-away*)

*Conference Ends*

## **COMPANION MEETINGS**

### **Thursday 12 May**

09.10–17.00 [Room Priorzaal – First Floor]  
Association of Clinical Electron Microscopists

## **KEYNOTE AND NAMED LECTURES**

### **Wednesday 11 May**

12.00–13.00 [Room Refter – Storey] (*Sponsored by: Ferring Pharmaceuticals*)

Keynote Lecture: *Mechanisms Regulating Combined Gut and Joint Inflammation in Spondyloarthritis*  
Prof D Elewaut, Ghent

17.30–18.30 [Aula - Ghent University]

Public Lecture: *Old and New Challenges in Global Health*  
Prof P Piot, London

### **Thursday 12 May**

12.00–13.00 [Room Refter – Storey]

CL Oakley Lecture: *Predicting Benefits from Anti-Angiogenic Therapies*  
Dr A Jubb, Oxford

17.00–18.00 [Room Refter – Storey]

Doniach Lecture: *Colorectal Cancer: of Dukes and Genes*  
Prof FT Bosman, Lausanne

### **Friday 13 May**

12.00–13.00 [Room Refter – Storey]

George Cunningham Lecture: *The Terminal Ileum, Follicle Associated Epithelium and M Cells: How they Manage to Keep our Gut Going Right or Wrong*  
Prof CA Cuvelier, Ghent

## **ORAL COMMUNICATIONS** [Room Rector Vermeylen – Second Floor]

### **Sessions will be held as follows:**

Tuesday 10 May	13.00–15.30
Wednesday 11 May	09.00–12.00 and 15.00–17.00
Thursday 12 May	09.00–12.00

### **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** [Room Refter – Storey]

The six highest-ranked submitted oral abstracts will be presented on Thursday 11 May 15.00–17.00.

### **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** [Corridor]

### **Poster Size**

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

### **Viewing**

Wednesday 11 May	13.00–15.00
Thursday 12 May	13.00–15.00

### **Formal Poster Viewing and Chairman's Rounds**

Wednesday 11 May	14.00–15.00
Thursday 12 May	14.15–15.00

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

## **PRIZES**

### **BDIAP POSTER PRIZES — NEW**

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.

### **Winners**

Winners will be announced at the Conference Dinner on 12 May.

### **Note to presenters**

Ideally, posters should be in place by 13.00 hrs on Tuesday 10 May and removed by 12.00 hrs on Friday 13 May.

### **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 & SESSIONS**

### **Competition**

*Tumours of the Skeleton: Test Your Knowledge up to the Bare Bone*

### **Viewing Virtual slides** [Room Sacriste – Storey]

Slides images will be available for viewing on:

Tuesday 10 May	13.00–17.00
Wednesday 11 May	09.00–17.00
Thursday 12 May	09.00–17.00 <i>(Please note the competition closes at 15.30)</i>

### **Competition**

There will be a slide competition using slide images, which will be available during the days/times shown above.

### **Prize**

A case of champagne. The winner will be announced at the Conference Dinner on Thursday 12 May. *At the discretion of the winner, by tradition, this is shared amongst those present at the dinner!*

### **Competition Case Discussion Session** [Room Priorzaal – First Floor]

Friday 13 May 09.00–09.50

### **Soft Tissue Slide Session** [Room Priorzaal – First Floor]

Friday 13 May 09.50–12.00

## **SYMPOSIA**

### **Tuesday 10 May**

[Room Rafter – Storey]

13.00–15.30 *Advances in Gynaecological Pathology*

[Room Rector Vermeylen – Second Floor]

16.00–18.00 *Satellite Symposium sponsored by Roche: targeted Therapies: An Update on the Her1 and Her2 Stories*

### **Wednesday 11 May**

[Room Rafter – Storey]

09.00–12.00 *The Pathologist as Part of the Puzzle in Diagnosing Inflammatory Disorders*  
15.00–17.00 *Lung Pathology Updated*

### **Thursday 12 May**

[Room Rafter – Storey]

09.00–12.00 *Clinicopathological and Molecular Advances in Benign and Malignant Liver Tumours*

### **Friday 13 May**

[Room Rafter – Storey]

09.00–12.00 *Recent Evolutions in Endocrine Pathology*

## **TRAINEES PROGRAMME**

### **Wednesday 11 May**

[Room Priorzaal – First Floor]

13.30–14.30

*Meet the Experts: Diagnostic Dilemmas in Thyroid Pathology*

### **Thursday 12 May**

[Room Rector Vermeylen – Second Floor]

13.15–14.15

*Meet the Experts: Preneoplastic Lesions of the Breast*

### **Friday 13 May**

[Room Rector Vermeylen – Second Floor]

08.30–10.50

*Symposium: Urological Neoplasia*

## **CONTINUING PROFESSIONAL DEVELOPMENT (CPD)**

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

	<b>Full Day</b>	<b>Half Day</b>
Tuesday	5 credits	Not applicable
Wednesday	8 credits	4 credits
Thursday	7 credits	3 credits
Friday	3 credits	Not applicable

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

## **TRADE EXHIBITION** [Corridor]

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

<b>EARLY BIRD REGISTRATION FEES</b> UNTIL MIDNIGHT ON MONDAY 11 APRIL 2011			
<b>Delegate Type</b>	<b>Fee Categories</b>	<b>Per Day or Part Day</b>	<b>Conference Dinner</b>
BDIAP or Pathological Society Members	Ordinary Members, Consultant and/or equivalent position	£ 105.00	£ 55
BDIAP or Pathological Society Concessionary Members	Biomedical Scientists; Honorary or Senior Members; PhD Students; Post-Doctoral Fellows, Technicians and Trainees	£ 31.50	£ 55
Undergraduate Students *		£ 31.50	£ 55
Non-Members	Consultant and/or equivalent position	£ 157.50	£ 55
Non-Members Concessionary *	Biomedical Scientists; PhD Students; Post-Doctoral Fellows, Technicians and Trainees	£ 47.50	£ 55

<b>LATE REGISTRATION FEES</b> FROM MIDNIGHT (00.01 hr) ON TUESDAY 12 APRIL 2011			
<b>Delegate Type</b>	<b>Fee Categories</b>	<b>Per Day or Part Day</b>	<b>Conference Dinner</b>
BDIAP or Pathological Society Members	Ordinary Members, Consultant and/or equivalent position	£ 157.50	£ 55
BDIAP or Pathological Society Concessionary Members	Biomedical Scientists; Honorary or Senior Members; PhD Students; Post-Doctoral Fellows, Technicians and Trainees	£ 47.50	£ 55
Undergraduate Students *		£ 47.50	£ 55
Non-Members	Consultant and/or equivalent position	£ 236.50	£ 55
Non-Members Concessionary *	Biomedical Scientists; PhD Students; Post-Doctoral Fellows, Technicians and Trainees	£ 78.50	£ 55

### **REGISTRATION**

Registration is ONLY available on-line via this link:

[Direct Link  
REGISTRATION](#)

### **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 NTN's where applicable. Proof must be by way of a statement from the Head of Department.

Please email to: [julie@pathsoc.org](mailto:julie@pathsoc.org) (see registration website for template wording).

### **ADVANCE REGISTRATION**

**Advance registration will close on Friday 29 April 2011.** 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 12 April 2011. Thereafter a 25% charge will be made for cancellations received before Tuesday 26 April 2011. No refunds will be made after 26 April 2011.

## **DELEGATE ENROLMENT (AT THE MEETING)**

Enrolment at the Delegate Reception Desk will take place from:

Tuesday 10 May	from 12.00
Wednesday 11 May	from 08.00
Thursday 12 May	from 08.00
Friday 13 May	from 08.15

## **ENQUIRIES**

Before the Meeting enquiries should be addressed to:

### **British Division of the IAP**

PO Box 73, Westbury-on-Trym, Bristol BS9 1RY

Tel: +44 (0)117 907 7940

Fax: +44 (0)117 907 7941

Email: [bdiap@blueyonder.co.uk](mailto:bdiap@blueyonder.co.uk)

### **Pathological Society of Great Britain & Ireland**

2 Carlton House Terrace, London SW1Y 5AF

Tel: +44 (0)20 7976 1260

Fax: +44 (0)20 7930 2981

Email: [admin@pathsoc.org](mailto:admin@pathsoc.org)

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## **GENERAL ARRANGEMENTS**

### **PRESENTATION CHECKING AND PREVIEW**

This will be available in: [Room Sacriste – Storey].

### **ORAL PRESENTATIONS/LECTURES**

#### **Presentation format**

Powerpoint Only

Must be PC compatible

Must be on memory sticks only

Presenters must attend their nominated lecture theatre 30 minutes before their presentation time

### **INTERNET ACCESS**

Internet access will be available in: [Room Sacriste – Storey]. Wireless access will also be available.

### **MESSAGES**

During the Meeting, messages for delegates may be left at the following UK telephone number:  
**+44 (0)7818 640887**

There is also a phone located beside the meeting registration desk : **+32 (0)9 264 83 05**

There will also be a message board located beside the Registration Desk.

### **REFRESHMENTS**

All refreshments will be served in the [Kapittelzaal – Storey] 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.

### **TRAVEL**

Please use this link or refer to: [www.path.org.uk](http://www.path.org.uk)

## ACCOMMODATION

Discounted hotel accommodation has been organised for delegates, use this link or via: [www.path.org.uk](http://www.path.org.uk)

## DISCLAIMER

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

## SOCIAL ACTIVITIES

### Tuesday 10 May

18.00–20.00

Welcome Reception – *Hosted by the Lord Mayor*, Pacification Room, Ghent Town Hall  
*Please reserve your free ticket when registering*

### Wednesday 11 May

19.00–20.30

Guided Tour of Museum of History of Medicine, Het Pand  
— *followed by Reception*

### Thursday 12 May

19.00 –22.30

Conference Dinner, Augustine Monastery, Ghent  
*Please reserve your ticket when registering (cost £55) – places are limited*

## LOCAL PLACES OF INTEREST

For information please visit: [www.visitgent.be](http://www.visitgent.be)

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## FUTURE MEETINGS

### British Division of the IAP

**2011**

**25–26 November**

**London**

*Pathology of Infection*

**2012**

**30 September–5 October**

**Capetown**

*IAP International Congress*

**2013**

### Pathological Society of Great Britain & Ireland

**2011**

**16 November**

**Royal College of Pathologists, London**

**Educational Day**

*The Borderlands of Molecular Pathology & Urogenital Pathology – What Should a Diagnostic Pathologist Know? How Might Molecular Pathology Change the Practice of GU Pathology.*

**2012**

**5–6 January**

**London**

*Winter Meeting*

**3–5 July**

**Sheffield**

*Summer Meeting*

**2013**

**January**

***Exact date and venue to be confirmed***

*Joint Meeting with the Dutch Pathological Society*

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## JOINT MEETINGS

### **of the British Division of the IAP and the Pathological Society**

**2013**

**18–21 June**

**Edinburgh**

*Edinburgh Pathology 2013*

**TUESDAY 10 MAY**

▶ 12.00

Reception

**REGISTRATION and COFFEE**

▶ 12.45 – 13.00

Room Refter – Storey

**WELCOME ADDRESS**

Chair: Prof CA Cuvelier, Ghent University, Ghent, Belgium  
P van Cauwenberge, Rector, Ghent University, Ghent, Belgium

▶ 13.00 – 17.00

Room Sacriste – Storey

**SLIDE SEMINAR COMPETITION VIEWING**

***Tumours of the Skeleton: Test Your Knowledge up to the Bare Bone***

▶ 13.00 – 15.30

Room Refter – Storey

**SYMPOSIUM**

***Advances in Gynaecological Pathology***

Chair: Prof P Delvenne, University Hospital of Liege, Liege, Belgium  
Prof CS Herrington, University of Dundee, Dundee, UK

13.00–13.30

**[S1] *HPV Proteins and Dendritic Cells in the “Metaplasia-Dysplasia-Cancer” Sequence of the Uterine Cervix***

Ⓟ Prof PH Delvenne

*Chu de Liège, Liège, Belgium*

Human papillomavirus (HPV) infection, particularly type 16, is causally associated with cancer of the uterine cervix. The persistence or progression of cervical lesions suggests that viral antigens are not adequately presented to the immune system. This hypothesis is reinforced by the observation that most squamous intraepithelial lesions (SILs) show quantitative and functional alterations of antigen-presenting cells, such as dendritic/Langerhans cells (DC/LC). The purpose of this study was to determine the effects of HPV proteins on DC/LC recruitment and functions. As the infiltration of immature LC in the squamous epithelium is controlled by several soluble and adhesion molecules, the possible role of HPV16 E6 and E7 viral oncoproteins in the reduced levels of these factors observed in SILs was investigated by silencing HPV16 E6 and E7 oncogenes by RNA interference (siRNA). This treatment induced an increased expression of Macrophage Inflammatory Protein 3a/CCL20 and E-cadherin in HPV16-positive keratinocytes (KC) and a significant adhesion of DC/LC to squamous cells, suggesting that HPV16 E6/E7-induced alterations of LC/KC functions may play a role in the defective immune response during cervical carcinogenesis. We also demonstrated that, in addition to viral early oncoproteins, HPV16 L1 Virus Like Particles (VLP) are able to affect directly Langerhans cells. Finally, the process of epithelial metaplasia (EpM) which is observed in the transformation zone of the uterine cervix was shown to be involved in cancer development by altering the expression of adhesion molecules important for Kc-LC interactions.

13.30–14.00

**[S2] *Immunohistochemistry in Gynaecological Pathology- An Update***

Ⓟ Prof WG McCluggage

*Royal Victoria Hospital, Belfast, United Kingdom*

Immunohistochemistry plays an important role in various diagnostic scenarios in gynaecological pathology. However, immunohistochemistry is sometimes overdone and it is always to be remembered that immunohistochemistry is an adjunct technique and an aid to careful morphological examination. Since no antibody is totally specific for any given tumour and since unexpected positive and negative staining reactions may occur, panels of markers should always be used and these panels should be carefully focused depending on the differential diagnosis under consideration. In many diagnostic scenarios, especially in the examination of an unusual ovarian neoplasm, judicious sampling is sometimes more useful than immunostains. However, when carefully used, immunohistochemistry can be extremely useful and is paramount in diagnosis in many cases. Several topics are covered in this talk which aims to concentrate on new developments regarding immunohistochemistry in the female genital tract. Topics discussed include markers of value in the typing of ovarian and endometrial carcinomas and in the distinction between a uterine corpus and cervical origin for an adenocarcinoma. Cervical neuroendocrine carcinomas and the value of HMGA2 as a useful marker of uterine serous carcinoma and vulvovaginal aggressive angiosarcoma are also discussed. p53 is often used as a marker in gynaecological pathology but the significance of the various staining patterns is often poorly understood; this is clarified for the practicing pathologist.

14.00–14.30

**[S3] *Role of Matrix Metalloproteinases in Endometrial Pathology***

Ⓟ Prof E Marbaix

*Université Catholique de Louvain, Brussels, Belgium*

Matrix metalloproteinases (MMPs) are a family of 23 enzymes, able to degrade all constituents of the extracellular matrix (ECM) and to affect cell behaviour by cleaving or releasing from the ECM growth factors,

TUESDAY 10 MAY — *continued*

cytokines and chemokines. Traditionally subclassified as collagenases (MMP-1, -8, -13), gelatinases (MMP-2, -9), stromelysins (MMP-3, -10), membrane-type (MT-)MMPs or other MMPs, they are synthesized as zymogens (proMMPs) and constitutively secreted, except in leukocytes where proMMP-8, -9 and -25 are stored in granules. MMPs activity is regulated at the level of their expression, activation by removal of the propeptide covering the catalytic site, inhibition by specific tissue inhibitors (TIMPs) and clearance by the scavenger membrane receptor LRP-1 (low density lipoprotein receptor-related protein-1).

Most MMPs are expressed in human endometrium where their activity is tightly controlled by progesterone throughout the menstrual cycle. Progesterone strongly represses the expression of MMP-1, -3, -8 and -10, which is limited to the functionalis at menstruation. In contrast, it poorly inhibits the expression of the gelatinases.

However, activity of these MMPs is also essentially limited to the menstrual phase. Indeed, proMMP-9 is only activated at menstruation and both (pro)MMP-2 and -9 are cleared from the ECM by endocytosis through LRP-1, except at menstruation when LRP-1 is shed from the plasma membrane of stromal cells.

Disruption of this tight control of MMPs activity occurs during dysfunctional bleeding episodes, leading to menstrual-like tissue breakdown and bleeding. Paradoxically these episodes are frequent during the first months of long-term contraceptive treatment with progestins. MMPs are also involved in the progression of endometriosis. Gelatinases expression and/or activity is increased in high grade endometrial adenocarcinomas, in particular at the invasive edge of serous carcinoma.

14.30–15.00

**[S4] Molecular Pathology in Gynaecological Pathology**

Ⓟ Prof CS Herrington

*University of Dundee, Dundee, United Kingdom*

Cervical squamous cell and adenocarcinomas are almost universally related to HPV infection, which induces cell cycle control dysregulation and consequent genetic instability. This mechanism is also thought to underly HPV-associated vulval carcinoma. There is increasing recognition that vulval squamous cell carcinoma occurs in two clinico-pathological forms: HPV-associated carcinoma in younger women, associated with usual type vulval intraepithelial neoplasia (VIN); and HPV-negative carcinoma in older women, associated with lichen sclerosis and differentiated type VIN. The molecular mechanisms by which HPV-negative vulval carcinoma develops are largely unknown. Endometrial carcinomas are subdivided into type 1 and type 2 tumours, the former comprising endometrioid and mucinous tumours and the latter clear cell and serous carcinomas. Endometrioid tumours are associated particularly with abnormalities of *PTEN*, *CTNNB1* and *PIK3CA*, and microsatellite instability, whereas serous carcinomas harbour *TP53* mutations. Ovarian carcinomas can also be subdivided into type 1 and type 2 tumours. The former comprise endometrioid, mucinous, clear cell and transitional tumours, all of which are associated with a 'borderline' counterpart and are genetically stable but each develops through a different molecular pathway. Type 2 tumours, which include high-grade serous carcinomas, the majority of which are most likely of Fallopian tube origin, are genetically unstable, with *TP53* mutation dominating their molecular pathology. Finally, some rarer lesions of the female genital tract are associated with specific molecular abnormalities, for example adult-type granulosa cell tumours (*FOXL2* mutation); endometrial stromal sarcoma (*JAZF1-JJAZ1* fusion); and aggressive angiomxoma (*HMGGA2* gene rearrangement).

15.00–15.30

**[S5] Gestational Trophoblastic Neoplasia: Prognostic Markers and Outcome**

Ⓟ Prof M Wells

*Department of Oncology, University of Sheffield School of Medicine, Sheffield, United Kingdom*

It is important to draw a distinction between molar and non-molar disease and a clinical risk score is crucial in determining the management of patients, particularly the institution of chemotherapy. Once the histopathologist has confirmed the microscopic diagnosis of complete or partial mole, his/her role is limited because treatment is essentially titrated against the serum  $\beta$ HCG level. Persistent trophoblastic disease (PTD) is a clinical diagnosis based on persistently elevated or rising  $\beta$ HCG levels and is usually due to invasive mole or choriocarcinoma. Partial mole is not an innocuous lesion, but the risk of PTD is much less (0.5%) than for complete mole (15%).

Much research has focused on identifying pathobiological parameters in moles that are predictive of PTD, including apoptotic indices and telomerase activity. However, none of these have attained the status of routine application and, following a diagnosis of mole, all patients are monitored, though the monitoring period for complete is longer than for partial mole. Hysterectomy has a place in the management of recalcitrant disease. Neoplasms of the extravillous, non-villous or "intermediate" trophoblast include placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT). Such tumours are more likely than choriocarcinoma to be chemoresistant and, though rare, have a higher mortality in the presence of metastatic extrauterine disease. Histological factors associated with a poor prognosis include deep invasion, the presence of "clear" cells, extensive necrosis and a high mitotic index. Hysterectomy remains an important aspect of the management of PSTT and ETT. There is considerable current interest in the relationship between placental site nodule (hitherto believed to be an innocuous lesion), so-called atypical placental site nodule and ETT.

▶ 15.30 – 16.00

Kapittelzaal – Storey

COFFEE

## ORAL COMMUNICATIONS

**Categories: Breast, Hepatobiliary/Pancreas; Genitourinary/Renal; Cellular/Molecular**

Chair: Dr JJ Going, University of Glasgow

Dr KY Lambein, Ghent University Hospital, Ghent, Belgium

13.00–13.15

**[O1] False-positive Diagnoses in Breast Cancer Pathology**KL Turner<sup>1</sup>; Ⓟ R Liebmann<sup>2</sup><sup>1</sup>Barts and The London NHS Trust, London, United Kingdom; <sup>2</sup>Maidstone & Tunbridge Wells NHS Trust, Aylesford, Kent, United Kingdom

AIMS: Histological examination, as part of the triple assessment of breast disease, is essential for the planning of surgical and adjuvant treatment. It is recognised, however, that discriminating benign conditions from malignant can be problematic. The purpose of this study is to calculate the rate of false-positive diagnoses occurring in one geographical region and to raise awareness of the mimics and pitfalls involved with the diagnosis of breast disease.

METHODS: The Kent HER2 testing service, based in the molecular laboratory in Maidstone, is responsible for determining the HER2 status of every invasive malignant breast lesion diagnosed in the Kent and Sussex area. As part of this testing process, the block sent for analysis by one of 20 referring MDT lead breast pathologists, undergoes a secondary review by one of the specialised breast pathologists based in the Maidstone department. A search of the cases referred to the Kent HER2 testing service was used to identify any false-positive diagnoses. The false-positive rate was expressed as a percentage of the total cases referred and further clinical information related to these cases was obtained from the referring hospital.

RESULTS: Over a five year period, 8546 cases were referred for HER2 testing. From this cohort, two false-positive diagnoses were identified; a fibroadenoma and an area of sclerosing adenosis had been erroneously reported as invasive malignancy by the referring pathologist. This equates to a false-positive rate of 0.02%.

CONCLUSIONS: A false-positive rate of 0.02% is well below the 'acceptable' rate published by the NHSBSP.

Nevertheless, individual breast pathologists need to be aware of the possibility of false-positive diagnoses and take steps to minimise their occurrence. We believe this is best accomplished by ensuring familiarity with the common mimics and by attendance at multi-disciplinary meetings.

13.15–13.30

**[O2] Analysis of the Inflammatory Profile of DCIS in Relation to Altered Myoepithelial Cell phenotype and Disease Progression**

Ⓟ MD Allen; P Gopinath; K Ahmed; L Jones

*Barts Institute of Cancer, London, United Kingdom*

The majority of breast cancers progress through a pre-invasive stage, known as ductal carcinoma in-situ (DCIS). A key component in promoting tumour invasion and metastasis is inflammation, which has not been studied in detail in DCIS. Inflammation has been shown to have effects on breast tumour growth, metastasis and angiogenesis and recently COX-2 (an inflammatory mediator) was shown to be a predictor of DCIS recurrence. We have observed a consistent change in high grade DCIS; acquisition of  $\alpha v \beta 6$  integrin on myoepithelial cells, leading to enhanced tumour cell invasion. These data suggest that myoepithelial cells undergo a "switch" from an anti- to pro-tumour phenotype. We hypothesise that this altered myoepithelial phenotype may also modulate the inflammatory cell profile in DCIS that may contribute to disease progression.

The inflammatory infiltrate in 20  $\alpha v \beta 6$  positive DCIS and 20  $\alpha v \beta 6$  negative DCIS was characterised by IHC and IF-IHC, focussing on markers that distinguish pro-tumour Tumour Associated Macrophages (TAM), anti-tumour M1 macrophages and Regulatory T cells, as these populations are associated with poor prognosis in models of invasive breast cancer.

Significantly more staining for FOXP3 (T-reg marker,  $p < 0.0001$ ) and Arginase (TAM marker,  $p = 0.0004$ ), and significantly less staining for MHCII and CD69 (M1 markers,  $p < 0.0001$ ) was identified in  $\alpha v \beta 6$  positive DCIS cases compared with  $\alpha v \beta 6$  negative DCIS. Further work using dual immuno-fluorescent staining on the same set of cases indicated a shift in the balance of macrophages from M1 to TAM in  $\alpha v \beta 6$  positive DCIS cases (M1:TAM  $\alpha v \beta 6$  negative cases 35:1 compared with M1:TAM  $\alpha v \beta 6$  positive cases 5:1).

DCIS exhibiting  $\alpha v \beta 6$  positive myoepithelial cells demonstrate changes in the inflammatory infiltrate indicating a switch to a tumour promoting phenotype. Further investigation is required to determine the prognostic value and underlying mechanisms of this change.

13.30–13.45

**[O3] A New Pathological Response Index (PRI) for Neoadjuvant Chemotherapy (Neo-ACT) Accurately Predicts Clinical Outcomes of Locally Advanced Primary Breast Cancer (LABC)**Ⓟ TMA Abdel-Fatah<sup>1</sup>; P Mosely<sup>1</sup>; A Lee<sup>2</sup>; S Pinder<sup>3</sup>; JS Reis-Filho<sup>4</sup>; IO Ellis<sup>2</sup>; S Chan<sup>1</sup><sup>1</sup>Clinical Oncology, Nottingham University City Hospital Campus, Nottingham, United Kingdom; <sup>2</sup>Histopathology, Nottingham University City Hospital Campus, Nottingham, United Kingdom; <sup>3</sup>Kings College London and Guy's and St Thomas's Hospitals, London, United Kingdom; <sup>4</sup>The Breakthrough Breast Cancer Research Centre, London, United Kingdom

Residual cancer cell after Neo-ACT includes a wide range of responses from near-pathological-complete-response (pCR) to complete resistance. In this study we performed a comprehensive pathological assessment for 195 surgical specimens of LABC received anthracycline and/or Taxane-based Neo-ACT with long clinical follow-up to identify factors that could refine the pathological response and predict clinical outcome after Neo-ACT.

Multivariate Cox regression model revealed that large size of the residual invasive carcinoma (OR; 3.2, CI 95%; 1.6-6.1,  $p = 0.001$ ), presence of both lympho-vascular- invasion (OR; 2.4, CI 95%; 1.3-4.3,  $p = 0.004$ ) and 4 positive

axillary lymph node (LN) including at least one apical LN (OR; 4.2, CI 95%; 1.5-6.8, p=0.003) and absence of fibrosis (OR; 3.2, CI 95%; 2.2-8.0, p=0.00001) were significantly associated with a decreased progressive free survival (PFS). Subsequently, a calculated pathological response index (PRI) was generated using aforementioned pathological factors.

Patients with PRI-1 had a good clinical outcome in both ER+ and ER- tumours. Moreover, patients with PRI-1 who did not show pCR (n=54) had equivalent clinical outcomes as those with PRI-1 who did (n=38); p=NS. Patients with PRI-2, PRI-3 and PRI-4 had a 3-14 fold-increase risk of progression compared to those with PRI-1. Even ER+ patients with either PRI-4 or PRI-3 had 5-year-PFS-rates of 38%-45% despite ongoing treatment. In conclusion, a PRI including size of residual tumour, LN-pathological-stage, lympho-vascular-invasion and fibrosis may accurately predict the chance of disease progression, identify a greater proportion of patients (>twice as many as pCR) who could potentially be spared adjuvant therapy (near pCR) and define tumours with resistance to current adjuvant-therapy.

13.45–14.00

**[O4] Metasin: A Novel Rapid RT-PCR Assay for the Analysis of Sentinel Lymph Nodes from Patients with Breast Cancer, in the Intra-Operative Setting: Analysis of the First 1000 Cases**

S Al-Ramadhani<sup>1</sup>; P Balaraman<sup>1</sup>; D George<sup>1</sup>; M Morgan<sup>1</sup>; S Jader<sup>1</sup>; A McDowell<sup>2</sup>; FG Gabriel<sup>2</sup>; J McKenzie<sup>1</sup>; S Al-Sam<sup>1</sup>; S Holt<sup>3</sup>; R Mansel<sup>4</sup>; I Cree<sup>2</sup>; M Keshtgar<sup>5</sup>; N McDermott<sup>5</sup>; D Larsimont<sup>6</sup>; SA Spinette<sup>6</sup>; R Salgado<sup>6</sup>; E Arkoumani<sup>1</sup>; Ⓟ V Sundaresan<sup>1</sup>

<sup>1</sup>Princess Alexandra Hospital, Harlow, United Kingdom; <sup>2</sup>Queen Alexandra Hospital, Portsmouth, United Kingdom; <sup>3</sup>Prince Philip Hospital, Llanelli, United Kingdom; <sup>4</sup>Cardiff University Hospital, Cardiff, United Kingdom; <sup>5</sup>The Royal Free Hospital, London, United Kingdom; <sup>6</sup>Department of Pathology, Jules Bordet Institute, Brussels, Belgium

**INTRODUCTION:** We have established a RT-PCR assay for the rapid detection of metastatic breast cancer in lymph nodes in the operative setting. The predictive markers are CK19 and Mammaglobin. PBGD is the reference gene. The assay takes 26 mins with a time to result in under 46 mins for 75% of cases with 2 nodes. As part of a multi-centre collaborative study, we have examined over 1000 cases using Metasin. nearly half of these samples were analysed on the Veridex Genesearch-BLN assay (V-BLNA) with parallel histological analysis of half the nodes at 2mm. Detailed discordant analysis is currently in progress.

**RESULTS:** We present outcomes of the preliminary analysis of the first 400 cases (Harlow, Portsmouth & Llanelli).

**HISTOLOGY POSITIVES:** 89 of 106 (N=400) cases were positive by histology. In 84 of these Metasin and V-BLNA assays were both positive. 3 Histology positive cases were negative by both Metasin and V-BLNA.

**HISTOLOGY NEGATIVES:** 311 Cases were negative by histology. 11 of these Histology Negative cases were positive by both Metasin and V-BLNA and a further 3 of these cases were positive for Metasin only (V-BLNA negative).

**CONCLUSION:** The Metasin assay is fast and robust and comparable to the V-BLNA in sensitivity and specificity. The positive predictive value of Metasin is of the order of 99% with discrepancies accounted for by sampling discordance.

In 11 positive cases (but *histology negative*) show independent molecular evidence of positivity (positive by both Metasin and V-BLNA).

In 3 cases there is only histological evidence of metastatic disease. In a further 11 cases two independent molecular assays have confirmed the presence of metastatic disease, reinforcing the reality of sampling discordance. We minimise discordance by examining multiple levels (5 at 150um).

Metasin-BLNA is robust, cheap and effective.

These results challenge the dogma of the gold standard of histology over the *Molecular Approach*.

14.00–14.15

**[O5] Molecular Markers for the Detection of Metastatic Breast Cancer in Sentinel Lymph Nodes: An Adjunct to the Metasin BLNA?**

S Al-Ramadhani; P Balaraman; D George; S Jader; J McKenzie; S Al-Sam; M Morgan; E Arkoumani; Ⓟ V Sundaresan

Princess Alexandra Hospital, Harlow, United Kingdom

**INTRODUCTION:** Metastatic breast cancer in sentinel nodes is managed by axillary clearance. At present conventional histological examination of these lymph nodes is carried out to varying standards. Currently, many laboratories do not carry out levels.

We have already implemented intra-operative testing of sentinel lymph nodes at Harlow: alternate 2mm slices are subjected to the Metasin Assay and the remainder examined by conventional histology: now, we routinely carry out 5 levels at 150 microns.

Contentiously, ITCs have been reported as having an adverse impact on prognosis. Histology cannot routinely detect ITCs with any degree of certainty, given the need for extensive serial levels.

We have identified the molecular approach to be superior to conventional histopathology (see Metasin abstract) detecting metastatic disease in 11 of 400 histology negative cases by independent molecular mean (Metasin and Veridex Genesearch). This compares with 3 of 400 cases that were molecular assay negative but histology positive. We report the detection of metastatic breast cancer in 106 of 400 cases.

**PURPOSE OF STUDY:** Investigate if a 2nd tier of markers can be used outside of the intra-operative setting to detect all metastases in lymph nodes. If successful, then the entire node can be sacrificed for molecular analysis.

**METHODS:** To examine a cohort of 106 positive cases in our series of 400 with a series of molecular markers previously described for the detection of metastatic breast cancer: B305D/PIP1, GABA-D, B726R.

**RESULTS:** Preliminary findings indicate the feasibility of this approach.

**CONCLUSION:** This, two tiered approach can be implemented in the peri operative setting for the examination of the whole node. However, safe guards have to be implemented to facilitate the detection of rare instances of non-breast related primary lymphoid pathology: Is saving a 2 mm slice for histology-later, an acceptable compromise?

14.15–14.30

**[O6] Breast Cancer Survival Stratified by Automated Versus Visual Analysis of ER and PR Immunohistochemistry**Z Mohammed<sup>1</sup>; J Edwards<sup>1</sup>; C Orange<sup>1</sup>; EA Mallon<sup>2</sup>; DC McMillan<sup>1</sup>; Ⓟ JJ Going<sup>1</sup><sup>1</sup>University of Glasgow, Glasgow, United Kingdom; <sup>2</sup>Western Infirmary, Glasgow, United Kingdom

**Purpose:** A woman should be able to trust that the steroid receptor status of her cancer is reported correctly. Immunohistochemistry (IHC) allows for specific assessment of tumour cells and the role of automated image analysis (IA) in the assessment of receptor IHC in breast cancer is topical. We compared ER and PR status assessed visually and by IA, and their respective abilities to predict cancer-specific survival and recurrence in a cohort with mature follow up.

**Patients and methods:** Patients (n=525) treated for primary symptomatic operable breast cancer in Glasgow during 1995-8 were studied in triplicate tissue microarray using ER (Dako 6F11/12) and PR (Leica R636) IHC. Allred and weighted Histoscores were assigned visually (v-H Scores) and weighted H-scores by IA (ia-H Scores; Slidepath nuclear protocol). Interclass correlation coefficients, univariate and multivariate analyses were performed in SPSS v18.

**Results:** Minimum follow up was 11.8 years (median 13.8). There was excellent agreement between steroid receptor v-H and ia-H Scores and both methods predicted cancer-specific survival equally well overall and in the 384 patients who received endocrine treatment. Allred score was also effective.

**Conclusions:** Automated analysis of ER and PR status gave results in excellent agreement with visual analysis and equally effective (but not better) prediction of survival and tumour recurrence. Visual confirmation that the cells being analysed are representative of the invasive carcinoma remains essential and no quality assurance requirements are made redundant by image analysis if disasters like the Newfoundland ER testing debacle (Hede, K: JNCI 2008;100:837-) are to be avoided.

14.30–14.45

**[O7] Histological Diversity in Cholangiocellular Carcinoma Suggesting Different Cells of Origin: Intrahepatic Progenitor Cells Versus Hilar Mucin Producing Cells**

Ⓟ MK Komuta; OG Govaere; VV Vandecaveye; RD De Vos; CV Verslype;

WV Van Steenberg; RA Aerts; JP Pirenne; BT Topal; NF Nevens; VD Desmet; TR Roskams

KU Leuven, Leuven, Belgium

**Aim:** We investigated the clinicopathological and molecular features of 79 CCs and their relationship to Hepatic progenitor cells (HPCs) and compared the spectrum of CCs with keratin (K)19(+) hepatocellular carcinomas (HCCs) (thought to be of HPC origin) and K19(-)HCCs. **Methods:** We evaluated the immunohistochemical expression of Hep Par-1, canalicular polyclonal carcinoembryonic antigen (pCEA), CD10, K7, K19, neural cell adhesion molecule (NCAM), Epithelial cell adhesion molecule (EpCAM), AnnexinA3 and S100P. Gene expression profiling in different areas of CC was performed and compared with the profile of the K19(+)/(-)HCCs. **Results:** 41/79 (52%) CCs were pure mucin producing; 38/79 (48%) CCs showed mixed differentiation features: focal hepatocytic differentiation (trabecular structure, canalicular CD10/pCEA expression and submembranous K7 expression) and ductular features. CC with mixed features (Mixed CC) showed peripheral location, larger tumour size, less micro-vascular invasion, less lymph node involvement compared to CCs which showed hilar location, smaller tumour size, more microvascular invasion and more lymph node involvement (P<0.05). S100p expression was seen only in CCs, while NCAM expression was only immunoreactive in mixed-CCs. Annexin A3 showed more intense positivity in CCs than mixed CCs, while EpCAM expression pattern was similar in both groups. KRT19, S100P and ANXA3mRNA were significantly up-regulated (P<0.05) in CCs toward mixed-CCs. Molecular profiling showed high homology of mixed-CCs and K19(+)HCC, while mucin producing CCs and K19(-)HCCs were separate entities. **Conclusions:** Mixed CCs and K19(+)HCCs, have a similar molecular profile as the most peripheral ductules, containing HPCs, while mucin producing CCs have a similar profile to mucin producing hilar bile ducts and K19(-)HCCs to mature hepatocytes, possibly reflecting the different cells of origin.

14.45–15.00

**[O8] Expression of Glypican-3 in Solid-pseudopapillary Neoplasm of the Pancreas: A Series of 7 Cases**Ⓟ M Hav<sup>1</sup>; CA Cuvelier<sup>1</sup>; L Ferdinande<sup>1</sup>; A De Potter<sup>1</sup>; S Eav<sup>2</sup>; D Lem<sup>2</sup>; P Pattyn<sup>1</sup>; M Praet<sup>1</sup>; L Libbrecht<sup>1</sup><sup>1</sup>Ghent University Hospital, Ghent, Belgium; <sup>2</sup>Khmer-Soviet Friendship Hospital, Phnom Penh, Cambodia

**Purpose of the study:** solid-pseudopapillary neoplasm (SPN) of the pancreas is a relatively uncommon pancreatic neoplasm of low malignant potential, typically affecting young women. Almost all SPNs harbor mutations in the  $\beta$ -catenin gene, resulting in an activation of the Wnt-signaling pathway. In this study, we studied the expression of Glypican-3 (GPC3), one of the regulators of Wnt signaling, in SPNs.

**Methods:** this study consisted of 7 consecutive patients histologically diagnosed with SPN of the pancreas at Ghent University Hospital (4 cases) and Khmer-Soviet Friendship Hospital (3 cases) from 2006 to 2010. We examined the expression of GPC3 by immunohistochemistry. We also looked at immunoreactivity for Cytokeratin broad spectrum (CKbs),  $\beta$ -catenin, Cyclin-D1, Glutamin synthetase (GS), E-cadherin, Chromogranin, Synaptophysin, CD56, Progesterone receptor (PR) and Ki-67 in these tumours.

**Summary of results:** all tumours showed granular cytoplasmic expression of GPC3. Two of the tumours weakly expressed GPC3 in 10 to 20% of the tumour cells, while the other 5 revealed strong and diffuse immunoreactivity (mean proportion of tumour stained = 58%). All tumours were diffusely positive for GS, PR, CD56 and Cyclin-D1. They also showed nuclear and cytoplasmic localization of  $\beta$ -catenin and loss of membranous  $\beta$ -catenin and E-cadherin. There was no expression of CKbs or Chromogranin noted in all cases. Weak to moderate expression of Synaptophysin occurred in 2 cases. Ki-67 proliferation index was never > 2%. In this series, all patients are alive without disease progression at 4-year follow up.

**Conclusions:** this study is the first to demonstrate Glypican-3 expression in SPN of the pancreas. Glypican-3 can be a useful adjunct immunohistochemical marker in diagnosing pancreatic SPN. Unlike in hepatocellular carcinoma, over-expression of Glypican-3 did not predict poor clinical outcome of the patients in our series.

TUESDAY 10 MAY — *continued*15.00–15.15 **[O9] Clinically Significant BKV Shedding Occurs within Two Months of Transplantation**A Chakera<sup>1</sup>; OJ Dyer<sup>2</sup>; E Hughes<sup>1</sup>; S Bennett<sup>2</sup>; D Hughes<sup>1</sup>; Ⓟ ISD Roberts<sup>3</sup><sup>1</sup>Churchill Hospital, Oxford, United Kingdom; <sup>2</sup>University of Oxford, Oxford, United Kingdom; <sup>3</sup>John Radcliffe Hospital, Oxford, United Kingdom

Reactivation of polyoma virus BK (BKV) following renal transplantation can lead to allograft dysfunction or loss. Viremia precedes viremia and the development of polyoma virus nephropathy (PVN) and early detection can improve outcomes. Current guidelines recommend qPCR surveillance, however urinary decoy cell detection is a rapid and inexpensive alternative. We present the outcomes from an early intensive BKV surveillance programme using decoy cell detection.

Records for all recipients of kidney (n=211) or kidney-pancreas (n=102) transplants performed over 2 years in a single centre were reviewed. Follow-up was for a minimum of one year. Urine cytology screening was performed 2 weekly from 0-3 months post-transplantation, monthly from 3-6 months and 2 monthly from 6-12 months. Immunosuppression was reduced in patients with sustained decoy cell positivity (≥positive urines >2 weeks apart).

2366 urine samples were screened for the presence of decoy cells (mean 8 samples/patient). Decoy cell positivity occurred in 56/313 patients (17.9%) with 24 patients (7.6%) becoming viremic and 3 patients (1%) developing biopsy-proven polyoma virus nephropathy (PVN). Sustained decoy cell positivity occurred in 32 patients (10.2%). 28 patients with sustained positivity had plasma qPCR of which 24 (85.7%) were positive. The median time following transplantation to decoy cell positivity was 110 days for all patients, 64 days for patients with sustained positivity and 59 days for patients with PVN. Patients with persistent decoy cell positivity had higher creatinine levels at all time points. Decoy cell screening resulted in predicted savings of 135,000 over 2 years, compared with routine surveillance by qPCR.

Clinically significant BKV reactivation occurs early after transplantation and can be reliably detected by decoy cell screening. A surveillance strategy for detecting BKV reactivation based on urine cytology is cost-effective.

15.15–15.30 **[O10] Detection of the TNFSF Members BAFF, APRIL, TWEAK and their Receptors in Normal Kidney and Renal Cell Carcinomas: Correlation with Clinical and Histological Development of the Disease**Ⓟ V Pelekanou\*<sup>1</sup>; G Notas<sup>1</sup>; K Theodoropoulou<sup>1</sup>; M Kampa<sup>1</sup>; D Takos<sup>2</sup>; VI Alexaki<sup>1</sup>; J Radojicic<sup>3</sup>; F Sofras<sup>2</sup>; A Tsapis<sup>4</sup>; EN Stathopoulos<sup>3</sup>; E Castanas<sup>1</sup><sup>1</sup>Laboratory of Experimental Endocrinology, University of Crete, School of Medicine, Heraklion, Greece;<sup>2</sup>Department of Urology, University of Crete, School of Medicine, Heraklion, Greece; <sup>3</sup>Department of Pathology, University of Crete, School of Medicine, Heraklion, Greece; <sup>4</sup>Inserm, U976, Université Paris-Diderot, Paris, France;

\*Present affiliation: Pathology, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

**INTRODUCTION:** In renal cell carcinoma (RCC), surgery and systemic chemotherapy/immunotherapy have a limited effectiveness. Novel therapies, targeting VEGF, PDGF, and c-kit using tyrosine kinase inhibitors and m-TOR are in development. Although therapies targeting TNF-alpha have shown limited efficacy, anti-TRAIL (TNFSF10) antibodies have shown enhanced activity. The presence and significance of other members of the TNFSF has not been explored.

**PURPOSE OF THE STUDY:** To evaluate the presence and significance of the TNFSF members APRIL, BAFF, TWEAK (TNFSF13, 13B and 12) and their receptors (BCMA, TACI, BAFFR, Fn14, TNFRSF17, TNFRSF13B, TNFRSF13C, TNFRSF12A) in RCC.

**METHODS:** TNFSF members APRIL, BAFF, TWEAK and their receptors (BCMA, TACI, BAFFR, Fn14) were assayed by standardized immunohistochemistry protocols in 86 conventional type clear cell RCC. Our findings were correlated with histological data and, in a limited series, follow-up of patients. mRNA transcripts of the TNFSF members in the specimens were also assayed and an analysis of published gene-array data of GEO database was also performed.

**RESULTS:** We observed a differential expression of the TNFSF ligands and receptors in cancerous and non-cancerous renal structures. BAFF was found in all RCC; APRIL expression is associated with an aggressive phenotype, correlating negatively with patients' disease-free survival, while TWEAK and its receptor Fn14 are heterogeneously expressed, correlating negatively with the grade and survival of RCC patients. A partial correlation of IHC and molecular biology data was found.

**CONCLUSIONS:** This is the first study, presenting together the TNFSF members APRIL, BAFF, TWEAK and their receptors in different areas of normal renal tissue and RCC, suggesting a potential role of these TNFSF members in renal tumour biology.

▶ 15.30 – 16.00

Kapittelzaal – Storey

COFFEE

**Detailed  
Programme**

*Tuesday  
10 May 2011*

Ⓟ indicates  
presenter

[S00] indicates  
abstract number

▶ 16.00 – 18.00

Room Rector Vermeylen – Second Floor

**SATELLITE SYMPOSIUM — *Sponsored by Roche***

***Targetted Therapies: An Update on the Her1 and Her2 Stories***

Chair: Prof M Praet, Ghent University, Ghent, Belgium

Dr K Lambein, Ghent University Hospital, Ghent, Belgium

16.00–17.00

***Her2 testing in Breast Cancer: Counting (on) the genes?***

***Introduction***

Dr K Lambein

***The Pathologist's Perspective***

Prof V Bossuyt, Yale University, USA

***The Clinician's Perspective***

Dr E de Azambuja, Bordet Institute, Brussels, Belgium

17.00–17.25

***Belgian Guidelines on Her2 Testing in Gastric Cancer***

Prof A Hoorens, Brussels University Hospital (UZ Brussel), Belgium

17.25–17.50

***Her1/EGFR Testing in Lung Cancer: Methods and Relevance***

Prof P Pauwels, Antwerp University Hospital, Antwerp, Belgium

17.50–18.00

***Conclusions and Chair***

Prof M Praet and Dr K Lambein

▶ 18.00 – 20.00

Pacification Room · Town Hall

**WELCOME RECEPTION – *Hosted by the Lord Mayor***

▶ 08.00

Reception

**REGISTRATION and COFFEE**

▶ 09.00 – 17.00

Room Sacriste – Storey

**SLIDE SEMINAR COMPETITION VIEWING**

***Tumours of the Skeleton: Test Your Knowledge up to the Bare Bone***

▶ 09.00 – 12.00

Room Refter – Storey

**SYMPOSIUM**

***The Pathologist as part of the Puzzle in Diagnosing Inflammatory Disorders***

Chair: Prof P Demetter, ULB, Erasme, Brussels, Belgium

Prof NA Shepherd, Gloucestershire Cellular Pathology Laboratory, Cheltenham, UK

09.00–09.30

**[S6] *Pulmonary Manifestations in Systemic Inflammatory Disease***

Ⓟ Prof AG Nicholson

*Royal Brompton Hospital, London, United Kingdom*

Pathologists are not infrequently involved in the multidisciplinary diagnosis of pulmonary involvement by systemic disease. In particular, patients with connective tissue disorders (CTDs) may suffer from lung disease, although both the incidence of lung involvement and separate histologic patterns vary for different disorders, as well as the prognostic significance of patterns when compared to idiopathic disease. Pulmonary manifestations may also precede the CTDs. Other anatomic compartments should also be assessed: as an example, rheumatoid disease is not only associated with patterns of interstitial pneumonia but also pleurisy, rheumatoid nodules, apical fibrosis, airways disease, pulmonary hypertension, and malignancy. There are many disorders where disease presentation is more common in other organ systems: for example, inflammatory bowel disease and metabolic disorders. A few basic principles are therefore worth following: Firstly, before looking down at the microscope, review the possible pulmonary patterns of disease (there are a lot more than you think). Clinical correlation is essential – not just post-biopsy but pre-biopsy, as it may be easier to biopsy other sites, or even not at all. Iatrogenic lung disease (primarily drug reactions) in relation to treatment of other organ systems not infrequently occur. Secondly, when considering histological patterns down the microscope: only a few systemic disorders will have specific histologic features in the lung. The histological features seen in association with systemic disorders will often overlap with those seen in relation to drug reactions for their treatment. One histologic pattern of disease may progress to another in relation to the same systemic disease. For example, a patient with polymyositis/dermatomyositis might present with organising pneumonia that develops into fibrotic NSIP and then a few years later might relapse with diffuse alveolar damage.

09.30–10.00

**[S7] *The (Under) Diagnosis of IgG4-related Systemic Sclerosing Disease***

Ⓟ Dr AC Bateman

*Southampton University Hospitals NHS Trust, Southampton, United Kingdom*

IgG4-related systemic sclerosing disease is an emerging and generally under-recognized condition, although its existence was first proposed in 1961. It is commonly a multisystem disorder but involvement of a single site – or a small number of sites – may occur in some patients. The condition is characterised by lymphoplasmacytic inflammation with variable degrees of myofibroblastic scar tissue formation. It may present as a semi-discrete mass or as a diffuse process in which the inflammatory component is predominant. Much of the initial work on this condition was focussed on pancreatic involvement i.e. autoimmune pancreatitis. Other affected sites include the biliary tree (simulating primary sclerosing cholangitis), colon (simulating inflammatory bowel disease), stomach (refractory gastric ulceration), salivary glands (chronic sialadenitis), kidney (interstitial nephritis), lungs (interstitial pneumonia), retroperitoneum (simulating retroperitoneal fibrosis), orbit (pseudotumour) and meninges (chronic meningeal thickening). The presence of prominent IgG4-positive plasma cells within the inflammatory infiltrate is very characteristic but not universal. This feature may be present in tissues not showing clinical evidence of disease involvement (e.g. the duodenum) and biopsy of such sites can provide supporting evidence for the diagnosis. The serum total immunoglobulin and IgG4 concentrations may be raised. Within the pancreas, an alternative pattern of inflammation characterised by neutrophilic infiltration of ducts may occur. Immune complexes containing IgG4 have recently been identified within the basement membranes of involved organs, suggesting that this antibody class is important in the pathogenesis of the condition rather than just representing an epiphenomenon. The disease is usually responsive to immunosuppressant therapy and therefore its accurate and timely recognition is particularly important.

10.00–10.30

**[S8] *Reporting Inflammation within the Liver : Also a Matter of Clinical Context***

Ⓟ Prof C Sempoux

*Dept of Pathology, Cliniques Universitaires St-Luc, UCL, Brussels, Belgium*

Despite important advances in imaging techniques and development of reliable biological tests, liver biopsy is still an essential component in management of most liver diseases. To make the most out of his/her biopsy, the pathologist needs good sampling and access to special stains but should also be supplied with all relevant clinical and laboratory data. In the normal liver, occasional inflammatory cells may be present in sinusoids and

normal portal tracts (PT) contain few lymphocytes, macrophages and mast cells but no polymorphonuclear leucocytes or plasma cells. Minor inflammatory changes include non specific reactive hepatitis and the consequences of vicinity of space-occupying lesion. Acute hepatitis is mainly due to hepatotropic or non hepatotropic viruses, autoimmune or drug-induced liver diseases. A biopsy is performed in case of unclear or multiple possible etiologies or if the disease is atypical or prolonged. Histological manifestations are diffuse lobular inflammation together with necrosis. Chronic hepatitis is defined as a persistent or progressive inflammation of the liver over 6 months and is characterized histologically by chronic inflammatory cells within the PT together with parenchymal inflammation, hepatocellular injury and fibrosis. Etiology includes mainly viruses (B or C), auto-immune, drug-induced or alcoholic liver diseases. The biopsy will verify the diagnosis and exclude other causes, assess grade and stage, guide management or help for follow-up and for special studies. Several difficult differential diagnoses exist because of overlapping features (auto-immune and drug-induced liver disease, acute rejection and hepatitis C. The pathologist will then confront its histological analysis to the clinical data to reach a precise diagnosis because the optimal interpretation of a liver disease is only achieved by clinicians and pathologists working together.

10.30–11.00

**COFFEE** [Kapittelzaal – Storey]

11.00–11.30

**[S9] Diagnostic Approach to Refractory Coeliac Disease and its Complications**

Ⓟ Prof K Sheahan

*St Vincent's University Hospital, Dublin, Ireland*

Refractory coeliac disease is a rare clinical entity. Because of this, few clinicians or medical centres have experience in dealing with a large number of these patients. The disease is commoner in females and is a disease of adults over the age of 50. Similar to coeliac disease, it is not a histological diagnosis but requires close correlation with clinical and other laboratory findings. It can present in a variety of ways including persistent diarrhoea, weight loss, multiple vitamin deficiencies, anaemia, fatigue and malaise. The majority of patients show an initial improvement on a gluten-free diet but relapse (secondary refractory coeliac disease). Some patients have no initial response to a gluten-free diet (primary refractory coeliac disease or unclassified sprue). Immunohistochemistry, flow cytometry and T cell receptor gene rearrangement studies are useful in subclassifying refractory coeliac disease. Refractory coeliac disease type 1 shows no T cell abnormalities, has a better prognosis and a better response immunosuppressants. The presence of clonal intraepithelial T lymphocytes likely indicates refractory coeliac disease type 2 and a poor prognosis. These patients have a higher mortality and an increased risk of lymphoma. In the differential diagnosis, a variety of uncommon clinical entities needs to be excluded including autoimmune enteropathy and common variable immunodeficiency. Collagenous sprue is a rare variant of refractory coeliac disease. Recent studies suggest that this entity may have a better prognosis than previously considered. Collagenous sprue may be associated with abnormal collagen deposition throughout the gastro-intestinal tract. Accurate diagnosis and subclassification of refractory coeliac disease plays an important role in the management of these patients.

11.30–12.00

**[S10] The Importance of Clinicopathological Confrontation in Inflammatory Bowel Disease**

Ⓟ Prof Dr Em K Geboes

*University Hospital KULeuven, Sint Niklaas, Belgium*

The diagnosis of IBD usually relies on a combination of features and the differential diagnosis includes a variety of conditions.

The pathologist plays a major part in the diagnosis and in follow up. This implies that it is useful for the pathologist to know if biopsy samples are obtained for initial diagnosis or during follow up. The diagnostic accuracy improves when multiple biopsies are available. A correct diagnosis can be reached in approximately 70% of the cases : adults and children.

While overall a correct diagnosis of IBD can be reached in 90-95% of the patients when endoscopy and pathology are combined, some cases remain difficult : young children (< 12 years of age) and patients with associated liver disease. This implies that the pathologists should be aware of the age of the patient and concurrent disease.

Several conditions can mimic IBD. Examples of these are some genetic disorders, drug-induced colitis, diverticular disease associated colitis... This implies that the pathologist should know the age of the patient, if and what drugs the patient is taking, the location of the biopsy site and the sex of the patient.

The current treatment used for IBD has a variable effect upon the histology with a change in the distribution pattern, one of the features used for the differential diagnosis of ulcerative colitis and Crohn's disease. It is important for the pathologist to know if the patient has a history of IBD or inflammatory diarrhoea, and if so, it is appropriate to have an idea of the duration of the disease and if the patient has been treated.

When the biopsies are obtained during follow up the priority is to assess disease activity and, or, to detect dysplasia.

In conclusion it is clear that the diagnostic yield of biopsy samples increases when the pathologist receives appropriate material and essential information. In difficult situations, a direct contact is essential.

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ProgrammeWednesday  
11 May 2011Ⓟ indicates  
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abstract number

## ORAL COMMUNICATIONS

**Categories: Gastrointestinal**Chair: Dr RFT McMahon, University of Manchester, UK  
Prof M Pignatelli, University of Glasgow, UK

- 09.00–09.15 **[O11] Development of a Histopathologic Prognosis Score for Locally Advanced Gastric Carcinoma Treated with Neoadjuvant Chemotherapy**  
Ⓟ R Langer<sup>1</sup>; D Reim<sup>2</sup>; A Novotny<sup>2</sup>; C Meyer zum Bueschenfelde<sup>3</sup>; J Engel<sup>4</sup>; H Friess<sup>2</sup>; H Hoefler<sup>1</sup>; K Becker<sup>1</sup>  
<sup>1</sup>Institute of Pathology, Technische Universitaet Muenchen, Muenchen, Germany; <sup>2</sup>Department of Surgery, Klinikum Rechts der Isar, Technische Universitaet Muenchen, Muenchen, Germany; <sup>3</sup>Asklepios Klinik Altona, Hamburg, Germany; <sup>4</sup>Tumorzentrum Muenchen, IBE, Ludwig Maximilians Universitaet Muenchen, Muenchen, Germany  
Purpose of the study: For patients with locally advanced gastric carcinomas, who undergo multimodal treatment, conventional postoperative staging classifications used for non-treated tumours may not accurately determine prognosis.  
Methods: We evaluated 428 gastric carcinoma specimens following a cisplatin based neoadjuvant chemotherapy, in order to determine if a combination score including the factors ypT-category, ypN-category according to the current UICC classification and the degree of histopathological tumour regression (according to Becker) correlates with patients' survival and can identify subgroups with differing outcome. For that purpose the single factors each were assigned a value from 1-3, i.e. UICC ypT0-ypT1=1pt; ypT3=2pts; ypT4=3pts; UICC ypN0=1pt; ypN1-2=2pts; ypN3= 3pts; <10% residual tumour=1pt; 10-50% residual tumour=2pts. >50% residual tumour=3pts. Thereafter a three tiered score basing on the sum value of these factors was determined: group A: 3-4 points, group B: 5-7 points, group C: 8-9 points.  
Summary of results: Patients median overall survival (OS) was 36 months (95% CI 27-45 months). The prognostic score showed a clear discrimination of three significantly (p<0.001) different prognostic groups (group A: n=76, OS median not reached; group B: n= 210; median OS 72 months, 95% CI 40-105 months; group C: n = 142, median OS 13 months, 95% CI 11-15 months). There was no improvement of significance by adding any of other tumour related prognostic factors (i.e. completeness of tumour resection; tumour diameter; lymphatic vessel invasion; tumour grading or Lauren's classification) to this score.  
Conclusion: The proposed prognostic score reveals the most accurate prediction of survival for gastric carcinoma patients after neoadjuvant chemotherapy followed by surgery. It clearly identifies three subgroups with different clinical outcome and may be crucial for further therapeutic decisions.
- 09.15–09.30 **[O12] Identification of NRAS and KRAS-146 Mutations and Double-Mutant Cases in 817 Patients with Advanced Colorectal Cancer (aCRC).**  
Ⓟ SD Richman; P Chambers; GJ Hemmings; M Taylor; MT Seymour; P Quirke  
*Leeds Institute of Molecular Medicine, Leeds, United Kingdom*  
Introduction: Advances in treatments for aCRC have seen the introduction of drugs targeting the epidermal growth factor receptor (EGFr) and mutation status of KRAS is a known predictive biomarker of response. Such mutations are found in approximately 45% of patients, but other pathway proteins also carry mutations, accounting for an additional 10-15% of mutations. Here we assess mutation status in 817 patients for KRAS-146 and NRAS.  
Samples and methodology: 1195 patients were enrolled in the PICCOLO aCRC clinical trial. Surplus pathological tumour material was obtained with prior consent. Pyrosequencing was carried out to assess mutation status at KRAS codons 12/13, 61 & 146, BRAF codon 600, NRAS codons 12/13 & 61. Complete pyrosequencing data was available for 817 cases.  
Results: Of the 817 samples, 26 (3.2%) were NRAS mutant, with 13 (1.6%) and 13 (1.6%) for codons 12/13 and 61 respectively. 30 (3.7%) of cases were mutant at KRAS-146. We identified 3 (0.40%) double mutants; 2 with KRAS 12/13 + KRAS 146 mutations and 1 with KRAS 146 + NRAS 61 mutations. Efficacy data was not available at the time of abstract submission.  
Conclusion: We have identified a further 7% of patients harbouring a mutation (in NRAS or KRAS-146). We have yet to ascertain their prognosis or response to anti-EGFr therapy. It is of particular interest to ascertain the function and outcome of the 3 double mutants, making up almost half a percent of cases.
- 09.30–09.45 **[O13] Focal Active Colitis: A Prospective Study of Clinico-pathological Correlations in 90 Patients**  
S Shetty<sup>1</sup>; SM Anjarwalla<sup>2</sup>; J Gupta<sup>2</sup>; CJW Foy<sup>1</sup>; IS Shaw<sup>1</sup>; RM Valori<sup>1</sup>; Ⓟ NA Shepherd<sup>2</sup>  
<sup>1</sup>Gloucestershire Royal Hospital, Gloucester, United Kingdom; <sup>2</sup>Gloucestershire Cellular Pathology Laboratory, Cheltenham, United Kingdom  
BACKGROUND: Considerable controversy exists in the literature concerning the clinical implication of a diagnosis of focal active colitis (FAC) made on sigmoidoscopic and/or colonoscopic biopsies.  
AIM: To assess the clinical implication of a diagnosis of FAC in 90 adults, representing the largest and only prospective study of FAC with a total case number representing about half of the FAC patient number in the world literature. To analyse pathological parameters which may allow identification of the likely ultimate diagnosis.  
METHODS: Patients were assessed by comprehensive clinical follow-up and study questionnaires. 15 histopathological features were scored and correlated with clinical outcome.

RESULTS: In 24% of patients, drugs, especially NSAIDs, were implicated. Infection was a likely cause of FAC in 19%. In 14 patients (15.6%), predominantly women, a diagnosis of chronic inflammatory bowel disease was ultimately made. Most were Crohn's disease: the majority subsequently developed Crohn's disease restricted to the colon and/or rectum but a minority showed involvement of other parts of the gut. This is the first study in which FAC has presaged an ultimate diagnosis of ulcerative colitis in adults (in two patients). A specific subtype of FAC, termed basal FAC, was significantly associated with drugs. These excepted, this study has found no particular histopathological parameters of FAC, such as amount, location and/or distribution, to correlate with clinical outcome or allowed selection of patients more likely to represent with chronic inflammatory bowel disease.

CONCLUSION: Focal active colitis is a relatively common finding and its causes varied. This study has provided powerful additional information about the implication of a diagnosis of FAC. Further, in a small but not inconsiderable case number, the ultimate diagnosis will be chronic inflammatory bowel disease.

09.45–10.00

**[O14] Investigation of the Localisation of the Putative Stem Cell Marker CD24 in Colorectal Cancer Cell Lines and Identification of Potential Interaction Partners**

Ⓟ KB Kindle; MAH Ahmed; DA Jackson; M Ilyas

University of Nottingham, Division of Pathology, Nottingham, United Kingdom

Colorectal cancer cell lines were used as a model system to investigate the subcellular localisation of endogenous CD24 and to characterise potential CD24 interaction partners in subcellular fractions. Subcellular fractions of SW620, GP2D, HT29 and HCT116 colorectal cancer cells were assessed for CD24 protein expression by western blot analysis using the CD24-specific SWA11 antibody. Co-immunoprecipitation studies of cytoplasmic and nuclear GP2D cell extracts using SWA11 or control antibodies followed by MALDI-TOF mass spectrometry were carried out to identify potential CD24-interacting proteins. The resulting potential interacting proteins were verified in co-immunoprecipitation experiments.

We have found that CD24 protein does not only localise to the membraneous and cytoplasmic, but also the nuclear fractions of CD24 positive colorectal cancer cell lines such as SW620, GP2D and HT29. We have identified Clathrin heavy chain, Scar, L7a and L11a as potential CD24 interacting proteins and were able to show that Clathrin heavy chain and L7 are *bona fide* CD24 interaction partners.

We conclude that in addition to its membraneous localisation and its potential role as a P-selectin receptor, CD24 may have a function in the nucleus of colorectal cancer cells, and that clathrin-coated vesicles may be involved in its co-translocation to the nucleus. Further studies to study the nuclear translocation event and the role of CD24 in the nucleus will be performed, including the effect of P-selectin binding and pre-incubation of cells with endocytosis inhibitors on CD24 nuclear localisation.

10.00–10.15

**[O15] Assessment and Prognostic Value of Regression after Neoadjuvant Therapy in Rectal Cancer: The Role of Tumour Shrinkage and Fragmentation**

Ⓟ M Hav; CA Cuvelier; K Geboes; P Pattyn; M Praet; L Libbrecht

Ghent University Hospital, Ghent, Belgium

Purpose of the study: most patients with rectal cancer receive neoadjuvant therapy, causing a decrease in tumour mass that varies between patients. This study evaluates the prognostic relevance of different ways to assess tumour regression, with special emphasis on tumour shrinkage and fragmentation.

Methods: 76 consecutive patients with rectal cancer who received neoadjuvant radio(chemo)therapy between 2005 and 2009 were included. Besides evaluating the well-recognized pathological features, extramural tumour deposits (ETD), lymph node ratio (LNR), T-downstaging, circumferential resection margin (CRM) and Dworak regression grade were examined.

Summary of results: cT, cN, tumour differentiation and perineural, lymphovascular and extramural vascular invasion showed no prognostic relevance. Positive ypN, especially higher LNR, correlated with a shorter DFS. Patients with ypT<3 or T-downstaging had a longer DFS, indicating a more favorable prognosis when there is decrease in maximum infiltrative depth, further referred to as tumour shrinkage. Increase of CRM was associated with a longer DFS, implying that tumour shrinkage reflects good response to neoadjuvant therapy. LNR was much lower in patients with T-downstaging and correlated inversely with CRM, indicating that primary tumour shrinkage is associated with a decrease in nodal tumour load. Dworak grade did not correlate either with T-downstaging or ypT, and higher Dworak grade was not associated with increased CRM, suggesting that tumour mass decrease is sometimes associated with tumour fragmentation rather than shrinkage.

Conclusions: assessment of tumour shrinkage after neoadjuvant therapy via T-downstaging or CRM correlated better with DFS. Assessing regression based on the amount of tumour in relation to stroma does not accurately discern tumour fragmentation from shrinkage, which is most likely the reason why Dworak regression grading did not have a prognostic value.

10.15–10.30

**[O16] MicroRNAs Located on 13q and 20q Are Differentially Expressed Between Normal Mucosa, Adenomas and Carcinomas of the Large Intestine**

Ⓟ LM Timmer<sup>1</sup>; JS Bolijn<sup>1</sup>; B Carvalho<sup>1</sup>; CJJ Mulder<sup>1</sup>; E Cuppen<sup>2</sup>; GA Meijer<sup>1</sup>; B Diosdado<sup>1</sup>

<sup>1</sup>VU University Medical Center, Amsterdam, Netherlands; <sup>2</sup>Hubrecht Institute and University Medical Center Utrecht, Netherlands

In colorectal cancer (CRC) miRNA expression profiling studies have reported differences in expression between carcinomas and controls, microsatellite stable and unstable, chromosomal unstable tumours, and demonstrated prognostic value for miRNAs. However, the role of miRNAs in CRC pathogenesis has been only partially investigated. CRC results from gradual accumulation of multiple genetic and epigenetic changes in colorectal epithelial cells. The majority of CRCs shows an accumulation of chromosomal abnormalities. Up to 15% of the annotated miRNAs are located at regions of chromosomal instability implicated in colorectal adenoma to carcinoma progression. Two of the most frequent chromosomal aberrations in CRC are gain of 13q (>50%) and 20q (>65%). A total of 36 miRNAs are located on these chromosomal arms. However, the leading cause of the miRNA's aberrant expression and pathways through which they contribute to CRC have not been elucidated.

**WEDNESDAY 11 MAY — continued**

The aim of this study is to investigate expression of miRNAs located on 13q and 20q in normal colon mucosa, adenomas and CRC. DNA and total RNA was isolated from 48 colorectal adenomas, 51 CRCs and 10 normal mucosa samples and DNA copy number gain of 13q and/or 20q was determined. Expression levels of 17 miRNAs located on 13q and 19 on 20q were measured by TaqMan miRNA assays.

11 Of the miRNAs located on 13q and 8 located on 20q were detected in colon tissue. 15 Of these miRNAs were significantly differentially expressed between colorectal tumours compared to controls and 13 between carcinomas and adenomas ( $p < 0.05$ ). In addition, 11 miRNAs were significantly differentially expressed between tumours with or without 13q and/or 20q gain ( $p < 0.05$ ).

Gene dosage effects of miRNAs located on chromosomes 13 and 20 play an important role in CRC progression, and taking this into account is essential to achieve a comprehensive understanding of the pathogenesis of this malignancy.

▶ 10.30 – 11.00

Kapittelzaal – Storey

**COFFEE**

▶ 11.00 – 12.00

Room Rector Vermeylen – Second Floor

**ORAL COMMUNICATIONS**

**Categories: Gastrointestinal**

Chair: Dr L Ferdinande, Ghent University Hospital, Ghent, Belgium  
Dr J Van Huysse, AZ Sint-Jan Brugge-Oostende AV, Bruges, Belgium

11.00–11.15

**[O17] Grading the Plane of Surgery in Abdominoperineal Excision Specimens Resected for Low Rectal Cancer**

Ⓟ NP West<sup>1</sup>; HJ Rutten<sup>2</sup>; I van Lijnschoten<sup>3</sup>; P Quirke<sup>1</sup>

<sup>1</sup>Leeds Institute of Molecular Medicine, Leeds, United Kingdom; <sup>2</sup>The Catharina Hospital, Eindhoven, Netherlands; <sup>3</sup>The Pathology & Medical Microbiology Institute, Eindhoven, Netherlands

Standard abdominoperineal excision (APE) for low rectal cancer is well recognised to be associated with poorer outcomes when compared to higher tumours treated by anterior resection. We have previously demonstrated poor surgical planes, high circumferential resection margin (CRM) involvement and increased perforation rates with standard APE. However, we have also shown that resection in the extra-levator (EL) APE plane removes more tissue around the tumour and improves short term pathological outcomes. We aimed to grade the plane of surgery in a prospective series of APE specimens where EL resection was attempted. We received the specimen photographs and clinicopathological data for 57 APE cases performed in one institution. The plane of resection in the area of the mesorectum and sphincters was independently graded by two observers prior to discussion and agreement of a final grade. All cases received pre-operative radiotherapy +/- chemotherapy for advanced disease (T3 or T4). There was initial agreement on the grading of the mesorectum in 70% of cases ( $\kappa = 0.497$ ) and of the sphincters in 71% ( $\kappa = 0.477$ ). After discussion, the mesorectal gradings were agreed as: mesorectal 54%, intramesorectal 34% and muscularis propria 13%. The sphincter gradings were agreed as: EL 58%, on sphincter 35% and in sphincter 7%. The overall CRM involvement rate was 19% and was not significantly related to the plane of surgery. We have shown that grading the plane of APE surgery using whole specimen photographs is feasible and reproducible. The mesorectal/sphincter gradings and CRM involvement rates reported in this series are considerably better than those reported in APE specimens from the earlier Dutch TME study, although further improvement is still possible. Photography and pathological grading of the plane of APE surgery should be routinely performed in order to feed back to surgeons about the quality of the specimen produced.

11.15–11.30

**[O18] The Use of Three Dimensional Reconstruction from Pre-Operative Magnetic Resonance Images to Investigate the Optimum Resection Planes for the Treatment of Low Rectal Cancer**

Ⓟ M East; NP West; P Quirke

*Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom*

Use of the extra-levator (EL) plane during abdominoperineal excision for low rectal cancer has been shown to decrease the risk of circumferential resection margin involvement and intraoperative perforation compared to the standard sphincteric plane. This study sought to quantify the volume of additional tissue that may be resected using the EL plane with three dimensional reconstruction of in vivo magnetic resonance images. Pre-operative images from 10 low rectal cancer patients were identified. Three dimensional models of potential pathological specimens were created in Osirix by annotating the theoretical resection planes. Virtual cross-sectional slices were created every 3mm from the distal aspect of the model in Rapidform Basis and the area of tissue outside the smooth muscle tube quantified using Aperio ImageScope V10.

Considerable variation was noted in the anatomy of the external sphincter and levator ani muscle complex between patients. The mean length of the complex was 75mm (range 45 to 105mm) providing a mean additional 1160mm<sup>2</sup> of tissue per slice outside the smooth muscle tube in the distal 75mm of bowel. Such variation may alter the risk of incomplete excision between patients and requires further study.

These results demonstrate the potential amount of additional tissue that may be removed with the EL plane compared to the sphincteric plane using three dimensional image reconstruction. This may allow us to predict optimum specimens against which the final operative specimen can be compared for quality control purposes. Such models may assist the surgeon to identify these optimum planes during the operation.

11.30–11.45

**[O19] The Utility of Diagnostic Biopsies for Predictive Mutation Detection in Colorectal Cancer**Ⓟ WM Fadhil<sup>1</sup>; S Ibrahim<sup>1</sup>; R Seth<sup>2</sup>; G AbuAli<sup>3</sup>; K Ragunath<sup>4</sup>; P Kaye<sup>5</sup>; M Ilyas<sup>1</sup>

<sup>1</sup>University of Nottingham, Division of Pathology, Nottingham, United Kingdom; <sup>2</sup>Molecular Diagnostics Lab, Clinical Pathology, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom; <sup>3</sup>Division of Experimental Medicine, Department of Medicine, Imperial College London, London, United Kingdom; <sup>4</sup>Nottingham Digestive Diseases Centre, NIHR Biomedical Research Unit, QMC, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom; <sup>5</sup>Division of Histopathology, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom

Background: Neoadjuvant therapy may become important in the management of colorectal cancer. If so, predictive testing will necessarily be undertaken on pre-operative diagnostic biopsy samples. We sought to evaluate whether a diagnostic biopsy samples was representative of the tumour.

Methods: A series of thirty cases of paired diagnostic biopsy specimens and subsequent resection specimens were randomly selected for analysis. All samples (n=60) were screened for mutation in KRAS (Codon 12/13, 61 and 146), BRAF (Codon 600 and exon 11), PIK3CA (exon 1, exon 9 and exon 20) using the Quick Multiplex Consensus (QMC) PCR protocol followed by high resolution melting (HRM) analysis. Screening for TP53 mutation (exon 5 – 8) and the presence of microsatellite instability (using a panel of 6 mononucleotide markers) was by PCR followed by HRM.

Results: A total of 570 paired PCR tests were performed for mutation detection and identical results were obtained in both biopsy and resection specimen in 569 tests (> 99% concordance). Four cases (13%) demonstrated microsatellite instability and, in all four cases, instability was seen at identical mononucleotide markers.

Conclusion: Even though diagnostic biopsies are a tiny sample of the tumour, they are sufficiently representative of the tumour for use in predictive mutation detection.

11.45–12.00

**[O20] Assay Result Variability During Determination of Mismatch Repair Deficiency Status Using Immunohistochemistry in Colorectal Cancer - A Transatlantic Comparative Study**Ⓟ G Hutchins<sup>1</sup>; K Handley<sup>2</sup>; L Magill<sup>2</sup>; F Baehner<sup>3</sup>; M Lopatin<sup>3</sup>; H Yaziji<sup>4</sup>; M Lee<sup>3</sup>; M Seymour<sup>5</sup>; D Kerr<sup>6</sup>; R Gray<sup>2</sup>; P Quirke<sup>1</sup>

<sup>1</sup>Leeds Institute of Molecular Medicine, Leeds, United Kingdom; <sup>2</sup>University of Birmingham, Birmingham, United Kingdom; <sup>3</sup>Genomic Health Inc., Redwood City, CA, United States; <sup>4</sup>Vitro Molecular Laboratories LLC, Miami, FL, United States; <sup>5</sup>CRUK Cancer Centre, Leeds, United Kingdom; <sup>6</sup>Sidra Medical and Research Center, Doha, Qatar

Background: Colorectal cancer patients with deficient mismatch repair (dMMR) have significantly fewer recurrences and may respond less well to chemotherapy. Immunohistochemical (IHC) determination of MMR status is thus recommended to identify patients in whom adjuvant therapy is not indicated, but little is known regarding the variability of assay results. We aimed to define MMR IHC assay variability in formalin-fixed, paraffin-embedded (FFPE) material from the QUASAR colorectal cancer trial contained within tissue microarrays (TMAs).

Methods: TMA sections of QUASAR FFPE material were distributed to 2 independent laboratories (LIMM, Leeds, UK and Vitro Molecular Laboratories [VML], USA) for MMR IHC assays. TMA sections were stained with MLH1/MSH2 using techniques blinded to the other laboratory. Each stained section was double-scored independently and results compared to determine inter-assay variability.

Results: Matched MMR data were available for 1224 cases of MLH1 and 1223 cases of MSH2. Of these, loss of expression of MMR (dMMR) was reported in 160 cases (13.1%) by VML and 179 cases (14.6%) by Leeds. 140 (11.4%) were dMMR in both labs, 20 cases (1.6%) by VML alone and 39 (3.2%) by Leeds alone. Discordant dMMR status was observed in 56/166 (34%) dMMR cases identified with MLH1 and 10/34 (29%) cases identified with MSH2. Kappa coefficients for inter-assay agreement were 0.798 (95% CI = 0.748 - 0.848) for MMR status overall, 0.778 (95% CI = 0.722 - 0.835) for MLH1 and 0.823 (95% CI = 0.714 - 0.932) for MSH2. 85% (33/39) of discordant Leeds dMMR colon cancers were in the right colon where dMMR is more common, compared to 47% of VML discordant dMMR cases.

Conclusions: Independent determination of MMR status by IHC on TMAs is associated with excellent inter-assay agreement. The reasons for MMR case discordance are under further investigation. These results further support routine MMR testing by IHC.

▶ 12.00 – 13.00

Room Refter – Storey

**KEYNOTE LECTURE — Sponsored by Ferring Pharmaceuticals**

Chair: Prof CA Cuvelier, Ghent University, Ghent, Belgium

**[S11] Mechanisms Regulating Combined Gut and Joint Inflammation in Spondyloarthritis**

Ⓟ Prof D Elewaut

Ghent University Hospital, Ghent, Belgium

Over the past years, it has become clear that TNF is a key player in the pathogenesis of spondyloarthritis but the mechanisms by which this occurs are only partially known. Particularly, the cellular targets sufficient to mediate the articular and extra-articular manifestations of spondyloarthritis remained to be defined, as well as the cellular constituents capable of modulating this TNF driven inflammation. Recently, we reported a peculiar role for mesenchymal cells in a mouse model of spondyloarthritis, characterized by enhanced TNF mRNA stability, resulting in Crohn's like ileitis as well as peripheral arthritis. Hence, TNF-R1 expression on mesenchymal

**WEDNESDAY 11 MAY — continued**

cells was sufficient to mediate combined gut and joint pathologies in this model of murine spondyloarthritis. However, it remained unclear whether regulatory T cell subsets could modulate this inflammation. More recently, we uncovered that a particular regulatory T cell lineage, invariant NKT (iNKT) cells, are natural regulators of TNF driven inflammation by modulating maturation and differentiation of antigen presenting cells in a pathway that is strictly dependent upon TNF. Altogether, these observations provide new insights in the regulatory as well as the effector mechanisms of spondyloarthritis.

▶ 13.00 – 14.00

Kapittelzaal – Storey

**LUNCH and TRADE STANDS**

▶ 13.30 – 14.30

Room Priorzaal – First Floor

**TRAINEES SESSION – MEET THE EXPERTS**

Chair: Dr L Browning, John Radcliffe Hospital, Oxford, UK

**[S12] Diagnostic Dilemmas in Thyroid Pathology**

Ⓟ Prof I Salmon

*Erasmie ULB, Brussels, Belgium*

During the past several decades, an increasing incidence of thyroid cancer has been reported. Is it a real increase in thyroid cancers or an increase in cancer diagnoses? The question is still open. Moreover our WHO classification system has evolved over time resulting in modification of the distribution of thyroid cancer subtypes. The diagnosis of papillary thyroid carcinoma (PTC) is based on distinctive nuclear features such as enlarged with intranuclear cytoplasmic invaginations (pseudoinclusions), clear or ground glass nuclei and nuclear grooves. As a consequence of this PTC nuclear hallmark, fine needle aspiration cytology is an effective diagnostic method for PTC. But be careful in the evaluation of Hashimoto thyroiditis which are also associated with "papillary nuclear features". It is obvious that follicular thyroid carcinomas (FTC) are yet over-diagnosed. This is related to the fact that some benign lesions such as follicular thyroid adenomas (FTA) are misdiagnosed as minimally invasive follicular thyroid carcinoma (FTC) or confused with follicular variant of papillary thyroid carcinoma (FVPTC). It is essential that precise histological criteria be applied to the diagnostic of follicular tumours. The distinction between FTA and FTC is based on histologic highlighting of capsular and vascular invasion. Capsular invasion is defined by tumour penetration through the tumour capsule outside a fine needle aspiration biopsy site. The vascular invasion diagnosis requires intravascular tumour cells covered by endothelial cells. Is capsular invasion without vascular invasion sufficient for FTC diagnosis? It is still a matter to debate. If many biomarkers seem useful, their application in daily practice is not so common and guidelines for adjunctive tests are not yet available.

▶ 14.00 – 15.00

Corridor

**CHAIRMAN'S POSTER ROUNDS**

CATEGORY	POSTER NUMBER	CHAIR
Breast	P1–P11	Dr R Liebmann, Kent and Dr K Lambein, Ghent
Cellular/Molecular Pathology	P12–P14	Dr MJ Arends, Cambridge and Prof M Ilyas, Nottingham
Experimental Tumour Pathology	P15	
Gastrointestinal	P16–P24	Dr RFT McMahon, Manchester and Prof M Pignatelli, Bristol
Neonatal/Paediatric	P25–P34	Prof M Lammens, Ghent/Nijmegen and Dr C Van den Broecke, Ghent
Neuropathology/Ophthalmic	P35	
Technical Advances	P36–P41	Dr MJ Arends, Cambridge and Prof M Ilyas, Nottingham

▶ 15.00 – 17.00

Room Refter – Storey

**SYMPOSIUM**

***Lung Pathology Updated***

Chair: Prof M Praet, Ghent University, Ghent, Belgium

Dr RL Attanoos, University Hospital Llandough, Penarth, UK

15.00–15.30

**[S13] The Broad Spectrum of Small Airways Disease**

Ⓟ Prof AG Nicholson

*Royal Brompton Hospital, London, United Kingdom*

Disorders of the small airways are not uncommon, occur in a wide variety of diseases and pathologists need to be aware of the broad spectrum of diseases that can affect the small airways. In the normal lung they contribute little to airway resistance, but can have a major impact on lung function when diseased. As such, patients

with severe clinical symptoms may exhibit relatively minor pathological changes. There are many proposed classification schemes for small airways diseases. These separate disorders into primary and secondary, with the primary disorders subdivided into those with non-specific histology (acute, acute on chronic, chronic, fibrosing versus non-fibrosing), those with features that point towards an aetiology (granulomatous, eosinophilic, follicular), and those that relate to specific diseases such as diffuse panbronchiolitis, diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH) and neuroendocrine cell hyperplasia of infancy (NEHI). An EVG stain is essential and is especially useful in cases lacking inflammation, where the lung may appear almost normal on first examination. Examination of multiple levels is also often helpful in identifying constrictive obliterative bronchiolitis. Although changes may be non-specific, intensity and subtype of inflammation, together with the presence/absence and nature of fibrosis, as well as degree of luminal obliteration are useful data with regards to management of the patient, independent of aetiology. All anatomic compartments of the lung should be reviewed, as small airways disease may be one of several anatomic compartments involved by pathology. Multidisciplinary review likely obtains the most accurate final clinicopathological diagnosis. Such reviews may also highlight the fact that there often may be relatively minor changes on biopsy, whilst there are significant obstructive symptoms clinically.

15.30–16.00

**[S14] Diagnostic Algorithm in Interstitial Lung Disease**

P Prof Dr W Timens

*University Medical Center Groningen, Groningen, Netherlands*

In diagnostic pathology of interstitial (or also called diffuse) lung disease in general interstitial pathology but also intra-alveolar pathology is included. In diffuse lung disease this is a pattern-based diagnosis. Some entities are characterized by specific histological hallmarks that allow in restricted cases to make a diagnosis with use of transbronchial biopsies. In most cases a .VATS -video assisted thoracoscopy- or open lung biopsy is needed to get an adequate view on the pattern of pathological changes. Within this pattern based approach, attention is paid to distribution in severity over the different lung areas and in addition variability in time (age) of the abnormal areas. So when looking at interstitial fibrosis it is of importance to recognise distribution but also by the presence of older and younger fibrotic changes, with a clear distinction between real interstitial proliferation and intra-alveolar or intrabronchial proliferation. With respect to inflammation again the localisation, distribution and differential in constituent inflammatory cells is of importance. In interpretation of the different patterns sufficient knowledge should be present of the exact localisation of the biopsies. The biopsies should be taken of two, preferably of three localisations including more and less involved areas of the lung based on CT-scan. For interpretation of the biopsy findings, clinical and radiological information is essential and the pathologist should be familiar with elementary knowledge about interpretation of CT-scans of the lung. Of course this does not replace the involvement of a radiologist in making the final clinical diagnosis; this always should be a multidisciplinary approach involving at least pulmonary physician, radiologist and pathologist.

16.00–16.30

**[S15] EGFR Mutations in Lung to Treat or not to Treat**

P Dr E Thunnissen

*VUmc, Amsterdam, Netherlands*

Until recently, for practical purposes distinguishing squamous cell carcinomas (SqCC) from non-squamous cell carcinomas has become increasingly more important for the use of chemotherapy or specific treatment for driver mutations such as activating EGFR mutations and EML4-Alk rearrangements with tyrosine kinase inhibitors and crizotinib, respectively.

The clinical characteristics ethnicity, smoking history and gender have been associated with the presence of EGFR mutations. However, these clinical characteristics cannot be used for selection of EGFR mutation analysis, as patients who might benefit from EGFR-TKI treatment would be excluded (men 25%, (ex)smokers 32%). Activating EGFR mutations are called deletions in exon 19 (~45%) and pointmutation in exon 21 (~40%). Other mutations occur in exon 18, 20 and 21. The activating mutations are associated with a ~70% chance of response on EGFR TKI lasting 9-14 months compared to 25% response rate lasting 6 months for chemotherapy. The median survival of patients with EGFR mutation is 27 months compared to 10 months for patients without mutations. In cases with a recurrence after EGFR-TKI a second acquired EGFR mutation (T790M ~50%) is present. After recurrence additional treatment with another ('irreversible') EGFR-TKI is possible or alternatively chemotherapy (still in clinical trial).

In determining EGFR mutations pathologists should be aware of fraction of tumour cells in the selection process for DNA analysis, as this is directly linked to the technique used for mutation analysis: e.g. PCR-sequencing is associated with analytical sensitivity of 20%, while others claim <1-10%. Thus (manual/instrument based) microdissection is not infrequently required to obtain sufficient fraction of tumour DNA. Proficiency testing for EGFR mutation analysis is useful. External quality assurance for EGFR mutation analysis organized by ESP/EQMN is in progress.

16.30–17.00

**[S16] Molecular Background in Thoracic Neoplasia, Mesothelioma included: A Practical Update**

P Prof S Lantuejoul

*CHU Michallon, J Fourier University, Grenoble, France*

Lung cancer is the leading cause of cancer death in the world, and the majority of them are non-small cell lung carcinoma (NSCLC), comprising two major histological subgroups, the squamous cell carcinoma and the adenocarcinoma. Malignant mesothelioma (MM) is an aggressive neoplasm of serosal cavities, and its main risk factor is asbestos exposure. Lung carcinogenesis as well as asbestos-related tumorogenesis include genetic susceptibility, DNA damage, proliferative signalling pathways, tumour-associated angiogenesis, and cell survival pathways. Whereas p16(INK4a)/p14(ARF) and neurofibromatosis type 2 (NF2), which encodes Merlin, has been reported in MM, as well as receptor tyrosine kinases activation, including the EGFR family and MET, and subsequent deregulations of MAPK and PI3K-AKT signalling cascades, no biomarkers are recommended

WEDNESDAY 11 MAY — *continued*

to date as regards diagnosis or targeted therapies in MM. In contrast, with the recent discovery in a subset of adenocarcinoma of activating mutations of growth promoting oncogenes, including EGFR, Her2, Braf, PI3KCA, EML4-ALK, which are responsible for some of them of tyrosine kinase activities targeted by specific inhibitors, their identification along with a reliable diagnosis of the histological subtype of NSCLC, is highly recommended for patients. However, as most NSCLC are only diagnosed on small specimen, we need tools for making the histopathological diagnosis as precise as possible, and recommendations in order to avoid material waste for the management of small specimen as regards molecular biology and FISH analyses.

▶ 15.00 – 17.00

Room Rector Vermeylen – Second Floor

## ORAL COMMUNICATIONS

**Categories: Gastrointestinal; Experimental Tumour Pathology; Technical Advances; Cellular/Molecular**

Chair: Dr MJ Arends, University of Cambridge, UK  
Prof M Ilyas, University of Nottingham, UK

15.00–15.15

**[O21] TPX2 and AURKA promote 20q Amplicon Driven Colorectal Adenoma-to-Carcinoma Progression**

AH Sillars-Hardebol<sup>1</sup>; Ⓟ B Carvalho<sup>1</sup>; M Tijssen<sup>1</sup>; JAM Beliën<sup>1</sup>; M de Wit<sup>1</sup>; PM Delis-van Diemen<sup>1</sup>; F Pontén<sup>2</sup>; MA van de Wiel<sup>3</sup>; RJA Fijneman<sup>1</sup>; GA Meijer<sup>1</sup>

<sup>1</sup>Department of Pathology, VU University Medical Center, Amsterdam, Netherlands; <sup>2</sup>Department of Genetics and Pathology, The Rudbeck Laboratory, Uppsala University, Uppsala, Sweden; <sup>3</sup>Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, Netherlands

Background: Gain of a large segment of chromosome 20q is associated with progression of colorectal adenomas into carcinomas, implying that multiple genes on the 20q amplicon drive carcinogenesis. Candidate driver genes are expected to be expressed at mRNA and protein levels that correlate with the 20q amplicon DNA copy number status, while functionally affecting one or several cancer-related processes. Integration of CGH profiles with mRNA profiles of a series of colorectal tumours revealed thirty-two candidate genes whose DNA copy number status correlated with mRNA expression levels.

Aim: To functionally analyse the effects of the candidate oncogenes on cancer-related processes by downregulation using siRNA strategies.

Results: Downmodulation of TPX2 (20q11.2) and AURKA (20q13.2) mRNA expression in CRC cell lines with 20q gain affected cell viability, anchorage-independent growth, and invasion. Moreover, immunohistochemical evaluation demonstrated a significant correlation between their protein levels and 20q DNA copy number status in a series of colorectal adenomas and carcinomas.

Conclusion: These data demonstrate that at least two genes located on distinct regions of chromosome 20q promote colorectal adenoma-to-carcinoma progression and indicate that TPX2, like AURKA, is a promising target for anti-cancer drug development.

15.15–15.30

**[O22] Evaluation of Beta-Glucan Particles as Mucosal Delivery System in the Peyer's Patch Regions of the Murine Small Intestine**

Ⓟ R De Smet<sup>1</sup>; T Demoor<sup>1</sup>; S Verschuere<sup>1</sup>; M Dierendonck<sup>2</sup>; BG De Geest<sup>2</sup>; CA Cuvelier<sup>1</sup>

<sup>1</sup>Department of Pathology, Ghent University, Ghent, Belgium; <sup>2</sup>Department of Pharmaceutics, Ghent University, Ghent, Belgium

Oral vaccination is essential to generate protective local immunity against intestinal pathogens. However, antigen delivery to the inductive sites for mucosal immunity (the small intestine Peyer's patches, PP) has proven to be particularly challenging. We evaluated the potential of beta-glucan microcapsules to deliver antigen transmucosally in the PP regions of the murine small intestine.

Beta-glucan microcapsules (3–5 µm) were prepared from *Saccharomyces cerevisiae* and loaded with Alexa Fluor 488-conjugated bovine serum albumin. Particles were administered to male C57BL/6 mice (8–10 weeks old) via intestinal loops at a particle concentration of 100\*10<sup>6</sup> /ml. After one hour of incubation, transmucosal particle transport and uptake in the PP was evaluated by flow cytometry, confocal microscopy and transmission electron microscopy.

Using flow cytometry, we could not observe any particle uptake in the main antigen presenting cell population, the dendritic cells. Interestingly, flow cytometric analysis indicated a modest but clear uptake of particles in the B-cell population. Confocal microscopic images showed yeast particles localized in the Follicle Associated Epithelium. Moreover, transmission electron microscopy demonstrated transcellular transport of yeast particles in M-cells. Our data suggest that M-cells, but not subepithelial dendritic cells, are crucial for the transmucosal transport of beta-glucan particles from the intestinal lumen to the PP.

15.30–15.45

**[O23] Clinicopathological Review of Schistosomal Appendicitis in Southwestern Nigeria**

AO Adisa; Ⓟ AE Omonisi; SA Osason; OI Alatise

Obafemi Awolowo University Teaching Hospitals Complex, ILE-IFE, Nigeria

Purpose of the Study: To describe the pattern and frequency of schistosomal appendicitis in Ile-Ife, Southwestern Nigeria.

Method: The clinical records and histopathological slides of all patients diagnosed with schistosomal appendicitis between January 1989 and December 2006 in Ile-Ife, Southwest Nigeria, were reviewed.

15.45–16.00

**[O24] CD24 Inhibition Augments the Suppression of Cell Motility and Tumorigenicity of Colorectal Cancer Cells Induced by Low Dose PI3 Kinase Inhibitor**

Ⓟ M Ahmed<sup>1, 2</sup>; K Kindle<sup>2</sup>; D Jackson<sup>2</sup>; M Ilyas<sup>2</sup>

<sup>1</sup>Dept of Pathology, Suez Canal University, Ismailia, Egypt; <sup>2</sup>Queen's Medical Centre, Division of Pathology, Nottingham, United Kingdom

**Background and aims:** CD24 is a GPI anchored cell surface molecule that has been reported to have a role in tumourigenesis and progression in different types of cancer either in solid or hematologic malignancies. We reported CD24 as a marker that enhances colorectal cancer (CRC) motility and tumorigenicity. The ultimate downstream signalling pathways of CD24 are largely unclear until recently. We aimed to investigate the possible downstream targets of CD24 and the potential cooperation between CD24 and a crucial signalling pathway PI3 kinase (PI3K) - AKT frequently deregulated in CRC.

**Methods and results:** We used an antibody phosphor-array to look for possible downstream targets of CD24 after gene knockdown in the cell line GP2D (which expresses high levels of CD24). After CD24 knockdown, AKT activation at the S473 phosphorylation site was markedly reduced, in addition, a number of AKT downstream targets showed suppression of activation. Full activation of AKT needs phosphorylation on both site S473 and T308, therefore, we used the PI3Kinhibitor LY294002 at a recommended low dose to inhibit the T308 site in combination with CD24 knockdown in DLD1 and GP2D. Our results showed that the combination of CD24 and low dose LY294002 resulted in a comparable results of using LY294002 alone at a 5 times dose and which would result in inhibition of both phosphorylation sites. Those observations reflected functional effects that were confirmed by studies with respect to migration ( $p < 0.01$ ), invasion ( $p < 0.01$ ), and 3D colony formation in soft agar ( $p < 0.01$ ).

**Conclusions:** We conclude that CD24 may act through activation of AKT to affect a number of cellular functions in CRC. We speculate that when AKT is to be targeted, CD24 inhibition could be used in concert with low doses of the PI3K inhibitor LY294002 accordingly reducing the risk of the reported toxicity of high doses of such inhibitors.

16.00–16.15

**[O25] Loss of Lamin A/C Expression in Stage II and III Colon Cancer is Associated with Disease Recurrence**

EJT Belt<sup>1</sup>; Ⓟ RJA Fijneman<sup>1</sup>; EG van den Berg<sup>1</sup>; H Bril<sup>2</sup>; PM Delis-van Diemen<sup>1</sup>; M Tijssen<sup>1</sup>; HFB van Essen<sup>1</sup>; ESM de Lange-de Klerk<sup>1</sup>; JAM Belien<sup>1</sup>; HBA Stockmann<sup>2</sup>; S Meijer<sup>1</sup>; GA Meijer<sup>1</sup>

<sup>1</sup>VU University Medical Center, Amsterdam, Netherlands; <sup>2</sup>Kennemer Gasthuis, Haarlem, Netherlands

Worldwide nearly one million people are diagnosed with colorectal cancer each year, half of whom die within 5 years. Adjuvant (5-FU based) chemotherapy increases median 5-year survival of stage III colon cancer patients. However, prognostic biomarkers are needed to improve identification of patient subgroups who will truly benefit from adjuvant therapy. Loss of the nuclear lamina protein lamin A/C (LMNA) has been observed in several human malignancies. The present study aimed to investigate associations between LMNA expression and clinical outcome in colon cancer patients.

Clinicopathological data and formalin-fixed paraffin embedded tissues were collected from 370 stage II and III colon cancer patients. Tissue microarrays were constructed, stained for lamin A/C, and evaluated microscopically. Microsatellite instability status was determined for 318 tumours.

Low levels of LMNA expression were observed in 17.8% of colon tumours, with disease recurrence occurring in 45.5% of stage II and III colon cancer patients with LMNA-low expressing tumours compared to 29.6% of patients with LMNA-high expressing tumours ( $p=0.01$ ). For stage II patients, disease recurrence was observed for 35.7% of LMNA-low compared to 20.3% of LMNA-high expressing tumours ( $p=0.03$ ). Microsatellite stable (MSS) tumours exhibited more frequently low LMNA expression than microsatellite instable (MSI) tumours (21% vs 9.8%;  $p=0.05$ ). Interestingly, disease recurrence among LMNA-low and LMNA-high expressing MSS tumours varied significantly for stage III patients who lacked adjuvant chemotherapy (100% vs 37.8%;  $p<0.01$ ) while such difference was absent from patients who received adjuvant chemotherapy (46.7% vs 46.0%;  $p=0.96$ ).

Our data demonstrate that low expression of LMNA is associated with an increased disease recurrence in stage II and III colon cancer patients, and imply that these patients in particular may benefit from adjuvant chemotherapy.

WEDNESDAY 11 MAY — *continued*

16.15–16.30

**[O26] MMP9 Is a Prognostic Biomarker for Metastatic Colon Cancer**

Ⓟ JAC Goos; RJA Fijneman; AC Hiemstra; AA Geldof; GA Meijer; OS Hoekstra

*VU University Medical Center, Amsterdam, Netherlands*

Of all colorectal cancer (CRC) patients each year more than 45% die as a consequence of metastases, of which the majority is located in the liver. Although patient selection for hepatectomy by 18FDG PET has significantly reduced futile surgery, 70% of all operated patients still die of metastases within 5 years after hepatectomy. To improve prediction of patient outcome, novel PET tracers with better prognostic value are needed. Matrix metalloproteinases, frequently associated with several types of cancer, might serve as prognostic biomarkers that can be used in PET imaging.

To investigate the prognostic value of the expression of one of these matrix metalloproteinases, MMP9, in to the liver metastasized colon cancer, formalin-fixed paraffin-embedded colon cancer liver metastases, collected from 85 patients having had curative hepatectomy between 1990 and 2009, were incorporated into tissue microarrays (TMAs). MMP9 expression in both epithelial and stromal cells was assessed by immunohistochemistry and expression was correlated to patient survival data.

Mean age of the colon cancer patients (62.1% males, 37.9% females) was 62.0 (standard deviation 10.5). Chemotherapy was received by 45.9% (15.3% neoadjuvant, 14.1% adjuvant, 16.5% palliative) and radiofrequency ablation (RFA) was performed in 10.8%. Median overall survival was 35.0 months (standard deviation 5.7). High expression of MMP9 by epithelial colon cancer cells within the liver metastases was associated with increased survival rates ( $p=0.007$  for disease-free survival and  $p=0.056$  for overall survival). MMP9 expression in stromal cells was not associated with patient survival.

Our results suggest that elevated levels of MMP9 in metastatic epithelial colon cancer cells are indicative of a good prognosis. Whether MMP9 qualifies as a target with prognostic relevance for imaging of lesions in patients with metastatic colorectal cancer remains to be determined.

16.30–16.45

**[O27] High Resolution Melting Analysis (HRM) is a Novel and Robust Method for Detection of Microsatellite Instability in Colorectal Cancer**

Ⓟ WM Fadhil; M Ilyas

*University of Nottingham, Division of Pathology, Nottingham, United Kingdom*

Microsatellite instability (MSI) in colorectal cancers (CRC) arises due to a loss of function of the mismatch repair (MMR) proteins. In sporadic tumours, the presence of MSI has prognostic implications and, more importantly, it may also predict cancer response/ resistance to certain chemotherapies. We aimed to develop a clinically applicable and robust assay that utilises the capability of HRM analysis to detect DNA sequence alterations. One hundred and forty CRC tumours were first stained for all 4 MMR proteins and reviewed blindly. These tumours were then tested for MSI using PCR followed by HRM. New primers were designed to amplify across six mononucleotide genomic regions. All HRM experiments were done in duplicates and analysed using two different systems; a high-throughput 7500 fast real time PCR systems (Applied biosystems) and HR1 high resolution instrument (Idaho Technology).

Eight MLH1/PMS2 deficient tumours and one MSH2/MSH6 deficient tumour were identified by immunohistochemistry (IHC). HRM analysis revealed 100% concordance between both machines and the duplicates showed identical melting. Comparing the outcome of HRM to that of IHC, the MMR deficient cases were picked up by HRM. All MLH1/PMS2 deficient samples showed aberrant melting in the whole set of MSI markers, while the MSH2/MSH6 deficient sample were detected by four MSI markers only. Eight tumours showed aberrant melting in one marker and one tumour showed aberrant melting in two markers markers by HRM. It is well known that the main drawback of using HRM for mutation screening is difficulty to discriminate SNPs from mutations. In line with the Bethesda panel, we would define MSI positive cases when aberrant melting is seen in 3 or more loci. Alternately, matched normal tissue could be used in each case. In summary, HRM analysis is a robust and highly sensitive technique which can be used for rapid and accurate MSI testing.

16.45–17.00

**[O28] The CD24 and Kras Signalling Pathways Converge on Cten to Promote Cell Motility in the Colon.**

Ⓟ S Al-Ghamdi; MA Ahmed; A Albasri; S Ibrahim; D Jackson; K Kindle; M Ilyas

*University of Nottingham, Nottingham, United Kingdom*

CD24 and Kras represent two different mechanisms of inducing cell motility. CD24 is a heavily glycosylated GPI anchored cell membrane molecule which positively regulates cell motility. Kras is a forms part of signal transduction mechanism for the receptors of a number of motility and growth inducing factors. Induction of motility in most cases will require re-modelling of focal adhesions (points of attachment between cell membrane and extracellular matrix) and we have previously shown that Cten, which is located at focal adhesions, is able to positively regulate cell motility.

We investigated whether Cten may play in a role both CD24 and Kras mediated cell motility in the colon. We manipulated CD24 levels through (i) gene knockdown in the cell lines SW620 and DLD1 and (ii) forced expression of CD24 in HCT116 and RKO. The changes in CD24 expression were mirrored by identical changes in Cten expression suggesting that CD24 may regulate Cten. We have previously found an association between KRAS mutation and high Cten expression in our colorectal cancer cell lines. In order to test this relationship, we knocked down Kras in SW620 and DLD1 (both mutant for KRAS) and found that this resulted in down-regulation of Cten and an inhibition of cell motility ( $p<0.001$ ). Restoration of Cten (by forced expression) after knockdown of Kras rescued the cell motility ( $p<0.001$ ). Kras signals through Braf and the cell line Colo205 is mutant for BRAF and shows high Cten expression. Knockdown of Kras in Colo205 did not affect Cten levels whilst knockdown of Braf resulted in down-regulation of Cten and inhibition of cell motility.

We conclude that Cten may be a focal point for the motility inducing activities of CD24 and Kras. This may be due to its ability to uncouple integrins from the actin cytoskeleton and thereby re-model focal adhesions. We speculate that Cten may also mediate cell motility from other signalling pathways.

▶ 17.30 – 18.30

Aula · Ghent University

**PUBLIC LECTURE**

Chair: Prof CA Cuvelier, Ghent University, Ghent, Belgium

**[S17] *Old and New Challenges in Global Health***

Ⓟ Prof P Piot

*London School of Hygiene & Tropical Medicine, London, United Kingdom*

This public lecture will review progress against the health Millennium Development Goals, and discuss the rapid epidemiological transition affecting most countries in the world, with a major shift from infectious diseases to non-communicable diseases, including diabetes, cardiovascular diseases, chronic obstructive pulmonary disease and mental illness, combined with a growing insolvency of health systems. Challenges and solutions for this new health landscape will be discussed.

▶ 19.00 – 20.30

Het Pand Museum

**GUIDED TOUR OF MUSEUM OF HISTORY OF MEDICINE**

*followed by* — **RECEPTION**

**THURSDAY 12 MAY**

▶ 08.00

Reception

**REGISTRATION and COFFEE**

▶ 09.00 – 17.00

Room Sacriste – Storey

**SLIDE SEMINAR COMPETITION VIEWING**

***Tumours of the Skeleton: Test Your Knowledge up to the Bare Bone***

▶ 09.00 – 12.00

Room Refter – Storey

**SYMPOSIUM**

***Clinicopathological and Molecular Advances in Benign and Malignant Liver Tumours***

Chair: Dr L Libbrecht, Ghent University Hospital, Ghent, Belgium

Prof AD Burt, University of Newcastle, Newcastle-upon-Tyne, UK

09.00–09.30

**[S18] *Clinical Viewpoint on Diagnosis and Management of Liver Tumours***

Ⓟ Prof Dr H Van Vlierberghe

*Ghent University Hospital, Ghent, Belgium*

In the work out of liver lesions, a clinician should make a distinction between a focal lesion found in a person with a normal (non-cirrhotic) liver or in a cirrhotic liver. If no underlying liver disease is diagnosed, the majority of the liver lesions are benign. Radiological examination can make a distinction between the most frequent lesions: hemangioma, focal nodular hyperplasia, cyst, adenoma or focal steatosis. In the absence of symptoms and with the exception of adenomas, the lesions need no treatment and oral contraceptives do not need to be stopped. On the contrary, for adenomas, there is a need to stop contraception and in lesions bigger than 5 cm, surgical resection is advised due to a potential of malignant degeneration. A recent pathological classification system could distinguish several subtypes of adenomas: 1/those carrying mutation in the TCF/HNF1alpha (with a low risk of malignant degeneration), 2/ those adenomas with an activation of beta-catenin (with a substantial risk of malignant degeneration) and 3/ an inflammatory subgroup of adenomas. If a focal lesion is found on a cirrhotic background, the suspicion for a hepatocellular carcinoma (HCC) should be high. The recent AASLD guidelines stipulate that the diagnosis in the majority of these lesions can be made through well performed imaging. If the findings are not characteristic or the vascular profile is not typical, a second contrast enhanced study should be performed, or the lesion should be biopsied. Tissue that is not clearly HCC should be stained with all the available markers including CD34, CK7, glypican 3, HSP-70, and glutamine synthetase to improve diagnostic accuracy. Treatment of HCC is a multidisciplinary approach where the choice of treatment is guided by the performance status of the patient, the severity of the underlying liver disease and the oncological staging.

09.30–10.00

***Histopathology and Immunohistochemistry of Benign and Malignant Liver Tumours***

Ⓟ Dr L Libbrecht, Ghent University Hospital, Ghent, Belgium

10.00–10.30

**[S19] *Dysplastic Nodules and Early Hepatocellular Carcinoma***

Ⓟ Dr A Quaglia

*King's College Hospital, London, United Kingdom*

Hepatocellular carcinoma (HCC) is considered the fifth commonest cancer worldwide and its incidence is increasing. The main risk factor for HCC is cirrhosis. HCC is believed to originate as a proliferative focus which eventually evolves into a nodular hepatocellular lesion. Further progression can occur with a nodule-in-nodule pattern. These lesions range in size from 1 mm up to approximately 20 mm, have the potential to progress to frank HCC, and are designated as low grade and high grade dysplastic nodules (DN) based on subtle histological criteria. Progression from DN and HCC is associated with arterialisation and sinusoidal capillarization, and radiologically, by contrast up-take in the arterial phase and wash-out in the venous phase. The histological distinction between high grade DN and early HCC remains conceptually controversial and practically difficult, and the use of criteria such as stromal invasion, ductular reaction and immunohistochemical markers derived from molecular studies has been invoked. These proposed immunohistochemical markers include in particular heath-shock protein 70, glypican 3 and glutamine synthetase. The subtle histological criteria to differentiate between low and high grade DN and between high grade DN and HCC have been described recently in details by the International Consensus Group for Hepatocellular Neoplasia (Hepatology 2009; 49(2):658). Based on the current pathological and imaging criteria, HCC development can probably be defined by three phases: 1) non invasive stage, premalignant DN, iso or hypovascularised with portal perfusion; 2) Well differentiated (early) vaguely nodular with peripheral replacing pattern HCC, with residual portal perfusion with or without invasive features; 3) Moderately differentiated progressed distinctly nodular fully arterialised HCC with or without invasive features.

10.30–11.00

**COFFEE [Kapittelzaal – Storey]**

11.00–11.30

**[S20] Molecular Features and Classification of Hepatocellular Adenomas**

P Prof J Zucman-Rossi

*Inserm U674, Paris, France*

Recently, analysis of the genotype-phenotype correlation in hepatocellular adenomas (HCA) enabled the identification of well-defined subtypes of adenomas leading to propose a new molecular classification of these tumours in 3 major subgroups. 1-HNF1-inactivated HCA (H-HCA). In approximately 35% of the cases, HCA are defined by biallelic mutations inactivating the hepatocyte nuclear factor 1-alpha (HNF1A). These tumours are phenotypically characterized by a marked steatosis. In rare families with an inherited mutation in one allele of HNF1A, patients with maturity onset diabetes of the young type 3 (MODY3) are predisposed to develop familial liver adenomatosis. 2-B-catenin mutated HCA. These HCA represent about 15% of the cases. They frequently show cytologic abnormalities and pseudo-glandular formations, whereas steatosis is very unusual. Beta-catenin HCA are frequently diagnosed as borderline lesions between adenoma and HCC or associated with HCC. The highest risk of malignant transformation has been confirmed in several studies. 3-Inflammatory Hepatocellular Adenomas. Genotype-phenotype correlations revealed a homogeneous subgroup of tumours, the inflammatory HCA (IHCA, 35% to 45%), characterized by the presence of inflammatory infiltrates within the tumour. IHCA are frequently associated with obesity and more rarely with alcohol intake. IHCA are also frequently telangiectatic and this subgroup of lesions include most of the adenoma previously termed "telangiectatic focal nodular hyperplasia" or "telangiectatic adenoma." Recently, we identified recurrent somatic mutations of interleukin-6 signal transducer (IL6ST)-activating gp130 in 60% of the IHCA cases. We further demonstrated that the gp130 mutants identified in IHCA were able to activate STAT3 independently of the interleukin signalling Conclusion: Altogether, these observations revealed the broad diversity of the different subtypes of adenomas.

11.30–12.00

**[S21] Genomic Decoding of Liver Cancer: Mechanistic and Clinical Implications**

P Dr S Thorgeirsson

*National Cancer Institute, Bethesda, United States*

The variability in the prognosis of individuals with hepatocellular carcinoma (HCC) suggests that HCC may comprise several distinct biological phenotypes. These phenotypes may result from activation of different oncogenic pathways and/or from a different cell of origin. Comparative functional genomics approach has been used to gain insight into the cellular origin of HCC. We integrated gene expression data from rat fetal hepatoblasts and adult hepatocytes with HCC from human and mouse models. Individuals with HCC who shared a gene expression pattern with fetal hepatoblasts had a poor prognosis. The gene expression program that distinguished this subtype from other types of HCC included markers of hepatic oval cells, suggesting that HCC of this subtype may arise from hepatic progenitor cells. Analyses of gene networks showed that activation of AP-1 transcription factors in this newly identified HCC subtype might have key roles in tumour development. It is well established that recurrent genomic loci with DNA copy number changes might harbor potential driver genes in tumorigenesis. We have recently performed fine-resolution genome-wide tiling profiles of DNA copy numbers in human hepatocellular carcinoma (HCC). Comparison of copy number changes with corresponding transcription level changes in the same patients identified twenty-five copy number-dependent regions and fifty potential driver genes. Unbiased estimation of functional relevance of these regions and genes was evaluated by their prognostic impacts, and revealed their central role in the course of HCC progression. In particular, driver genes located on chromosomes 8q and 1q were the most highly predictive for survival. In addition, systematic prediction of the drug responses of the fifty driver genes identified therapeutic targets for HCC (e.g., EGFR tyrosine kinase).

▶ 09.00 – 10.30

Room Rector Vermeylen – Second Floor

**ORAL COMMUNICATIONS****Categories: Gynaecological; Autopsy/Forensic; Cardiovascular/Pulmonary; Neonatal/Paediatric**

Chair: Dr EW Benbow, University of Manchester, UK

Dr C Van den Broecke, Ghent University Hospital, Ghent, Belgium

09.00–09.15

**[O29] The Expression of Interleukin-8 and the Interleukin-8 Receptors (CXCR1 and CXCR2) in Endometrial Carcinoma**P LJ Ewington<sup>1</sup>; A Taylor<sup>2</sup>; R Sriraksa<sup>3</sup>; Y Horimoto<sup>4</sup>; E Lam<sup>4</sup>; MA El-Bahrawy<sup>5</sup>

<sup>1</sup>Faculty of Medicine, Imperial College London, London, United Kingdom; <sup>2</sup>Department of Oncology, Imperial College NHS Trust, London, United Kingdom; <sup>3</sup>Centre for Research and Development of Medical Diagnostic Laboratories, Khon Kaen University, Khon Kaen, Thailand; <sup>4</sup>Department of Surgery and Cancer, Imperial College London, London, United Kingdom; <sup>5</sup>Department of Histopathology, Imperial College London, London, United Kingdom

Endometrial cancer is the most common gynaecological malignancy in the United Kingdom. Interleukin-8 (IL-8) is a pro-inflammatory cytokine which exerts its effects via binding to the chemokine receptors CXCR1 and CXCR2. Following ligand binding, various signalling cascades are activated which ultimately promote angiogenesis, mitogenesis and motogenesis. IL-8 is over expressed in endometrial carcinoma, but the expression of CXCR1 and CXCR2 in endometrial carcinoma has not been previously investigated. We studied the expression of CXCR1 and CXCR2 in endometrial carcinomas and normal endometrium by immunohistochemistry in 101 cases and by Real-time quantitative PCR (RT-qPCR) in 17 cases. The expression profile was correlated to the clinico-pathological features of the tumours. Immunohistochemistry showed CXCR1 and CXCR2 were expressed in all endometrial carcinomas, with CXCR1 showing stronger expression than CXCR2. There was no statistically significant correlation between staining intensity of both receptors and tumour type, tumour stage or the presence of lymphovascular space invasion. There was a statistically significant correlation between CXCR2 staining intensity and tumour grade (P=0.012),

THURSDAY 12 MAY — *continued*

but not between for CXCR1 staining intensity and tumour grade. On RT-qPCR there was significant increase in the level of expression of IL-8, CXCR1 and CXCR2 in 15/17 (median 41.8 folds), 15/17 (median 51.4 folds) and 16/17 (median 26.7 folds) tumours respectively in comparison to normal endometrium. There was an inverse relationship between the level of expression of CXCR1 and CXCR2 and disease free survival and overall survival. This is the first study to investigate the expression of CXCR1 and CXCR2 in endometrial carcinoma and the results suggest IL-8 and IL-8 receptors play a role in the pathogenesis of endometrial carcinoma, and represent potential prognostic biomarkers and therapeutic targets.

09.15–09.30

**[O30] Do Figo Stage 1A and Small (<2CM) 1B1 Cervical Adenocarcinomas Have a Good Prognosis and Warrant Less Radical Surgery**Ⓟ G McVeigh<sup>1</sup>; M Al-Kalbani<sup>2</sup>; H Nagar<sup>2</sup>; WG McCluggage<sup>1</sup><sup>1</sup>Royal Victoria Hospital, Belfast, United Kingdom; <sup>2</sup>Belfast City Hospital, Belfast, United Kingdom

Objectives: There is controversy regarding the optimal management of small cervical adenocarcinomas and more radical surgery is often undertaken compared to similar size squamous carcinomas. We wished to determine the risk of parametrial involvement and metastatic disease and the outcome in FIGO 1A and small (< 2 cm) 1B1 cervical adenocarcinomas. Methods: All women with a diagnosis of FIGO stage 1A1, 1A2 or 1B1 cervical adenocarcinoma with maximum tumour size of 2 cm were identified between 1999 and 2010 in Northern Ireland. A single pathologist reviewed all pathology prospectively at a cancer centre tumour board. Results: A total of 74 women were identified (mean age 39; range 25-72). In total, 36 women had stage 1A1, 9 stage 1A2 and 29 stage 1B1 cervical adenocarcinoma. Surgical treatment ranged from local excision (cone or LLETZ) to radical hysterectomy and pelvic lymph node dissection; adjuvant therapy was not administered in any case. No parametrial involvement was seen in the 36 women who underwent parametrial resection. No lymph node metastasis was identified in the 45 women who underwent pelvic lymph node dissection. Lymphovascular space invasion was identified in 6 cases. No tumour recurrence or metastasis was noted with an average follow up of 60 months. Conclusions: The optimal management of women with 1A or small 1B1 cervical adenocarcinoma is controversial and radical surgery is often undertaken. Our data suggests that there is an extremely low risk of parametrial and lymph node involvement with tumours < 2cm and a low recurrence rate. Less radical surgery may be warranted for small cervical adenocarcinomas and this should be addressed by future studies.

09.30–09.45

**[O31] The Pathology of Sudden Cardiac Death - Results from a Specialist Cardiac Pathology Service in the United Kingdom (UK)**SV de Noronha<sup>1</sup>; K Ohta-Ogo<sup>2</sup>; J Wells<sup>1</sup>; W Banya<sup>2</sup>; Ⓟ MN Sheppard<sup>3</sup><sup>1</sup>Imperial College, Royal Brompton & Harefield NHS Foundation Trust, London, United Kingdom; <sup>2</sup>Royal Brompton & Harefield NHS Foundation Trust, London, United Kingdom; <sup>3</sup>Royal Brompton & Harefield NHS Foundation Trust/NHLI, London, United Kingdom

Sudden cardiac death (SCD) in the young may be more common than previously thought with recent findings suggesting that there are at least 10 cases per week in the UK. We report the results of a novel fast track cardiac pathology service funded by the charity Cardiac Risk in the Young (CRY). This service offers a free specialist cardiac diagnosis with a median turnaround of 9 days and has proved to be successful with families and pathologists nationwide who wish to establish a specific cardiac cause quickly.

A total of 720 cases of SCD were referred from early 2007 to 2009, predominately male (2:1), median age 31 years. The main cardiac diagnoses were normal heart (n=320) (suggesting channelopathy), cardiomyopathy (n=204) and coronary artery pathology (27% of which was non-atherosclerotic). The most common cardiomyopathies were: Idiopathic LVH (n=54), HCM (n=42), ARVC and obesity cardiomyopathy (n=29, each). Most deaths took place at home (57%) at rest or during sleep (34%) and 14% during exertion. In a sample of 200 consecutive cases of SCD, diagnoses made by both the referring pathologist and MNS matched in 60% of cases ( $\kappa=0.49$ ). Referring pathologists were more inclined to diagnose pathology rather than designate the heart as normal e.g. ARVC was over-estimated by a factor of 4 when fatty infiltration of the right ventricle was identified but the heart was otherwise normal. Similarly, HCM was overestimated by a factor of 1.5 when cases lacked true myocyte disarray needed for pathological diagnosis and designated as ILVH instead.

This large study highlights the importance of inherited cardiac disease as a cause of SCD as at least 75% of our referrals are of potentially genetic origin. With the establishment of the CRY CCP, we are able to provide a prompt service to help families come to terms with a very traumatic event and facilitate their referral to specialist cardiological services for family screening.

09.45–10.00

**[O32] Extrapulmonary Small Cell Carcinoma: A Clinicopathological Study with Identification of Diagnostic Mimics**Ⓟ AM Quinn<sup>1</sup>; F Blackhall<sup>2</sup>; S Danson<sup>3</sup>; G Wilson<sup>4</sup>; J Brierley<sup>4</sup>; E White<sup>4</sup>; C Keeling<sup>4</sup>; A Clamp<sup>2</sup>; L Ashcroft<sup>2</sup>; PS Hasleton<sup>4</sup><sup>1</sup>Royal Preston Hospital, Preston, United Kingdom; <sup>2</sup>The Christie Hospital, Manchester, United Kingdom; <sup>3</sup>Weston Park Hospital, Sheffield, United Kingdom; <sup>4</sup>Manchester Royal Infirmary, Manchester, United Kingdom

Purpose of the Study: Extrapulmonary small cell carcinomas (EPSCC) are uncommon neoplasms, generally diagnosed using criteria based on analysis of pulmonary small cell carcinomas. The correct classification is required for treatment and prognosis. Accurate histological diagnosis is pivotal to this process. This study reviews the morphology and immunohistochemical staining patterns of a cohort diagnosed as EPSCC and large cell neuroendocrine carcinoma (LCNEC).

Methods: The pathology database at a tertiary hospital was searched from 01/01/1994 to 31/12/2003, using the term "small cell". Case notes of patients with a diagnosis of EPSCC were reviewed. The paraffin tumour block with the greatest percentage of viable neuroendocrine tumour was selected for a fresh haematoxylin and eosin

stain and immunohistochemical stains, including synaptophysin, TTF-1 and 34βE12. Additional stains were carried out on selected cases, where the diagnosis was uncertain. The stains were assessed by two pathologists. Summary of Results: In total 37 cases were reviewed. The commonest tumour locations were cervix (11) and bladder (10) followed by oesophagus (3), ovary (3), prostate (3), rectum (2), breast (1), kidney (1), stomach (1), liver (1) and jaw (1). 25 cases (68%) were diagnosed as EPSCC. The remaining cases were classified as 10 poorly differentiated carcinomas (PDC) (27%), 2 of which contained areas of neuroendocrine differentiation, and 2 cases of LCNEC (5%). TTF-1 was positive in 9 cases of EPSCC and none of the cases of PDC (p = 0.034). Synaptophysin was positive in 20 cases of EPSCC and 2 cases of PDC with neuroendocrine differentiation (p = 0.002), as well as 2 cases of LCNEC.

Conclusions: EPSCC, based on this small series, may be over-diagnosed. The commonest mistake was to confuse this tumour with a PDC. Special stains may reduce this discrepancy. TTF-1 may help to discriminate EPSCC from PDC, in combination with synaptophysin.

10.00–10.15

**[O33] Usefulness of Immunohistochemistry to Detect L858R and E746-A750 Mutation of EGFR in Non Small Cell Lung Cancer**

Z Mekinda<sup>1</sup>; M Dehoux<sup>1</sup>; M Lemercier<sup>1</sup>; N De Nève<sup>1</sup>; P Heimann<sup>1</sup>; I Salmon<sup>2</sup>;

Ⓟ M Remmelink<sup>1</sup>

<sup>1</sup>CUB-ULB Hôpital Erasme, Brussels, Belgium; <sup>2</sup>Hôpital Erasme, Brussels, Belgium

Introduction: EGFR receptor mutations are present in approximately 10% of non small cell lung cancer (NSCLC). Two mutations are particularly interesting: L858R on exon 21 and deletion E746\_A750 on exon 19 the detection of the mutation is done by sequencing.

Two specific antibodies against L858R and E746\_A750 were described.

Aim: Evaluation of the use of immunohistochemistry to detect L858R and E746\_A750del mutation in NSCLC and to place this result in an algorithm to decide to treat the patient with tyrosine kinase inhibitor.

Methods: First a prospective study : we realise evaluation of the staining obtained by immunohistochemistry against L858R on exon 21 and deletion E746\_A750 on exon 19. Second a retrospective study to evaluate the heterogeneity of the staining obtained by immunohistochemistry against L858R on exon 21 and deletion E746\_A750 on exon 19.

Results: For the prospective study (36 NSCLC) preliminary results show that among 28 wild type : 3 (11%) cases show expression of L858R ( 1 clearly positive with strong expression and 2 with very little focal expression one nuclear, and one membranous pattern); 4 (14%) cases shows expression of deletion E746\_A750 but with a very focal expression. 2 L858L mutated case show expression of L858R expression. On 3 del 19 cases 1 case shows expression of L858R with a light nuclear staining pattern but with a very strong expression of del 19 staining , 1 case a strong expression of del 19 staining and one is negative (false negative). For the retrospective study, the first serie of 50 cases analysed, 3 cases expressed L858R staining with one clearly positive this must be correlated with sequencing.

Conclusions: Our preliminary results show in our serie 1 false positive for L858R in a WT case and 1 false negative for a case with a deletion of 19. These case are clearly discordant. For the others cases, the staining is very subtle (doubtful) and must be correlated with CISH results.

10.15–10.30

**[O34] Label-Free Quantitative Mass Spectrometry Proteomic Analysis in Sudden Unexpected Death in Infancy (SUDI)**

Ⓟ JW Pryce<sup>1</sup>; W Heywood<sup>2</sup>; K Mills<sup>2</sup>; MA Weber<sup>3</sup>; NJ Sebire<sup>1</sup>

<sup>1</sup>Institute of Child Health, London, United Kingdom; <sup>2</sup>Biological Mass Spectrometry Centre, Institute of Child Health, London, United Kingdom; <sup>3</sup>Great Ormond Street Hospital, London, United Kingdom

Purpose of the study: Current methods of investigating SUDI identify a cause of death in a third of cases but the majority remain unexplained. Recent technical advances in proteomics offer novel methods for the investigation of SUDI. We describe proof of principle, providing a comparative analysis of liver proteomic analysis in sepsis and non-sepsis SUDI deaths.

Methods: Two paediatric SUDI autopsies were identified, where frozen liver samples were available, one representing definite systemic sepsis and one in whom the cause remained undetermined with sterile cultures. Liver samples underwent label-free quantitative mass spectrometry analysis (MSE).

Results: Case A had negative ancillary tests and a final cause of death as unexplained SUDI (uSUDI); Case B had proven Streptococcal Sepsis. 193 protein sequences were identified in A vs. 135 in B. Of these, 8 were differentially identified, demonstrating at least a 2-fold difference (considered significant) between cases. There were 4 proteins which were significantly increased in sepsis, compared to uSUDI, including Histone H3.3 and Annexin A2. Of the proteins which were significantly reduced in the sepsis case, these included Calreticulin and Cytochrome P450 2C9.

Conclusion: Proteomic analysis of autopsy liver tissue in SUDI is possible and demonstrates differential protein expression according to cause / mode of death. These findings demonstrate possible sepsis-specific changes. Cytochrome P450 2C9 is down regulated in the presence of inflammatory cytokines, and extracellular histone release may contribute to organ failure and death in sepsis. Proteomic analysis may develop an important role in investigating the cause / mode of death in future. Larger studies are in progress to determine efficacy in a large cohort of cases.

▶ 10.30 – 11.00

Kapittelzaal – Storey

**COFFEE**

## ORAL COMMUNICATIONS

**Categories: Cellular/Molecular; Osteoarticular/Soft Tissue**

Chair: Dr R Byers, University of Manchester, UK

Dr RG Forsyth, Ghent University Hospital, Ghent, Belgium

11.00–11.15 **[O35] Involvement of Vascular Endothelial Growth Factor Receptors in Endothelial Cell Response to Galectin-1 and Galectin-3**Ⓟ N D'Haene<sup>1</sup>; S Sauvage<sup>1</sup>; C Maris<sup>1</sup>; AL Trepant<sup>1</sup>; M Le Mercier<sup>1</sup>; C Decaestecker<sup>2</sup>; I Salmon<sup>1</sup><sup>1</sup>Department of Pathology Erasme Hospital, Brussels, Belgium; <sup>2</sup>Laboratory of Image Synthesis and Analysis, Faculty of Applied Sciences; Université Libre de Bruxelles (ULB), Brussels, Belgium

Tumour-associated endothelial cells (TAEC) differ from normal endothelial cells (EC). In the current study, we confirm that TAEC are characterized by higher VEGFR1 expression and lower VEGFR2 expression compared to normal EC. Characterization of two EC lines (EA.hy926 and HUVEC) revealed that EA.hy926 cells more closely resemble TAEC than HUVEC in terms of morphology, gene expression and protein expression. Because galectin-1 and galectin-3 are involved in angiogenesis, we analyzed the effects of extracellular galectin-1, galectin-3 or their combination in EA.hy926 and HUVEC. The combination of galectin-1 and galectin-3 had an additive effect on HUVEC tube formation via Vascular Endothelial Growth Factor Receptor-2 (VEGFR2) activation only and a synergistic effect on EA.hy926 cell growth and tube formation. This synergistic effect may be explained by concurrent activation of VEGFR1 and VEGFR2. Downstream pathways of galectin-induced VEGFR activation involved extracellular signal-regulated kinase 1/2 and heat-shock protein 27. Collectively, these data suggest that galectin-1 and -3 have a synergistic effect on angiogenesis in the tumour environment.

11.15–11.30 **[O36] Giant Cell Tumour of Bone: The Extracellular Matrix Integrity Plays A Critical Role In Its Biology And Clinical Behaviour**Ⓟ MCS Lieveld<sup>1</sup>; AM Cleton-Jansen<sup>2</sup>; E Korshing<sup>3</sup>; MS Benassi<sup>4</sup>; P Picci<sup>4</sup>; G Sys<sup>5</sup>; B Poffijn<sup>5</sup>; NA Athanasou<sup>6</sup>; PCW Hogendoorn<sup>2</sup>; RG Forsyth<sup>1</sup><sup>1</sup>N. Goormaghtigh Institute of Pathology, University Hospital Ghent, Ghent, Belgium; <sup>2</sup>Dept of Pathology, Leiden University Medical Center, Leiden, Netherlands; <sup>3</sup>Institute of Bioinformatics, University of Muenster, Muenster, Germany; <sup>4</sup>Laboratorio di Ricerca Oncologica, Istituto Ortopedico Rizzoli, Bologna, Italy; <sup>5</sup>Department of Orthopaedic Surgery, University Hospital Ghent, Ghent, Belgium; <sup>6</sup>Department of Pathology, Nuffield Department of Orthopaedic Surgery, Nuffield Orthopaedic Centre, Oxford, United Kingdom

Purpose of the study: Giant cell tumour of bone (GCTB) displays unpredictable and worrisome clinical features such as recurrences and occasionally metastatic disease. Research aimed at understanding its biology has been challenging because of its heterogeneous composition of mononuclear and multinucleated cells. Therefore, predicting its behavior only by morphology has been largely frustrating.

Materials and methods: In this study, gene expression profiles of seven strict clinically defined groups of GCTB were determined by use of the Illumina Human -6 v2 Expression BeadChip microarrays and interpreted by hierarchical clustering and balanced score testing (n=33). The most promising differentially expressed genes were validated by qPCR as potential biomarkers in a larger GCTB group (n=41). Corresponding protein expression was validated by immunohistochemistry.

Results: Unsupervised hierarchical clustering reveals three major clusters: a metastatic and a heterogeneous, non-metastatic GCTB cluster and an ABC cluster. Volcano plots indicate lumican (LUM) and decorin (DCN) as most promising, differentially lower expressed in the metastatic group. In search for genes associated with recurrences, dermatopontin (DPT) was also found showing a differentially lower expression in recurrences. Hierarchical clustering suggests that non-metastatic GCTB lesions share a common genetic expression profile, which differs significantly from lung metastases.

Discussion: Differentially expressed genes related to the extracellular matrix integrity (LUM, DCN, DPT) turns out to be most promising as biomarkers for metastatic and recurrent disease. Lower expression of these proteins indicates loss of extracellular matrix integrity and therefore an impaired defense against tumoral expansion and spread. In conclusion, the extracellular matrix integrity plays a critical role in the biology of GCTB.

11.30–11.45 **[O37] Characterisation of Wnt Signaling Pathway in Rhabdomyosarcoma**Ⓟ AS Rao<sup>1</sup>; S Cialfi<sup>2</sup>; C Dominici<sup>2</sup>; S Yao<sup>3</sup>; CS Foster<sup>3</sup>; G Kokai<sup>1</sup>; TR Helliwell<sup>3</sup>; HP McDowell<sup>4</sup><sup>1</sup>Department of Paediatric Histopathology, Royal Liverpool Children's NHS Trust, Liverpool, United Kingdom; <sup>2</sup>Department of Paediatrics, La Sapienza University, Rome, Italy; <sup>3</sup>Department of Histopathology, Royal Liverpool University Hospital, Liverpool, United Kingdom; <sup>4</sup>Department of Paediatric Oncology, Royal Liverpool Children's NHS Trust, Liverpool, United Kingdom

Beta-catenin, a multifunctional nuclear transcription factor in the canonical Wnt signaling pathway, is active in myogenesis and embryonal somite patterning. Dysregulation of Wnt signaling facilitates cancer invasion and metastasis in various tumours. We undertook this work to characterise Wnt/beta-catenin signaling in rhabdomyosarcoma (RMS) and to investigate if Wnt/beta-catenin pathway is functionally active, in order to improve our understanding of the molecular mechanisms operative in RMS.

Beta-catenin expression was evaluated on previously confirmed RMS cases by tissue microarray analysis (n = 35). Our data indicated that 17/34 RMS (alveolar RMS - 9/14; embryonal RMS - 8/20) expressed beta-catenin in either cytoplasm or membrane or both. Nuclear positivity was seen in 2/34 cases of embryonal RMS. One case was excluded from study.

11.45–12.00

**[O38] Chondroclasts Are Mature Osteoclasts Which Are Capable Of Cartilage Matrix Resorption**

H Knowles<sup>1</sup>; MS Thompson<sup>1</sup>; J Grünhagen<sup>1</sup>; TG Kashima<sup>2</sup>; XG Cheng<sup>1</sup>; Ⓟ NA Athanasou<sup>3</sup>

<sup>1</sup>Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom; <sup>2</sup>Department of Histopathology, Nuffield Orthopaedic Centre, Oxford, United Kingdom; <sup>3</sup>University of Oxford / Nuffield Orthopaedic Centre, Nuffield Department of Orthopaedics, Rheumatology, United Kingdom

Osteoclasts are multinucleated cells which are specialised to carry out mineralised bone resorption.

Multinucleated cells found at sites of unmineralised hyaline cartilage erosion, termed chondroclasts, but their relationship to osteoclasts and their precise nature is uncertain.

Neoplastic and non-neoplastic subchondral bone lesions showing evidence of cartilage resorption were examined histologically and multinucleated cells resorbing cartilage were characterised immunohistochemically. In cell culture studies, mature human osteoclasts derived from monocyte precursors and giant cell tumour of bone (GCTB) were cultured for up to 48 hours on slices of human cartilage and release of glycosaminoglycans (GAG) and MMP13 activity measured by ELISA.

Multinucleated cells actively resorbing cartilage (chondroclasts) were frequently seen in GCTBs that had extended through the subchondral bone plate; these cells were directly apposed to the resorbed cartilage surface or separated from it by a layer of mononuclear stromal cells. Chondroclasts expressed an osteoclast-like immunophenotype (CD45+, CD14-, HLA-DR-, CD163-, CD51+). Non-neoplastic lesions exhibiting cartilage resorption (eg rheumatoid disease, bone infection) also contained chondroclasts on the surface of mineralised and unmineralised cartilage. Monocyte-derived and GCTB-derived osteoclasts cultured on cartilage resulted in GAG release and increased MMP13 activity relative to negative control.

These findings indicate that mature osteoclasts are capable of cartilage matrix resorption and that they share phenotypic features with multinucleated cells that are termed chondroclasts. These multinucleated cells are likely to play a role in the degradation of mineralised and unmineralised cartilage in joint disease and in the chondrolysis associated with the growth of subchondral benign and malignant neoplastic lesions of bone.

▶ 09.10 – 17.00

Room Priorzaal – First Floor

**COMPANION MEETING – ASSOCIATION OF CLINICAL ELECTRON MICROSCOPISTS**  
— see separate programme

▶ 12.00 – 13.00

Room Refter – Storey

**PATHOLOGICAL SOCIETY OF GREAT BRITAIN & IRELAND'S  
30<sup>th</sup> CL OAKLEY LECTURE**

Chair: Prof IO Ellis, Meetings Secretary, Pathological Society of Great Britain & Ireland

**[S22] Predicting Benefit from Anti-Angiogenic Therapies**

Ⓟ Dr AM Jubb

University of Oxford, Oxford, United Kingdom

Angiogenesis is a universal requirement for solid tumour growth beyond the limits of oxygen diffusion. Among the regulators of angiogenesis, preclinical data support a dominant role for vascular endothelial growth factor-A (VEGF) in early malignancy. These observations prompted the development of bevacizumab, a monoclonal antibody against VEGF. As VEGF is widely expressed in cancer, the assumption was made that bevacizumab would show efficacy in unselected patients. Indeed, in the pivotal phase 3 trial, the addition of bevacizumab to chemotherapy demonstrated a 4.5 month improvement in median overall survival in metastatic colorectal cancer. Using tissues from this trial, we were able to refute preclinical data suggesting that p53 and k-ras mutations predict the relative sensitivity of tumours to anti-VEGF therapies. This was to prove pivotal when bevacizumab's competitor, cetuximab, was shown to only work in colorectal cancers with wild-type k-ras. Moreover, unlike other targeted therapies (e.g. trastuzumab), we demonstrated that the efficacy of bevacizumab was not predicted by the expression of its target (VEGF). However, it soon became apparent that response rates were not able to distinguish benefit from bevacizumab. Moreover, bevacizumab failed to demonstrate meaningful improvements in progression-free or overall survival in breast cancer. We subsequently investigated several putative biomarkers of bevacizumab activity that had been identified as predictive markers from preclinical studies. These preliminary data suggest that DLL4, neuropilin-1, and VEGF-C may all predict benefit from bevacizumab. This presentation will review the clinical development of bevacizumab and its putative biomarkers. In addition, future directions for bevacizumab biomarker development will be explored, including the use of novel neoadjuvant phase II studies with primary endpoints that include biomarker discovery.

**THURSDAY 12 MAY — continued**

▶ 13.00 – 14.00

Corridor

**LUNCH and TRADE STANDS**

▶ 13.15 – 14.15

Room Rector Vermeylen – Second Floor

**TRAINEES SESSION – MEET THE EXPERTS**

Chair: Dr K Lambein, Ghent University Hospital, Ghent, Belgium

***Preneoplastic Lesions of the Breast***

Prof S Pinder, Guy's Hospital, London, UK

▶ 13.30 – 14.30

Room Rector – Storey

**PATHOLOGICAL SOCIETY OF GREAT BRITAIN & IRELAND'S  
ANNUAL BUSINESS MEETING**

— *Members only*

(Agendas will be sent to Members)

▶ 14.15 – 15.00

Corridor

**CHAIRMAN'S POSTER ROUNDS**

CATEGORY	POSTER NUMBER	CHAIR
Autopsy/Forensic	P42	Dr EW Benbow, Manchester, Dr JWM Chow, London and Dr MN Sheppard, London
Cardiovascular/Pulmonary	P43	
Education & Audit	P44–P47	
Endocrine	P48	Dr AM McNicol, Brisbane
Genitourinary/Renal	P49, P51–P55*	Prof S Fleming, Dundee and Dr ISD Roberts, Oxford
Gynaecological	P56–P63	Prof P Delvenne, Liege and Dr K Lambein, Ghent
Head & Neck	P64–P65	Dr AM McNicol, Brisbane
Hepatobiliary/Pancreas	P66–P70	Prof AD Burt, Newcastle-upon-Tyne
Lymphoreticular	P72–P75*	Dr N Rooney, Bristol
Osteoarticular/Soft Tissue	P76–P77	Dr R Forsyth, Ghent and Dr N Kirkham, Newcastle-upon-Tyne
Skin	P78–P79	

\* P50 and P71 have been withdrawn

▶ 15.00 – 17.00

Room Rector – Storey

**PLENARY ORAL PRESENTATIONS**

Chair: Prof IO Ellis, University of Nottingham, Nottingham, UK

Dr ISD Roberts, John Radcliffe Hospital, Oxford, UK

15.00–15.15

**[PL1] *Mir141 and Mir200c Regulate Progenitor Cell Features in Hepatocellular carcinomas.***

Ⓟ O Govaere<sup>1</sup>; J Berkers<sup>1</sup>; L van Kempen<sup>2</sup>; K Van den Eynde<sup>1</sup>; M Komuta<sup>1</sup>; B Spee<sup>1</sup>; R Aerts<sup>1</sup>; B Topal<sup>1</sup>; F Nevens<sup>1</sup>; E Lerut<sup>1</sup>; J Van den Oord<sup>1</sup>; T Roskams<sup>1</sup>

<sup>1</sup>University Hospitals Leuven, Leuven, Belgium; <sup>2</sup>McGill University/Jewish General Hospital, Montreal, Canada

The heterogeneous nature of hepatocellular carcinomas (HCCs) is reflected by a variable clinical outcome. Keratin(K) 19 positivity in HCC has been correlated with a higher recurrence and shorter overall survival. Nevertheless the underlying mechanisms that regulate progenitor cell features in HCCs still remain unclear. In this study we want to unravel those mechanisms on an epigenetic level. Genome wide RT<sup>2</sup> miRNA PCR Arrays were performed on K19 positive and negative HCC liver biopsies(n=10). Synthetic miRNAs were transfected into PLC/PRF/5 cell line for transient overexpression and knockdown. The biological effect was objectivised by means of qPCR and correlated with human HCC samples(n=14). Localization of miRNAs and target proteins was obtained by means of in situ hybridization and immunohistochemistry(n=20). MicroRNA profiling of K19 positive HCCs reveals a signature involving metastasis pathways and cholangiocyte/hepatoblastoma characteristics. In addition there is a strong decline in the expression of mir-122, known to be enriched in healthy liver tissue. Mir-141, mir-200c and mir-429 are strongly up-regulated in K19 positive HCCs, whereas

mir-885-5p was significantly reduced. Overexpression of mir-141 as well as mir-200c in a PLC/PRF/5 cell line induced the expression of several known progenitor cell markers (i.e. KRT19, KRT7, EPCAM) and reduced typical hepatocytic markers (i.e. ALB, HNF4A). In situ hybridization revealed that mir-141 and 200c are located in cholangiocytes and hepatic progenitor cells, which supports the idea of progenitor-derived origin of K19 positive HCCs. The microRNA profile of K19 positive HCCs poses new insights into the pathogenesis of this aggressive subtype of HCCs. Several microRNAs regulate the progenitor features in HCCs and are also found in the non-neoplastic progenitor cells, indicating that the same mechanisms are active in human progenitor cells and K19 positive HCCs.

15.15–15.30

**[PL2] STAT3 Regulates the Expression and the Transcriptional Activity of  $\beta$ -Catenin in Colorectal Cancer**

Ⓟ S Ibrahim; K Baloch; S Al-Ghamdi; B Muhammad; AS Nateri; M Ilyas

*University of Nottingham, Nottingham, United Kingdom*

Aberrant Wnt signalling is involved in the development of a variety of different types of tumour. Colorectal cancer (CRC) is a paradigm of Wnt signalling induced carcinogenesis and, in this model, mutation of the APC gene results in increased levels of  $\beta$ -catenin protein. A variety of feedback and feed-forward loops operate to maintain  $\beta$ -catenin protein at "just right" levels. Activation of the Signal Transducers and Activator of Transcription 3 (STAT3) pathway is also a common early finding in diverse tumours. It is generally believed that this pathway affects  $\beta$ -catenin protein although the precise effects are uncertain. Herein we investigated the effect of STAT3 signalling on  $\beta$ -catenin expression. Expression of STAT3 was reduced by RNA interference in five different colorectal cancer cell lines (SW620, HCA46, HT29, SW480 & HCT116). The effect of STAT3 knockdown on  $\beta$ -catenin protein was assessed by Western blot and, in every cell line, a STAT3 knockdown resulted in a reduction in  $\beta$ -catenin protein levels. In order to ascertain whether this was mediated through altered gene transcription or altered degradation,  $\beta$ -catenin mRNA levels were measured by quantitative RT-PCR and protein degradation was prevented by proteasome inhibition. The levels of  $\beta$ -catenin mRNA fell in parallel with the protein levels whilst the inhibition of proteasomal degradation did not prevent a reduction in  $\beta$ -catenin protein after STAT3 knockdown.

Having shown that STAT3 regulates  $\beta$ -catenin, we sought to demonstrate the effect of these changes on transcription. The TOPflash/FOPflash dual luciferase reporter system is used to monitor  $\beta$ -catenin transcriptional activity and, with this system, we demonstrated that STAT3 knockdown resulted in a reduction in  $\beta$ -catenin mediated transcription.

15.30–15.45

**[PL3] Urine Cytology: Does it Have a Role in the Investigation of Haematuria?**

Ⓟ N Onwu<sup>1</sup>; CGT Blick<sup>2</sup>; S Nazir<sup>3</sup>; S Mallett<sup>3</sup>; BW Turney<sup>2</sup>; ISD Roberts<sup>1</sup>; JP Crew<sup>2</sup>; NC Cowan<sup>2</sup>

<sup>1</sup>The John Radcliffe Hospital, Oxford, United Kingdom; <sup>2</sup>The Churchill Hospital, Oxford, United Kingdom; <sup>3</sup>University of Oxford, Oxford, United Kingdom

Current guidelines recommend the use of urine cytology in the investigation of haematuria. In this study, we evaluate the diagnostic accuracy of urine cytology, CT urography (CTU) and flexible cystoscopy in a consecutive series of 778 patients referred to a one-stop haematuria diagnosis clinic. Criteria for referral were at least one episode of macroscopic haematuria and age >40 years. On the same day, patients underwent examination by a nurse specialist followed by urine cytology, CTU and flexible cystoscopy.

After a follow-up of 21-66 months, 156/778 (20.1%) patients were diagnosed with urothelial carcinoma (UC) of bladder on rigid cystoscopy and biopsy. Urine cytology was scored as: 0 = inadequate or no specimen, 1 = benign, 2 = atypical probably benign, 3 = atypia of uncertain significance, 4 = atypia suspicious of malignancy and 5 = malignant. The frequency of malignancy (bladder and upper tract UC) on follow-up, according to cytology was as follows: 13/45 (28.9%) scored 0, 44/511 (8.6%) scored 1, 13/61 (21.3%) scored 2, 40/80 (50%) scored 3, 23/31 (74.2%) scored 4 and 43/50 (86%) scored 5.

Urine cytology (4-5 positive) showed low sensitivity for UC bladder 0.38 (0.31-0.45) compared to CTU & flexible cystoscopy 1.00 (0.98-1.00). Specificity for all methods was identical 0.98 (0.97-0.99). There were no cases of histologically proven UC in whom urine cytology was positive and CTU and flexible cystoscopy were negative. The 52 patients with abnormal cytology, despite normal cystoscopy and upper tract imaging, were subjected to further evaluation. The cost of urine cytology and these additional investigations was £50,535.

We conclude that urine cytology performed in the context of a hospital haematuria rapid diagnosis clinic utilising CTU and flexible cystoscopy is a redundant test and can be dropped from the diagnosis pathway, saving money and unnecessary investigation.

15.45–16.00

**[PL4] Lineage Tracing to Seek Multipotential Progenitor Cells in Adult Human Kidney**

S Canadillas<sup>1</sup>; NT Gaisa<sup>1</sup>; R Jeffery<sup>1</sup>; J Becker<sup>2</sup>; MR Alison<sup>3</sup>; N Wright<sup>4</sup>; Ⓟ R Poulson<sup>1</sup>

<sup>1</sup>Histopathology Lab, CRUK-London Research Institute, London, United Kingdom; <sup>2</sup>Institut für Pathologie, Medizinische Hochschule Hannover, Hannover, Germany; <sup>3</sup>Queen Mary University of London, London, United Kingdom; <sup>4</sup>Barts and the London School of Medicine and Dentistry, London, United Kingdom

**PURPOSE** Replacement of epithelial cells within the nephrons of adult mammalian kidney is generally thought to be via division of differentiated cells, however recent evidence in mice supports a common origin of parietal/podocyte and proximal tubule lineages. We aimed to test an alternative hypothesis, namely that phenotypically distinct epithelia have a clonal origin.

**METHODS** We identified cell fates by lectin histochemistry and combined this with detection of patches of cells in which mitochondrial cytochrome C oxidase (CCO1) expression was absent. For detection of CCO1-null patches we used either: immunofluorescence-histochemistry for CCO1 and Porin on formalin fixed paraffin embedded tissue, or enzyme-histochemistry for CCO1 and succinate dehydrogenase (SDH), on frozen tissue. CCO1-active and deficient areas were laser-capture-microdissected. The entire mitochondrial genome (mtDNA) was amplified using a nested PCR protocol and sequenced for mtDNA-mutations.

THURSDAY 12 MAY — *continued*

RESULTS Putative clonal patches were readily detected in normal kidney, especially in elderly persons' tissue, consistent with the age-related accumulation of mtDNA-mutations reported in other organs. Cells within a CCO1-deficient region contained an identical mtDNA-mutation, suggesting a common adult progenitor. 3D-reconstruction revealed phenotypic boundaries within small CCO-null-patches, suggesting that a common progenitor provides for maintenance of different epithelial cell types, and with progeny not migrating far along tubules.

CONCLUSIONS Our results demonstrated that normal kidney shows CCO1-negative patches developed by mutations, indicating a clonal origin. Some patches showed different types of epithelium; these could not form if division of differentiated cells always produced identical daughters. Daughter cells might choose different fates by following cues from neighbouring cells and/or stroma.

16.00–16.30

**TEA** [Kapittelzaal – Storey]

16.30–16.45

**[PL5] Analysis of the Role of MicroRNAs within Stromal Fibroblasts in Breast Cancer**

Ⓟ ET Verghese; MA Hull; AM Hanby; TA Hughes

*Leeds University, Leeds, United Kingdom*

Both epithelial cells and adjacent stromal fibroblasts exhibit changes in gene expression during carcinogenesis. Molecular pathways responsible for these changes have been more thoroughly studied in epithelial cells than in fibroblasts, despite the fact that fibroblasts adjacent to carcinoma cells ("carcinoma-associated fibroblasts", CAFs) have important influences on cancer behaviour. MicroRNAs have been shown to play critical roles in controlling gene expression in epithelial cells of many cancers while potential analogous roles for microRNAs within CAFs remain un-explored.

In order to identify microRNAs that may act in CAFs to modify cancer behaviour we examined archival cancer tissue and used a tissue culture model. First, we micro-dissected normal fibroblasts (NFs) and CAFs from a breast cancer FFPE sample (grade-2 invasive-ductal-carcinoma, ER+ PR+ Her-2-) and determined expression levels of 723 individual microRNAs using microarrays. Secondly, we examined fibroblast microRNA expression in immortalised breast fibroblasts co-cultured with either a normal breast epithelial cell line, representing NFs, or with a breast carcinoma cell line, representing CAFs. In each case, expression in the NFs was compared to the CAFs and differentially expressed microRNAs were identified.

70 miRNA showed consistent differences in expression between NFs and CAFs in both models. 10 were selected for further analyses based on either the magnitude of differential expression (>10 fold), or evidence in literature for roles in cancer or fibroblast function. Expression was examined in 10 further matched pairs of NFs and CAFs from breast cancer FFPE samples; initial results show miR-26b to be down-regulated in CAFs in majority of cases.

This research was supported by a Pilot study grant from Path Soc and BCC.

16.45–17.00

**[PL6] Screening for Genes that Cooperate with Mutant RAS Identified NRBP1 as a Novel Tumour Suppressor that Regulates the WNT Pathway**Ⓟ MJ Arends<sup>1</sup>; CH Wilson<sup>2</sup>; GB Poulin<sup>3</sup>; C Crombie<sup>2</sup>; AG Rust<sup>2</sup>; NH March<sup>4</sup>; G Poulgiannis<sup>5</sup>; AG Fraser<sup>6</sup>; DJ Adams<sup>2</sup>

<sup>1</sup>University of Cambridge Pathology Department, Cambridge, United Kingdom; <sup>2</sup>Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, United Kingdom; <sup>3</sup>Faculty of Life Sciences, University of Manchester, Manchester, United Kingdom; <sup>4</sup>Cancer Research UK Cambridge Research Institute, Cambridge, United Kingdom; <sup>5</sup>Division of Systems Biology, Harvard Medical School, Boston, United States; <sup>6</sup>Donnelly CCB, University of Toronto, Toronto, Canada

Purpose: To discover novel cancer genes that can cooperate with mutant Ras. Methods: RNAi screening was used to identify genes that modulate vulva development in the nematode worm *C. elegans*, as there are many conserved genes involved in both development and carcinogenesis. A kinome-wide RNAi screen was performed in *C. elegans* worms with mutant *let60* gene (equivalent to gain-of-function mutant Ras). The gene identified was further investigated in mouse models and in human tumour data.

Results: This RNAi screen revealed that the worm orthologue of the nuclear receptor binding protein, *Nrbp1*, co-operates with mutant Ras to promote a multivulval phenotype in the worm. Suppression of *Nrbp1* in mouse NIH3T3 cells together with expression of mutant Ras resulted in enhanced transformation. Germline deletion of *Nrbp1* in the mouse resulted in embryonic lethality, whereas somatic deletion in all tissues of adult mice resulted in profound changes to the proliferation and differentiation of intestinal cell lineages with 80% of mice dying within 10 days. Expression analysis of intestinal tissues from these mice revealed transcriptional activation of Wnt pathway targets. Knockdown of NRBP1 in human HCT-116 and SW480 cell lines using siRNA confirmed activation of WNT reporters. Mosaic somatic deletion of *Nrbp1* in the mouse circumvented the lethality and resulted in intestinal tumourigenesis, with tumours staining positively for Wnt targets such as *c-Myc*. In humans, NRBP1 expression is lower in a range of tumours relative to matched controls and in lung adenocarcinomas low NRBP1 expression correlates with reduced survival.

Conclusion: Thus, we have shown that NRBP1 is a novel tumour suppressor gene that encodes a regulator of the WNT pathway.

**PATHOLOGICAL SOCIETY OF GREAT BRITAIN & IRELAND'S  
9<sup>th</sup> DONIACH LECTURE**

Chair: Prof AH Wyllie, President, Pathological Society of Great Britain & Ireland

**[S23] Colorectal Cancer : from Dukes to Genes**

Ⓟ Prof FT Bosman

*University Institute of Pathology, Lausanne, Switzerland*

As is almost invariably the case when a new disease entity is defined, characterising elements are those that all cases have in common. Surgeons involved in the care of colorectal cancer (CRC) patients soon realised that individual cases are different: tumours with the same name are heterogeneous. The differences in extension perceived by Dukes (1932), refined by Kirklin (1949) and subsequently Astler and Coller (1953) and Turnbull (1967) resulted in the Dukes classification of CRC, in use until the end of the 20th century. With the introduction of TNM for colon cancer (1983) and AJCC stage grouping, TNM has become the generally accepted approach towards staging, which remains the crucial parameter in clinical decision making. Exploration of its molecular characteristics has been popular ever since Fearon and Vogelstein (1990) proposed a genetic model for the development of CRC. Microsatellite instability and CpG island methylation were subsequently recognised as new molecular pathways. But only in the last 5 years has molecular analysis, focusing on the EGF-receptor and signaling pathways downstream of it –KRAS gene mutation status predicting the response to drugs targeting the EGFR, become an essential step in the assessment of CRC. In parallel, molecular analyses have shown that BRAF mutated cancers have a worse, microsatellite instable (MSI-H) cancers a better prognosis and respond differently to adjuvant therapies. Comprehensive molecular annotation of large CRC collections, for which detailed clinical data are available, allow us now to unravel heterogeneity of this disease at a molecular level. CRC will ultimately appear to be a collection of entities, defined by characteristic molecular profiles justifying specific therapeutic approaches. Clinical trials on which are grafted translational studies, focusing on molecular characterisation of tissue specimens, will allow us to reach this goal.

**CONFERENCE DINNER**

19.00–19.45	Organ Recital
19.45–20.15	Drinks Reception
20.15–22.30	Dinner

**FRIDAY 13 MAY**

▶ 08.15

Reception

**REGISTRATION and COFFEE**

▶ 08.30 – 12.00

Room Sacriste – Storey

**SLIDE SEMINAR CASE VIEWING**

***Tumours of the Skeleton: Test Your Knowledge up to the Bare Bone***

▶ 08.30 – 10.50

Room Rector Vermeylen – Second Floor

**TRAINEES SYMPOSIUM**

***Urological Neoplasia***

Chair: Dr S Verscheure, Ghent University Hospital, Ghent, Belgium

Dr L Ferdinande, Ghent University Hospital, Ghent, Belgium

08.30–09.00

**[S28] *Macroscopy of Urothelial and Kidney Neoplasms***

Ⓟ Dr DM Berney

*Barts and The London School of Medicine and Dentistry, London, United Kingdom*

Meticulous urological specimen handling is vital in urothelial and renal specimens, since macroscopic features result in clinico-pathologic knowledge that determines prognosis and additional treatment.

For renal tumours, assessment of fat invasion, both into the medullary sinus and into peri-nephric fat requires precise handling to sample the interface between the tumour and adipose tissue. Recording tumour size also impacts into the TNM staging. All potential lymph nodes, the adrenal if present, resection margins of the ureter and renal vein as well as potential areas of invasion into the main renal vein or its segmental tributaries should be identified. Areas where the cut surface of the tumour appears pale may indicate sarcomatoid change. The identification of necrosis is important for prognostic scoring and in the assessment of pre-treated samples. Areas where tumour is closest to a resection margin are especially important in partial nephrectomy specimens which are increasingly common. Radical cystectomies are difficult to orientate. In men, the prostate is also usually received, and in women, a hysterectomy is often performed. The specimen may be orientated by identification of the adjacent organs. Sampling of ureteric and urethral margins is important, as well as full thickness representative sections of the bladder wall to assess T staging. The presence of tumour in the perivesical fat should be noted as macroscopic identification of invasion upstages the tumour to the pT3b category. Thorough sampling of the prostate and representation of the prostatic resection margins are helpful to identify urothelial carcinoma and synchronous prostatic adenocarcinomas.

09.00–09.40

**[S29] *Problems and Pitfalls in Urothelial Biopsy Interpretation***

Ⓟ Dr GJL Van Leenders

*Erasmus Medical Center, Rotterdam, Netherlands*

In the WHO classification three groups of (pre)malignant urothelial lesions are recognized. Urothelial dysplasia and carcinoma-in-situ (CIS) are considered flat lesions (a), of which the latter urges clinical intervention by bladder instillations or surgery. Problems in the diagnosis of CIS can occur, especially in recognition of less frequent subtypes such as the small cell or micropapillary variant, and in the differential diagnosis of mimickers such as reactive atypia in the scope of inflammation or following previous radiation or chemotherapy. The most frequent group of urothelial tumours has a papillary growth pattern (b). Although usually straightforward, papillary cystitis and papillary nephrogenic adenoma can be misdiagnosed as urothelial carcinoma and lead to unnecessary treatment. A subgroup of urothelial tumours predominantly has an inverted growth pattern (c). Their relative infrequent occurrence can lead to confusion in their recognition. In addition, benign florid proliferation of Von Brunns nests and some aggressive variants of invasive urothelial carcinoma such as nested variant might result in the over- or under-diagnosis of a more serious lesion. Irrespective of WHO sub-classification, urothelial carcinomas can either be non-invasive (pTa/ pTis), invasive in the mucosa (pT1), detrusor muscle (pT2) or beyond (pT3, pT4). For clinical decision-making, specific distinction should be made between pTa/pTis/pT1 tumours and tumours that have infiltrated in deeper layers of the urinary bladder (pT2-4). Determining the level of invasion not infrequently gives rise to problems. The muscularis mucosae can be confused with detrusor muscle; extensive stromal reaction can histologically mimic the detrusor muscle; and it is not well defined whether detrusor invasion should be diagnosed if tumour is located adjacent to but not in between muscle fascicles.

09.40–10.10

**[S30] *The Role of Cytology in Detecting Urological Neoplasia***

Ⓟ Dr ISD Roberts

*John Radcliffe Hospital, Oxford, United Kingdom*

Urine cytology continues to be used for both the primary detection and surveillance of urothelial carcinoma. It has high specificity but low sensitivity, particularly in the detection of low grade urothelial tumours. Retrospective review of urine cytology, following definitive biopsy diagnosis, indicates that one third of discrepancies between cytology and histology are due to "errors" in interpretation. The other two thirds result from sampling error or poor specimen quality. Reactive urothelial changes associated with inflammation or stones may be difficult to distinguish from low grade neoplasia and "atypical cells" is a frequently used term. The meaning and use of "atypical" differs between pathologists, but is generally associated with an increased

risk of malignancy. Similarly the interpretation of an "atypical" report differs between urologists, with many regarding it as equivalent to benign. In bone marrow or renal transplant patients, polyoma virus infection results in "decoy" cells that resemble high grade urothelial carcinoma and that may result in a false positive diagnosis of malignancy. A number of urinary markers, including immunoassays and FISH, are available as a supplement or alternative to cytology. In general, they are more sensitive but less specific than urine cytology. When CT urography and flexible cystoscopy are used routinely for the investigation of haematuria, urine cytology is a redundant test, as a result of its low sensitivity.

10.10–10.50

**[S31] Differential Diagnosis of Malignant Kidney Tumours**

Ⓟ Prof Dr E Lerut

*University Hospitals Leuven, Leuven, Belgium*

A diverse spectrum of renal neoplasms can arise in the human kidney, depending on age and clinical features. In the main part of cases the diagnosis is made on histology only, although in a non-negligible number of cases immunohistochemical panels are to be used to make the diagnosis, to subtype the renal tumour, or to differentiate it from metastatic neoplasms. This presentation on renal malignancies will give an overview on macroscopic and microscopic findings with the focus on immunohistochemical panels useful in daily pathology practice. A brief part will cover genetic-morphological features as they are usable in the clinics.

10.50–11.00

**COFFEE [Kapittelzaal – Storey]**

▶ 09.00 – 12.00

Room Refter – Storey

**SYMPOSIUM**

***Recent Evolutions in Endocrine Pathology***

Chair: Dr A Hoorens, UZ, Brussels, Belgium

Prof GT Williams, Cardiff University, Cardiff, UK

09.00–09.30

**[S24] Thyroid Carcinoma after Chernobyl: An Update**

Ⓟ Prof Sir ED Williams

*Cambridge University, Cambridge, United Kingdom*

Millions of people were exposed in 1986 to radioactive isotopes in fallout from the Chernobyl accident, with in the first 20 years a large and continuing increase in thyroid carcinoma incidence. The increase in thyroid carcinoma, attributable to the very large amounts of iodine 131 released, was first noticed in children, with a strong relationship between young age at exposure and risk of developing papillary thyroid carcinoma (PTC). Those exposed at a young age carry their increased risk as they grow older. The extent of the increase, the reasons for the relationship to age at exposure, the reduction in attributable fraction with increasing latency, and the role of environmental factors will be discussed.

The large number of radiation induced PTCs has allowed new observations. The subtype, molecular and clinical findings change with latency. The molecular findings will be considered; the gene rearrangements common in these radiation induced tumours are regarded as reflecting their aetiology. To date rearrangements in RET predominate over point mutations in BRAF in these radiation induced tumours. More information is needed on both breakpoints in the rearrangements and on germline mutations conferring susceptibility to radiation induced PTCs, particularly DNA repair genes.

Current knowledge of radiation effects is largely dependent on evidence from exposure to very high dose rate whole body radiation from the atomic bombs, which led to increases in a wide range of malignancies including thyroid carcinomas. The radiation exposure to fallout after Chernobyl was very different, with a low dose rate and differential organ dose. The type and molecular pathology of the thyroid tumours is predicted to continue changing with increasing latency. Long latency tumours in other organs could occur in the future. A comprehensive follow up must continue for the lifetime of those exposed.

09.30–10.00

**[S25] Adrenal Cortical Lesions**

Ⓟ Prof AM McNicol

*The University of Queensland, Brisbane, Australia*

Adrenal cortical adenomas occur in about 5% of the population while adrenal cortical carcinoma is a rare, but very aggressive, tumour. Most carcinomas are easily diagnosed because they are obviously invasive or metastatic at presentation. However, it is important to identify malignant potential in intra-adrenal tumours. Multifactorial histological approaches have been the most commonly used approach in making the distinction between benign and malignant lesions and the uses and limitations of these will be discussed eg. in the diagnosis of oncocytic tumours.

There are now a number of published studies on molecular genetic changes in benign and malignant tumours, and some have suggested that particular changes have prognostic importance in carcinoma. Abnormalities in the  $\beta$ -catenin pathway and overexpression of fibroblast growth factor 2 (FGF2) in carcinomas appear to be important.

Adrenocortical hyperplasia has long been recognised as associated with Cushing's disease (pituitary-dependent Cushing's syndrome) and ectopic adrenocorticotrophin (ACTH) syndrome. It is now recognised that hyperplasia may also be associated with ACTH-independent Cushing's syndrome, in which the adrenal expresses aberrant receptors and responds to hormones other than ACTH.

FRIDAY 13 MAY — *continued*10.00–10.30 **[S26] Immunohistochemistry in Diagnosis of Paraganglioma and Pheochromocytoma**

Ⓟ Dr FH van Nederveen

*Erasmus MC, Rotterdam, Netherlands*

Pheochromocytomas (PCC) and paragangliomas (PGL) are rare tumours arising from the chromaffin cells in the sympathetic and parasympathetic nervous system. Both tumour types can arise in the context of hereditary tumour syndromes; a proportion of these patients have a positive family history, however, at least 10-30% of patients that are clinically sporadic harbour an SDHB, C or D germ line mutation. These patients are at risk for multiple (malignant) tumours, and therefore should be detected as soon as possible.

PCC arise in the context of Multiple Endocrine Neoplasia type 2 (MEN2), von Hippel-Lindau disease (VHL), neurofibromatosis type 1 (NF1), and the pheochromocytoma-paraganglioma syndrome, a syndrome caused by mutations in one of the genes coding for mitochondrial complex II (SDHA, SDHB, SDHC and SDHD).

PGL are either parasympathetic (head and neck region) or sympathetic (abdomen, bladder) of origin. pPGL are due to a hereditary tumour syndrome in ~70%, mostly due to mutations in one of the genes coding for mitochondrial complex II (SDHA, SDHB, SDHC and SDHD). In rare cases pPGL can arise in the context of VHL and MEN.

PCC and PGL arising in the context of SDHA, B, C or D mutations can be detected by immunohistochemical staining. This is based on the lack of detectable SDHB protein in these tumours, resulting in negative staining of tumour cells. In contrast, all tumours due to MEN2, VHL, NF1 will have positive staining. In addition, SDHA immunohistochemistry can be performed, where only SDHA-related PGL and PCC will show negative staining, whereas SDHB, C and D related cases will have positive staining of the intact SDHA complex.

By routinely doing SDHB immunohistochemistry, hereditary syndromes caused by germline mutations in SDHB, SDHC, or SDHD could be identified with a high degree of reliability.

10.30–11.00 **COFFEE** [Kapittelzaal – Storey]11.00–11.30 **[S27] Endocrine Tumours of the Pancreas: An Update**

Ⓟ Prof G Kloppel

*Department of Pathology, Technical University Munchen, Munchen, Germany*

Pancreatic neuroendocrine neoplasms (P-NENs) have received much attention in recent years regarding incidence, diagnosis, classification, prognosis and treatment. The most recent achievement is the 2010 WHO classification. It stratifies the P-NENs into three groups: neuroendocrine tumours (NETs) that are well differentiated and graded according to their proliferative activity in G1 or G2, and neuroendocrine carcinomas (NECs) that are poorly differentiated, graded G3 and subtyped into small and large cell NECs. Further prognostic stratification is then achieved by staging the tumour extension using the TNM classifications of ENETS and AJCC/UICC. This standardized categorization of P-NENs is the basis for the current therapeutic guidelines adjusted to growth and stage of the individual tumour.

Though all P-NENs have a malignant potential, they differ considerably in their metastasizing capacity.

In addition, they differ in their hormonal cell composition and consequently in the associated hormonal syndromes. Thus, P-NENs producing insulin, glucagon, somatostatin, pancreatic polypeptide, gastrin, vip, serotonin and other hormones show frequently distinct morphological patterns, transcription factor expression and biological behaviour. They seem also to differ at the genetic level. While the well differentiated P-NENs in MEN1 or the recently described glucagons cell adenomatosis require only few genetic changes for the progression from hyperplasia to neoplasia, the development of poorly differentiated P-NENs is based on profound genetic alterations.

11.30–12.00 **Review of the Neuroendocrine Tumours of the Gastrointestinal Tract**

Ⓟ Dr CS Verbeke, St James's University Hospital, Leeds, UK

▶ 09.00 – 09.50

Room Priorzaal – First Floor

**SLIDE SEMINAR COMPETITION DISCUSSION*****Tumours of the Skeleton: Test Your Knowledge up to the Bare Bone***

Chair: Dr R Forsyth, Ghent University Hospital, Ghent, Belgium

Prof PCW Hogendoorn, Leiden University Medical Centre, Leiden, Netherlands

▶ 09.50 – 12.00

Room Priorzaal – First Floor

**SLIDE SEMINAR SESSION**

***Soft Tissue Tumours***

Chair: Dr R Forsyth, Ghent University Hospital, Ghent, Belgium  
Prof PCW Hogendoorn, Leiden University Medical Centre, Leiden, Netherlands

09.50–10.10 ***Cellular Aggressive Angiomyxomyofibroblastoma: Three or One of a Kind?***  
Prof R Sciote, KUL, Leuven, Belgium

10.10–10.30 ***Soft Tissue Tumour and Arthroplasty: An Increasingly Common Combination***  
Prof NA Athanasou, Oxford University, Oxford, UK

10.30–11.00 **COFFEE** [Kapittelzaal – Storey]

11.00–11.20 ***Giant Cell Rich or Giant Cell Tumour: What's the Difference?***  
Dr R Forsyth, Ghent University Hospital, Ghent, Belgium

11.20–11.40 ***Myxoid Soft Tissue Tumours: Progress in Understanding of its Matrix***  
Prof Dr PCW Hogendoorn, LUMC, Leiden, Netherlands

11.40–12.00 ***Pseudomyogenic Hemangi endothelioma***  
Prof P Dei Tos, Treviso Hospital, Treviso, Italy

▶ 12.00 – 13.00

Room Refter – Storey

**THE BRITISH DIVISION OF THE INTERNATIONAL ACADEMY OF PATHOLOGY'S  
GEORGE CUNNINGHAM LECTURE**

Chair: Prof NA Shepherd, Gloucestershire Cellular Pathology Laboratory, Cheltenham, UK

**[S32] *The Terminal Ileum, Follicle Associated Epithelium and M cells: How they  
Manage to Keep our Gut Going Right or Wrong***

Ⓟ Prof CA Cuvelier

*Ghent University, Ghent, Belgium*

The ileal epithelial barrier separating the luminal content from the underlying internal environment and the gut-associated lymphoid tissue (GALT) is permeable and allows uptake of different-sized molecules through an intact layer by active and passive mechanisms. GALT, consists of Peyer's patches, subepithelial lymphoid follicles and mesenteric lymph nodes, and a specialized follicle-associated epithelium (FAE). There are fewer goblet cells resulting in better contacts between luminal content and FAE and there are M cells (membranous or microfold cells). Absence of secretory component in the FAE facilitates uptake of antigens from the intestinal lumen. Less secretory IgA makes the M cell environment more attractive to luminal microbes and antigens. M cell numbers may increase rapidly in inflammatory conditions.

Dendritic cells(DCs), in close contact with the epithelium, can sample mucosal antigens with dendrites extending via tight junctions into the lumen. These sampled luminal microorganisms are subsequently delivered to cells of the mucosal immune system allowing continuous immune surveillance by which protection against harmful pathogens or tolerance to commensal bacteria can be generated. When this delicate balance is disturbed a pathological immune response can occur (allergy, chronic inflammation).

Cross-talk between luminal microorganisms and antigens on the one hand and intestinal epithelium and DCs on the other hand modulates the intestinal immune system. Indeed the interaction of microorganisms and antigens with pattern-recognition (PRRs) or other receptors on the epithelial cells and/or DCs activate various signalling transduction pathways which lead to secretion of growth factors, chemokines and cytokines which influence the outcome of the immune response, but also in immune regulatory and antimicrobial peptides that influence the intestinal homeostasis.

▶ 13.00

Kapittelzaal – Storey

**LUNCH** — *packed lunches to take away*

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***End of Meeting***

## **TRADE EXHIBITION**

### **APERIO**

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# **Abstracts**

## Posters

**P1****C-met Defines a Distinct Subset of Triple Negative Breast Cancer in British Black Women**RL Bowen<sup>1</sup>; Ⓟ C Ho-Yen<sup>1</sup>; R Vaziri<sup>1</sup>; J Hulit<sup>1</sup>; D Ryan<sup>1</sup>; M Ornstein<sup>2</sup>; Y White<sup>2</sup>; C Choy<sup>2</sup>; S Kermorgant<sup>1</sup>; L Jones<sup>1</sup><sup>1</sup>Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; <sup>2</sup>Homerton University Hospital Trust, London, United Kingdom

**Background:** C-met is a receptor tyrosine kinase thought to be an independent poor prognostic factor in breast cancer and is associated with the aggressive basal-like (BL) sub-type. BL tumours are more prevalent in African-American women which may in part explain the poor prognosis for these patients. Cancers that lack expression of ER, PR and Her2 (Triple negative, TN) are often regarded as BL tumours, yet there is increasing evidence that TN tumours are heterogeneous, and can be further subdivided into BL (ER,PR,Her2 negative, CK5/6 or CK14 positive, EGFR positive) and unclassified (U)(negative for all markers). Further definition of the molecular profile and relative proportions of these sub-groups is crucial in understanding the progression of breast cancer in different ethnic groups and in targeting novel therapeutic strategies.

**Aim:** The aim of this study was to use an extended panel of immunohistochemical markers to compare sub-groups of TN tumours in black and white women and to assess the expression of c-met within these groups.

**Methods:** Tissue microarrays were constructed from 248 (113 black women, 135 white) cases of invasive breast carcinoma diagnosed at the Homerton hospital between 2006 and 2009. Immunohistochemistry was performed for ER,PR,Her2, Cytokeratins, EGFR and c-met.

**Results:** 28% of black women had TN tumours versus 17% of white women. Of the TN tumours, in black women 88% were BL and 12% were U; in white women 83% were BL and 17% were U. Overall, c-met was significantly over-expressed in BL compared with U tumours (76% positive versus 0%,  $p=0.006$ ). TN tumours in young black women showed increased expression of c-met compared with young white women (88% versus 0%,  $p=0.004$ ).

**Conclusion:** Our findings suggest that BL tumours are biologically distinct from U tumours and that BL tumours in young black women are frequently c-met positive, which may contribute to the poor clinical course in these patients.

**P2****Subcellular Localisation of Dicer Expression Correlates with Survival and Tumour Subtype in ER-Positive Breast Cancer**Ⓟ J Le Quesne<sup>1</sup>; J Warren<sup>1</sup>; W Howat<sup>1</sup>; F Blows<sup>2</sup>; P Pharoah<sup>2</sup>; C Caldas<sup>1</sup><sup>1</sup>CRUK Cambridge Research Institute, Cambridge, United Kingdom;<sup>2</sup>Strangeways Research Laboratory, Cambridge, United Kingdom

The Dicer protein is essential for the synthesis of nearly all human micro-RNAs, and reductions in its expression have been linked to malignant transformation and behaviour in several experimental systems. The loss of dicer expression has previously been linked to non-luminal subtypes of breast cancer, but no significant relationship with survival has been observed.

We sought to characterize the expression of Dicer by immunohistochemistry in a large set of breast tumours ( $n=3459$ ), and relate its expression to tumour type, micro-RNA expression, and survival. Standard immunohistochemical methods were used to quantify the expression of Dicer in breast tumour tissue microarrays, using automated immunostaining and image capture, followed by manual scoring. Other markers (ER, PR, HER2, CK5/6, EGFR, Ki-67) had previously been scored using similar methods. Micro-RNA expression data were obtained from tissue arrays by locked nucleic in situ hybridisation followed by fluorescent tyramide signal amplification.

Immunohistochemical positivity for Dicer was seen to vary markedly in the nuclear and cytoplasmic compartments of tumour tissue, and two intensity scores (from 0=negative to 3=strong) were derived accordingly. Both nuclear and cytoplasmic scores correlate with the expression of several micro-RNAs (e.g miR-205;  $P<1\times 10^{-6}$ ). Nuclear expression tends to be decreased in basal-type tumours ( $P<1\times 10^{-6}$ ), is negatively related to tumour size ( $P=0.00013$ ) and grade ( $P<1\times 10^{-6}$ ), and predicts survival in ER-positive tumours (HR=0.767 per increment [95% CI=0.622-0.946],  $P=0.013$ ).

Conversely, cytoplasmic expression predicts poor outcome in ER-positive tumours (HR= 1.293 per increment [95% CI=1.030-1.622],  $P=0.027$ ).

The subcellular location of the Dicer IHC signal is critical for its prognostic impact. This may explain why previous studies do not identify Dicer as a prognostic factor, and we propose models to explain these observations.

**P3****Tumour Macrophage Count in Breast Cancer Needle Biopsy has Limitation as a Potential Patient Selection Biomarker for Inhibitors of Colony Stimulating Factor Receptor (CSF1R): an Immunohistochemical Study with By-eye and Digital Image Analysis**Ⓟ C Womack<sup>1</sup>; M Jenkins<sup>1</sup>; M Cumberbatch<sup>1</sup>; G Bigley<sup>1</sup>; G Landberg<sup>2</sup><sup>1</sup>AstraZeneca, Macclesfield, United Kingdom; <sup>2</sup>University of Manchester, Manchester, United Kingdom

Abnormal expression of CSF1R has been shown in breast cancer cells, but efficacy from tyrosine kinase inhibition of the receptor is mediated primarily by effects on the stroma, specifically macrophages. Increased macrophage infiltration in breast cancer correlates with poor prognosis. We measured and correlated the incidence and distribution of tumour macrophages in a series of archival pre-surgical breast cancer biopsies with the corresponding surgical resection. The study was done to determine the feasibility of using macrophage count as an endpoint in a Phase I trial for CSF1R inhibition. Preclinical evidence suggested 80%+ reduction in counts are expected on treatment.

Twenty one breast cancer core biopsies with matched subsequent resection tumour samples were stained for CD68 using routine IHC methods. CD 68 positive macrophages were counted using Chromavision and Aperio systems and also by-eye.

The digital and by-eye analyses were several orders of magnitude different and so results from each method cannot be compared meaningfully. Comparisons made within a single method show similar levels of macrophage count on average, but with wide confidence intervals and an imperfect pairwise relationship between results from matching cores and resections.

Irrespective of system used, CD68 agreement between core biopsy and resected tumour is imprecise, limiting the utility of the core biopsies to predict individual patients who have high CD68 counts and could be selected for CSF1R inhibition. On average the core biopsies can give an approximate indication of the CD68 infiltration at a group level. If the treatment effect due to CSF1R inhibition is large (e.g. 80% hypothesised) then even with this imprecise marker, simulations show that it may be possible to detect an average decrease with reasonable power in a clinical trial.

**P4****Mammaglobin Expression and Receptor Status in Recurrent Breast Cancer**

Ⓟ EA Baker; L Noor; D Whetter; L Hall; J France; P Bhaskar

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Human mammaglobin has been reported to be exclusively expressed in mammary epithelium and over expressed in some breast cancers. The mammaglobin protein is dramatically increased in proliferating breast cells and its production ceases upon breast epithelial cell differentiation. Therefore, mammaglobin synthesis may be involved in breast cell proliferation which would correlate with the over expression seen in some breast cancers.

**Methods:** Primary and subsequent breast tumour tissue from 21 patients who had recurrent breast cancer were analysed by immunohistochemistry for mammaglobin A expression ( $n=44$ ). Stained sections were screened under the microscope with sections regarded as positive when >10% of lesional cells stained positive. For comparison purposes histological grade, tumour type, tumour size, ER, PR, Her-2 status (where available) and presence/absence of nodal metastasis were recorded. Controls were benign breast conditions. The study had ethics approval.

**Results:** Positive mammaglobin expression was observed in 67% of primary breast tumours and in 48% of the recurrent tumours. However the same mammaglobin expression was observed in only 43% paired primary and recurrent tumour samples. In two patients the tumour recurred twice and both of these tumours were mammaglobin negative. Mammaglobin expression was seen in 100% grade 1, 55% grade 2 and 56% grade 3 tumours. There were no significant correlations between mammaglobin expression with ER, PR or Her-2 status, nor with lymphatic or vascular invasion. **Conclusions:** Positive mammaglobin protein expression was found in a greater proportion of low grade breast tumours than higher grade. However a larger number of paired samples need to be analysed to determine the relevance to prognosis.

**P5****A Case Report Highlighting the Diagnostic Difficulties of Malignant Transformation in a Pleomorphic Salivary Adenoma of the Breast**

© SA Collis; CJ Ross; FM Nixon; AH Clark

*Arrowe Park, Wirral, United Kingdom*

**INTRODUCTION:** Pleomorphic adenomas of the breast are rare benign tumours. There are clinical, radiological, cytological and histological diagnostic difficulties in ascertaining whether the lesion is benign or malignant. If there is malignant transformation the diagnosis is made more difficult.

**CASE DESCRIPTION:** A 51 year old woman with a history of bilateral fibroadenomas underwent a routine screening mammogram, which detected a 17mm lobulated density in the right breast. The lesion was graded R3 on mammogram, U4 on ultrasound and C3 on fine needle aspirate. Due to the conflicting investigations complete excision was advised. On histological examination the lesion contained a benign myoepithelial component interspersed with an undifferentiated malignant component showing an almost transitional cell pattern. Immunohistochemical staining indicated the lesion was a carcinoma with the undifferentiated areas being strongly cytokeratin positive. Hormone receptors for oestrogen, progesterone and Herceptin were negative. The lesion was diagnosed as malignant transformation in a pleomorphic salivary adenoma of the breast. A differential diagnosis of malignant transformation in a so-called adenomyoepithelioma of the breast had also been considered.

**DISCUSSION:** Pleomorphic salivary adenomas are usually benign but any conflicting investigations warrant complete resection of the lesion with adequate sampling to exclude potential areas of malignant transformation as the initial fine needle aspirate or biopsy may have only sampled the benign areas.

**P6****A Case Report Highlighting the Diagnostic Difficulties of a Metaplastic Carcinoma of the Breast**

© SA Collis; FM Nixon; AH Clark

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**INTRODUCTION:** Metaplastic carcinomas of the breast are rare neoplasms. Their heterogeneous features can lead to diagnostic difficulty, potentially incorrect management and prognostic variability for the patient.

**CASE DESCRIPTION:** A 72 year old woman presented with a palpable mass in the right lower quadrant. The mass was deemed P5 on clinical examination, M5 on mammography and U5 on ultrasound imaging. A fine needle aspirate showed atypical spindle shaped cells and graded C4. The core biopsy showed a fibromatous type picture with no obvious epithelial neoplasia and therefore graded B2. Following discussion at MDT the decision was made to undertake an excisional biopsy. Histological examination showed an infiltrative spindle cell lesion with a partial storiform pattern. An extensive battery of immunohistochemistry was performed with the spindle shaped cells being positive for MNF 116 and CK5/6 providing the conformation that the lesion was a metaplastic carcinoma. The lesion was negative for oestrogen, progesterone and Herceptin hormone receptors. A further wider excision and lymph node sampling was performed.

**DISCUSSION:** Spindle cell lesions lacking a distinct epithelial component can be the most diagnostically difficult, especially bland spindle cell lesions. Metaplastic carcinoma of the breast forms a heterogeneous group of neoplasms, which tend to occur in older women and as a result can have a better prognosis. Diagnosis and effective management of such lesions is vital.

**P7****'Genesearch' BLN Assay for the Detection of Sentinel Node Metastasis in Breast Cancer Patients: A Large Single Centre Experience**

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**Background** Axillary lymph node status is the most important prognostic factor in breast cancer patients. The American Society of Clinical Oncology recommends axillary lymph node dissection (ALND) for patients with sentinel node (SN) metastases of >0.2mm. Intra-operative detection of SN metastases allows a one-step SN biopsy and ALND. This avoids surgical technical difficulties, comorbidity and increased costs associated with a second operation. 'Genesearch' Breast Lymph Node (BLN) Assay is a real time reverse transcriptase PCR method used to detect SN metastases of >0.2mm. Some studies have shown that this technique offers much higher sensitivities compared to alternative intra-operative detection methods such as touch imprint cytology and frozen section histology.

**Aims** To review our Trust's experience with the 'Genesearch' BLN Assay and compared the specificity and sensitivity of the technique to ranges reported in the literature.

**Methods** All cases of clinically node negative breast cancer which had used the 'Genesearch' BLN Assay for detection of SN metastases were reviewed along with the completed pathology report for the case. The final histological assessment of SN involvement in each case was used as the Gold Standard for comparison with the PCR results when calculating the sensitivity and specificity of the technique.

**Results** The assay was used to analyse 266 sentinel nodes. On a per node basis we achieved a sensitivity of 94% (Literature range 88.9-94.7%) and a specificity of 94.9% (Literature range 94.5-95%)

**Conclusions** The 'GeneSearch' BLN assay is an accurate rapid intra-operative diagnostic technique identifying clinically relevant SN metastases of >0.2mm. In our hands, excellent values for sensitivity and specificity were achieved. These results are superior to those reported for alternative intra-operative methods for the detection of SN metastases.

**P8****Subgross Pathology for the XXI Century**

© JJ Going; WA Smith

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**Purpose:** Morphological and molecular pathology are synergistic because molecular events modify cells, tissues and organs. Subgross morphology is informative but its techniques are prolonged and could interfere with subsequent immunohistochemistry (IHC) and molecular assays. We sought to accelerate staining and clearing of thick breast tissue sections to improve conformity with diagnostic time scales while retaining compatibility with histology and immunohistochemistry.

**Methods:** Three mm thick sections of normal human breast tissue and whole mouse mammary glands were stained using alum carmine, aceto-carmine, Harris's haematoxylin, cresyl violet, neutral red, thionin, DAPI, ethidium bromide (EB) or propidium iodide. Xylene, benzyl alcohol / benzyl benzoate (BABB), xylene - BABB (X-BABB), thiodiglycol (2,2'-thiodiethanol) and anethole were evaluated as clearing agents. Tissue was then paraffin embedded for ER, PR, CD31, E-cadherin and cytokeratin 7 IHC. Results: Haematoxylin and alum carmine were the optimal non-fluorescent stains, with strong nuclear staining and minimal background. Neither DAPI nor EB penetrated well into thick sections but PI did, yielding a high signal to noise ratio which was retained after embedding in BABB or X-BABB, which were clearly better than other clearing agents. Thiodiglycol alone was particularly poor. Anethole's disgusting odour precluded its use. All evaluated clearing agents preserved immunoreactivity for all markers. Conclusions: PI is a promising stain for subgross breast studies and is compatible with BABB as a clearing agent. It was hoped that thiodiglycol being water-miscible might accelerate tissue clearing by avoiding the need for dehydration through alcohols but retained lipids probably prevent satisfactory clearing. Further streamlining of subgross technique is required for its satisfactory integration into a diagnostic setting.

**P9****Rate and Follow-up of Adjuvant Trastuzumab Treatment in HER2+ Early Breast Cancer Patients in South Wales**S Bhatt<sup>1</sup>; R Webster<sup>2</sup>; G Bertelli<sup>3</sup>; J Abraham<sup>2</sup>; P Barrett-Lee<sup>2</sup>; Ⓟ B Jasani<sup>1</sup><sup>1</sup>School of Medicine, Cardiff University, Cardiff, United Kingdom; <sup>2</sup>Velindre Hospital Cancer Centre, Cardiff, United Kingdom; <sup>3</sup>ABM ULHB, Swansea, United Kingdom

**Aims:** To investigate the incidence of HER2+ve disease in early breast cancer and the rate of use of adjuvant trastuzumab in these patients. We also provide data on early clinical follow up of HER2+ve patients treated with trastuzumab. **Methods:** The data of total over 1000 new patients collected from South West and South East Wales Cancer Cancer Networks were analysed for HER2 status and trastuzumab use. Information was retrieved by hand using immunohistochemistry reports and patients' clinical notes. Clinical follow up data, for the Cardiff and Vale patients treated with trastuzumab, was calculated using the Kaplan-Meier method using SPSS. **Results:** In South West Wales, 10.4% of new patients were diagnosed as HER2+ve, of which 72.3% were treated with adjuvant trastuzumab. In South East Wales, 14.1% tested to be HER2+ve of which 76.8% were treated with adjuvant trastuzumab. These were followed up to have a two-year disease-free rate of 85.7% and overall survival rate of 94.3%. **Conclusion:** Our results are consistent with data presented in the two index clinical adjuvant trastuzumab trials and a recent review by Coulson et al based in Sheffield area. We discuss the possible reasons why ~25% eligible patients do not receive trastuzumab, as well as the cost-benefit of the lower rate of HER2+ivity in early breast cancer observed in our study as well as in concurrent UK-wide analyses conducted by UKNEQAS for IHC, compared to that anticipated from the initial metastatic breast cancer data.

**P10****Primary Localised Amyloidosis of the Breast : A report of 6 cases**Ⓟ P Rao<sup>1</sup>; N Dallimore<sup>2</sup>; V Shah<sup>2</sup><sup>1</sup>University Hospital of Wales, Cardiff, United Kingdom; <sup>2</sup>Royal Gwent Hospital, Newport, United Kingdom

Amyloidosis of the breast can occur as a part of a systemic process or as a primary localised disease. Primary localised amyloidosis of the breast is rare with few isolated case reports in the literature.

We describe 6 cases of primary amyloidosis of the breast, 4 cases presented as suspicious microcalcifications (R3 -1 case, R4 - 3 cases) on screening mammography and 2 cases as mass lesions. The presenting age ranged from 47yrs - 79 yrs. In 2 cases there was previous history of surgery at the same site, several years ago. In one of these 2 cases, there was an associated ill defined density on mammography. One case had bilateral R4 calcifications. In all 6 cases, the needle core biopsies showed deposition of Congo red positive amorphous eosinophilic material in the breast tissue with calcifications and foreign body type giant cell reaction. In 4 cases, there was subsequent excision biopsy which confirmed the diagnosis. In one case, amyloid deposition was seen in vicinity of a radial scar. There was no evidence of malignancy in any of the cases. None of the patients had clinical evidence of systemic amyloidosis. Localised amyloidosis of the breast is a rare entity that can clinically or radiologically mimic cancer.

**P11****Audit: Histological Reports of Breast Lesions in Pathology Department of Komfo Anokye Teaching Hospital Kumasi, Ghana in 2010**Ⓟ NA Titiloye<sup>1</sup>; O Owusu-Afryie<sup>2</sup>; AO Adebajji<sup>1</sup><sup>1</sup>KNUST, Kumasi, Ghana; <sup>2</sup>KATH, Kumasi, Ghana

**Background:** An analysis of histopathology report of breast biopsies in the year 2010 in our department was done with the aim of assessing the information contained.

**Methods:** Data analysis was with SPSS 16.

**Results:** A total of 659 breast cases were reported in the year 2010.

Biopsy types were truct, lumpectomy and mastectomy. Diagnosis were categorized as inflammatory 62(9.4%), benign 334 (50.8%), malignant 223(33.9%) and 39 cases (5.9%) were normal. Age patterns for various female categories were: benign 10-86years with modal class 20-29years (136 cases - 43.31%) and malignant 24-98years modal class 40-49years (76 cases -36.41%). Fibroadenoma were 210 (66.88%) and fibrocystic disease 63 (20.06%). No incidental finding was seen in all the 18 cases of reduction mammoplasty. Female breast cancer was 217 cases (34.61%). Invasive ductal carcinoma (nos) was the commonest histological variant with 187 cases (86.18%). Other variants include Invasive lobular Carcinoma (4-1.84%), Colloid Carcinoma (8-3.69%) and metaplastic carcinoma (3-1.38%). The histological grade are grade 3 (68 -36.56%), grade 2 (97-2.15%) and grade 1 (21-11.29%). Six insitu carcinoma cases were seen. Most of the invasive cancers were reported to be pTNM stage 3. Six cases (2.69% of all malignant cases) were male, with 5 reported as infiltrating ductal carcinoma and 1 insitu ductal carcinoma seen. None of our reports contain immunohistochemistry results as at time of sign out. **Conclusion:** Our data suggest that wide range of diagnosis were made on breast cases in the year 2010 and our reports answer significantly questions related to breast lesions. However, we recommend an inclusion of routine Immunocytochemistry report on all malignant cases as at time of sign out.

**P12****Validation of MS110, an Antibody to BRCA-1 for Immunohistochemistry**R Milner<sup>1</sup>; H Wombwell<sup>1</sup>; G Hughes<sup>1</sup>; A Kvist<sup>1</sup>; DR Hodgson<sup>1</sup>; C Harbron<sup>1</sup>; C Womack<sup>1</sup>; N Gray<sup>1</sup>; M O'Connor<sup>1</sup>; B Spaulding<sup>2</sup>; Ⓟ R Wellings<sup>1</sup><sup>1</sup>AstraZeneca, Alderley Park, United Kingdom; <sup>2</sup>DAKO, Carpinteria, United States

BRCA-1, a tumour suppressor gene involved in DNA repair has been extensively studied. Mutation of BRCA-1 has been shown to be involved in the etiology of certain types of cancer such as breast and ovarian. To date, there is no conclusive data describing the protein expression of BRCA-1 within normal and malignant tissue, by immunohistochemical (IHC) methods. Here, we describe an evaluation of a commercially available monoclonal antibody to BRCA-1 (clone MS110; # OP92, Calbiochem).

BRCA-1 expression and Western blot analysis of cell lines and HeLa nuclear fractions, using MS110 was consistent with the literature. Studies in formalin fixed paraffin embedded breast and ovarian cancer tissue revealed a dynamic range of BRCA-1 expression, from apparent loss of BRCA-1 protein (i.e. 0 score) to positive staining (3+) in a small proportion of samples.

Selectivity testing was conducted with green fluorescent protein (GFP)-tagged BRCA-1 coding constructs transfected in to Human BRCA-1 negative CHO cells. An overlay of BRCA-1 expression with MS110 binding was observed, indicating selectivity of the MS110 antibody for its target. We believe that MS110 is selective and therefore a useful tool for understanding expression of BRCA-1 protein in tissue. IHC may be a useful platform to aid understanding of BRCA-1 biology in relation to cancer. A technically validated, specific antibody is the first step toward defining cancers with aberrant BRCA1 expression.

**P13****The Role of Ultrasound Guided Fine Needle Aspiration Cytology in the Diagnosis of Hepatocellular Carcinoma: A Tertiary Hospital Experience**GO Omoniyi-Esan<sup>1</sup>; OC Famurewa<sup>1</sup>; Ⓟ AE Omonisi<sup>2</sup>; NA Titiloye<sup>2</sup>; OE Pelemo<sup>2</sup>; BJ Olasode<sup>1</sup><sup>1</sup>Obafemi Awolowo University, ILE-IFE, Nigeria; <sup>2</sup>Obafemi Awolowo University Teaching Hospitals Complex, ILE-IFE, Nigeria

**Purpose:** To describe the usefulness of Ultra-Sound Guided Fine Needle Aspiration Cytology (USSG-FNAC) in the diagnosis of hepatocellular carcinoma in resource limited setting like Africa.

**Methods:** We retrospectively reviewed USS-FNAC smear reports of 30 patients. **Results:** The age range is 13-72 years with a mean of 40 years. The male to female ratio is 5: 1. Most cases (28%) occurred within the 21-30 age groups. Twenty - two of the cases (73.3%) were positive for HBsAg while 8 of the cases (26.7%) were negative. None of the case was positive for HCV & HIV. The mean duration of symptoms before diagnosis was 6.4 weeks. Most of the patients presented with right hypochondrial pain (46.7%) and abdominal mass (40%). The cytological diagnosis had an accompanied histological diagnosis in 20 out of the 30 cases. Out of the 20 cases with proven histological results, cytological diagnosed cases were consistent with the 19 (95%) giving a diagnostic accuracy of 95% (suspicious for malignancy were regarded as malignant, and also confirmed by histology).

**Conclusions:** This study revealed the high diagnostic accuracy and sensitivity of USSG-FNAC in the diagnosis of hepatocellular carcinoma. Although, we are aware of the controversy that FNAC for the diagnosis of HCC may result in the implantation of tumour on the tissue track. But we found the procedure in our setting to be simple, safe, reliable and dependable. We recommend USSG-FNAC of the liver as a diagnostic investigation in the evaluation of patients suspected for hepatic malignancy but the histological diagnosis still remains the gold standard.

**P14****A Comparison of WT1, PTEN and the AKT Pathway in Ovarian Serous Carcinoma vs. Colorectal Adenocarcinoma.**

Ⓟ MA Gallacher; S Fleming

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WT1 was first described as a tumour suppressor gene. Recently it has been shown to be overexpressed in a number of adult malignancies leading to a reclassification as an oncogene. PTEN is a negative regulator of the AKT pathway and has a WT1/Egr1 recognition sequence in its promoter.

Previously we have reported that the majority of ovarian serous cancers stained positively for nuclear WT1, were negative for cytoplasmic WT1 and stained positively for cytoplasmic PTEN, cytoplasmic pPTEN and nuclear and cytoplasmic AKT1.

Further work has highlighted some interesting results when comparing ovarian serous carcinoma to colorectal adenocarcinoma. In contrast to the ovarian serous carcinoma all of the colorectal carcinoma cases were negative for nuclear WT1 while the majority were weakly positive for cytoplasmic WT1,  $p = \leq 0.000002$ . There was no significant difference between ovarian vs. colorectal PTEN, or AKT1.

In contrast to the ovarian serous carcinoma there is no statistically significant difference between colorectal cytoplasmic WT1 and colorectal nuclear or cytoplasmic PTEN, however, there is a significant difference between colorectal WT1 and colorectal AKT staining.

In conclusion WT1 appears to be expressed in other carcinomas rather than principally as an ovarian serous marker, however, it appears to be expressed in different parts of the cell depending on the tumour type. This could have implications for its mechanism of action and function.

In ovarian serous carcinomas WT1 appeared to display a negative relationship with PTEN. This is not the case in colorectal carcinomas and the AKT pathway may be controlled by a different mechanism.

This research was funded by the Centenary Fellowship Pathological Society of GB and Ireland and Tenovus Scotland.

**P15****Evaluation of the Use of Immunohistochemistry to Identify Protein Biomarkers in Cancer Clinical Trials**

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The analysis of protein biomarkers in human cancer clinical trials using immunohistochemistry (IHC) based techniques has an increasingly important role to play in the development of targeted therapeutics to identify target modulation by drug to confirm mechanism of action and drug effect; and to identify predictive biomarkers to identify patient populations that may respond or be resistant to a particular therapeutic. We reviewed publications between 2005 and 2010 relating to clinical trials involving the ten most prevalent human adult tumours. Of a total of 189 clinical trials (5% Phase I trials; 28% Phase II trials; 29% Phase III trials; and 38% other randomised controlled trials), over 120 different proteins were analysed by immunohistochemistry on tumour tissue samples ranging from growth factors, cell surface receptors, cell signalling molecules and cell cycle associated proteins. Disease pathways interrogated included proliferation, apoptosis, invasion and metastasis. The assays were used to provide information on prognosis (22% of trials); prediction of drug treatment response or resistance (45%); evidence of drug mechanism of action (21% of trials) or to aid patient selection for treatment (12% of trials). We analyse the trends according to type of drug, source of funding, year of trial onset, and contribution to decision making.

The identification of protein biomarkers in human tissues has a significant and increasing role to play in drug development, and the development of potential new clinical diagnostic tests for patient stratification. However care must be taken in trial design and issues relating to sample quality, IHC methodology and quantification.

**P16****Biopsies from the Endoscopically Normal Colorectum-Limited Clinical Value?**

Ⓟ OH O'Mahony; M Burgoyne

Southern General Hospital, Glasgow, United Kingdom

In many histopathology departments, colonic and rectal biopsies form a significant proportion of workload. Often, biopsies are taken from an endoscopically normal colon.

**Purpose of the study:** We aimed to determine the diagnostic yield of biopsy in patients with normal colonoscopy and sigmoidoscopy, and whether recorded symptoms were associated with a higher probability of abnormal histological findings.

**Patients/methods:** We performed a one year retrospective analysis (2008/9) in a tertiary care hospital. We analysed pathology request forms and endoscopy reports for all ileal, colonic and/or rectal biopsies taken at colonoscopy or sigmoidoscopy with normal appearing ileal and colorectal mucosa. We reviewed pathology reports for all biopsies including terminal ileum.

**Results:** 667 of 694 patients (455 female, 239 male, average age 50) fulfilling the criteria had at least one colonic or rectal biopsy. A total of 92 patients (13.8%) had abnormal histological findings. Of 487 biopsied patients with diarrhoea there was abnormal histology in 71 (14.6%). Of 180 biopsied patients without diarrhoea there was abnormal histology in 21 (11.7%) ( $df=1$ ;  $\div 2 = 0.93$   $p = 0.67$ ). Detected abnormalities included microscopic colitis, distorted mucosal architecture, ischaemia, polyps, melanosis, mucosal prolapse, and schistosomiasis.

**Conclusions:** Biopsy in the presence of a macroscopically normal colon at endoscopy has a low yield of abnormal histological findings. Diarrhoea does not identify patients with a higher risk of abnormal histology. This data is relevant to the cost-effectiveness of mucosal biopsy in the endoscopically normal colon and rectum.

**P17****βCatenin Expression in the Dysplastic Progression of Colorectal Adenoma: A Useful and Overlooked Diagnostic Tool**Ⓟ GD Robinson<sup>1</sup>; A Abraham<sup>1</sup>; A Madgwick<sup>2</sup><sup>1</sup>Milton Keynes General Hospital, Milton Keynes, United Kingdom; <sup>2</sup>University of Westminster, London, United Kingdom

βCatenin plays an integral role in colorectal carcinogenesis with altered localisation in adenomatous dysplastic cells resulting in transcription of target genes that can induce malignant growth. Nuclear expression of βCatenin has consistently been linked to the progression of dysplasia and malignancy. However, previous work has disregarded βCatenin as a diagnostically useful marker due to heterogeneity of staining patterns. The introduction of the NHS Bowel Cancer Screening Programme has brought with it new guidelines in adenoma reporting, using a two-tier system which classifies mild and moderately dysplastic lesions within the same 'low grade' group. This grouping affects subsequent patient surveillance and management.

A novel scoring system was designed based on immunocytochemical nuclear localisation of βCatenin. This system was applied to an unknown set of colorectal polyps (n=140) by two independent scorers.

Nuclear βCatenin expression patterns proved to reliably indicate severity of dysplasia in colorectal adenomas (p=0.001). Mildly and severely dysplastic adenomas show dramatic disparity in nuclear βCatenin patterns, diffuse cytoplasmic staining with paucity of nuclear expression versus intense nuclear staining with cytoplasmic clearing. However, moderately dysplastic lesions also displayed two discrete βCatenin expression patterns, those which mimic mild dysplasia and those comparable to the severely dysplastic group.

The application of βCatenin shows that some moderately dysplastic adenomas can imitate the βCatenin expression of severe dysplasia and could harbour the genetic capability to induce progression to colorectal carcinoma, and may require reclassification as high grade lesions. A pragmatic scoring system for βCatenin could serve as a putative marker of adenoma progression and provide a useful diagnostic and predictive tool.

**P18****Hepatocellular Carcinoma with Giant Hyaline Inclusions**Ⓟ JM Radhi<sup>1</sup>; Z Twaij<sup>2</sup><sup>1</sup>McMaster University, Hamilton, Canada; <sup>2</sup>Burnley Hospital, Burnley, United Kingdom

**Background:** Intracellular cytoplasmic hyaline inclusions have been reported in hepatocellular carcinoma. They presumably represent a disturbance in intermediate filament metabolism by the tumour cells. The nature of these inclusions can be determined in a majority of cases by immunohistochemical method or electron microscopy.

**Design:** We identified two unusual cases of hepatocellular carcinoma with giant intracytoplasmic inclusions. These were stained for PAS, PAS diastase, trichrome, and amyloid. Immunohistochemical markers for cytokeratin, ubiquitin, alpha-fetoprotein, alpha 1-antitrypsin, alpha 1-antichymotrypsin and fibrinogen were used, together with electron microscopy to determine the nature of these inclusions.

**Results:** Both cases showed hepatocellular carcinoma with numerous large intracytoplasmic hyaline bodies surrounded by clear halo. These inclusions were generally dark eosinophilic in colour with variable density and stained negative for PAS, PASD and trichrome. All immunohistochemistry markers were negative. Electron microscopy revealed fibrillary dense material.

**Conclusion:** Hyaline globules are considered useful in the diagnosis of hepatocellular carcinoma. The nature of these inclusions can be determined in most cases by the application of immunohistochemical markers or electron microscopy. Though the nature of these giant inclusions is not clear, they probably represent degenerated proteinaceous material.

**P19****Role of the Bone Marrow in TFF1 Knockout Mouse Gastric Adenomas**Ⓟ AC Le Brenne<sup>1</sup>; R Jeffery<sup>2</sup>; R Poulsom<sup>2</sup>; CL Tomasetto<sup>3</sup>; NA Wright<sup>2</sup>; WR Otto<sup>2</sup>; MR Alison<sup>1</sup><sup>1</sup>Queen Mary University of London, London, United Kingdom; <sup>2</sup>Cancer Research UK, London, United Kingdom; <sup>3</sup>The Institute of Genetics and Molecular and Cellular Biology, Strasbourg, France

The TFF-1 knockout [KO] mouse spontaneously develops antropyloric adenomas. To understand the potential role of bone marrow derived cells (BMDCs) in gastric carcinogenesis, we performed a sex-mismatched (male into female) bone marrow transplantation (BMT) experiment studying the following four groups: WT BM into WT mice, TFF-1 KO BM into WT, WT BM into TFF-1 KO, and TFF-1 KO BM into TFF-1 KO. We analysed the groups at 6 and 12 months after BMT to investigate long-term engraftment.

Histological analysis of tissues from the WT into WT mice showed normal morphology. KO into WT showed occasional hyperplasia and inflammation, but not the adenomas seen in KO into KO, which were tubulovillous, dysplastic, and often pedunculated. WT into KO mice showed no amelioration of KO tumours. Male bone-marrow derived myofibroblasts (Y chromosome ISH, α-smooth muscle actin IHC) were found between glands and which were increased in the tumour stroma, especially nearer the lumen (P=<0.01). ISH for Lgr5 revealed widespread expression within the gastric adenoma of one TFF-1 KO to KO mouse at 12 months. A trend was seen suggesting greater numbers of Y+ epithelial cells in the adenomas of this group. We have not formally excluded the possibility that these cells may be fusion events with CD45-positive BM cells.

We conclude that BM from TFF1 KO mice may on occasion be associated with inflammation and hyperplasia in WT recipients. The frequency of BM-derived myofibroblasts differs in adenomatous tissue. WT BM has no effect on the appearance of adenomas in KO mice.

**P20****Insulin-like Growth Factor 1 Receptor (tIGF1R) and Phospho-IGF1R (pIGF1R) Expression in Colorectal Cancer Resection Specimens have Limited Correlation with Clinical Outcome: a Tissue Microarray and Immunohistochemical Study**Ⓟ N Zeps<sup>1</sup>; L Spalding<sup>1</sup>; M Revill<sup>2</sup>; M Jenkins<sup>2</sup>; C Platell<sup>3</sup>; MV Warren<sup>4</sup>; I Chan<sup>4</sup>; NR Smith<sup>2</sup>; E Kilgour<sup>2</sup>; Ⓟ C Womack<sup>2</sup><sup>1</sup>St John of God Pathology, University of Western Australia, Perth, Australia; <sup>2</sup>AstraZeneca, Macclesfield, United Kingdom; <sup>3</sup>St John of God Colorectal Service, University of Western Australia, Perth, Australia; <sup>4</sup>Pathology Diagnostics Ltd, Cambridge, United Kingdom

Experimental and clinical evidence indicates that the membrane tyrosine receptor kinase IGF1R is important both in normal cell growth and also in tumorigenesis. We undertook IHC studies on colorectal cancer (CRC) tissue microarrays (TMA) using established, validated IHC methods using antibodies to total IGF1R (tIGF1R) and phospho IGF1R (pIGF1R) on two sets of CRC TMAs on which standard quality control checks had been performed. TMA Set 1 comprised samples from 80 donors with an equal mix of stage II/III and IV. Set 2 included predominantly Stage II (252) and III (279) cases from a single hospital with clinical outcome data. Both sets included non-neoplastic mucosa.

TMAs were scored by-eye according to an arbitrary scale of 0 (no stain) to 3 (strong) staining for each cellular component. Set 1 was analysed using in-house bioinformatics platform. For Set 2 relationship to clinical outcome was illustrated by Kaplan-Meier plots following standard statistical method.

Both TMA sets showed similar expression profiles with positive staining for both markers in the epithelium of tumour and non-neoplastic tissue: predominantly cytoplasmic for t-IGF1R and nuclear for pIGF1R. In Set 1 membrane staining was observed in around 50% of tumour samples but less than 10% normal with reciprocal results for pIGF1R. In set 2, 80 samples showed evidence of specific staining of the luminal surface of the epithelium for tIGF1R. Luminal staining for pIGF1R in 14 patients correlated with a worse survival outcome. tIGF1R expression in normal cells of CRC patients was an independent marker of a poor prognosis. Findings confirm tIGF1R and pIGF1R expression in CRC patient tumour and non-tumour epithelium. The association of pIGF1R on the luminal surface of CRC epithelium with a significantly worse prognosis should be interpreted with caution. No other clinicopathological features correlated with IGF1R expression.

**P21****Case Report of a Colon Stem Cell Carcinoma**

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A 39-year old female was admitted to undertake right hemicolectomy with lymphadenectomy. Epigastric pain was her chief complain since several months ago but it had been aggravated from one month ago. It was a colic pain with nausea and vomiting. Longterm treatment of chronic gastritis was not effective anymore. Spiral CT scan of abdomen/pelvis was done that demonstrated a 10\*7.5 cyst like area in RUQ with a/f level extending to subhepatic. The bowel loops in right side of abdomen were dilated, showed a/f level and suggested partial obstruction. Para aortic adenopathies were seen and a small hypodense nodule (1 cm) in medial segment of liver lobe noted. So right hemicolectomy and lymphadenectomy with liver wedge biopsy were performed. Pathology report: Gross sections of transverse colon showed mucosal thickening with firm consistency that was 7.2 in length. Mucosal atrophy was apparent after this part. Microscopic sections revealed neoplastic proliferation of small and rather uniform epithelial cells in diffuse pattern (IHC results: NSE & Chromogranin= negative, CK20= positive) which was predominant feature, but dual differentiation into adenocarcinoma and squamous cell carcinoma was also obvious, in a way that sometimes both of these features could be seen in one microscopic field. Although it's very rare, Colon Stem Cell Carcinoma was as final diagnosis.

**P22****Chromosomal Abnormalities, Pathological Factors and Survival Following Curative Resection for Colorectal Cancer**AGM Powell<sup>1</sup>; F Al Mulla<sup>2</sup>; PG Horgan<sup>1</sup>; J Edwards<sup>1</sup>; DC McMillan<sup>1</sup>; Ⓟ JJ Goings<sup>1</sup><sup>1</sup>University of Glasgow, Glasgow, United Kingdom; <sup>2</sup>University of Kuwait, Safat, Kuwait

Purpose: Not all Dukes' A and B colorectal cancer patients do well after surgery but we do not know how to predict who will do badly, and might therefore benefit most from adjuvant chemotherapy. Major chromosomal abnormalities detectable by comparative genomic hybridisation (CGH) are common in colorectal cancer and are known to influence outcome.

Patients and methods: 23 Dukes' A and 26 Dukes' B patients who underwent surgery with curative intent in Glasgow in 1991-1993, had classical and array CGH on formalin fixed paraffin embedded tumour tissue. There was complete follow up to 1/1/2004. Analysis of survival included clinical, pathological and CGH data in a multivariate (Cox) model.

Results: 24 (49%) patients died of their cancer. In univariate analysis no clinical or pathological factors were predictive but 1p-, 1q+, 4-, 4p-, 4q-, 5q-, 8p-, 9p-, 14q- separately predicted cancer death and in multivariate analysis 4p- (HR 4.76; 95% CI 2.0-11.5; P 0.001) and 5q- (HR 3.32; 95% CI 1.40-7.9; P 0.007) remained predictive. Loss of 4p and 5q were present in 33% and 27% of cases, respectively.

Conclusions: Adverse prognostic significance of 4p- is supported by previously published data. Loss of 5q has not previously been strongly associated with survival in colorectal cancer. These highly significant associations with survival in a relatively small series need confirmatory analysis in a larger independent cohort. The increased proportion of Dukes' A and B cancers detected by bowel screening makes this particularly timely.

**P23****An Audit of Duodenal Biopsy Histology with Evaluation of the Use of Coeliac Serology**

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Purpose of the Study: Current guidelines recommend the use of serology as a preliminary test where coeliac disease is suspected. Detection of IgA antibodies to tissue transglutaminase (tTG) and endomysium (EMA) should be followed by a duodenal biopsy to confirm the presence of villous atrophy. If serology is negative but the clinician is suspicious a duodenal biopsy should still be undertaken. The aims of this audit were to identify the number of biopsies with a histological diagnosis of coeliac disease and to examine the use of coeliac serology as part of diagnostic practice.

Methods: A SNOMED search identified duodenal biopsy reports for the year 2009. Data retrieved from the first 500 histopathology reports included age, sex, presenting symptoms and histology. Patient casenote numbers were used to access serology reports on the electronic hospital database.

Summary of Results: In 25 cases (5%) coeliac disease was diagnosed on histology, 14 (3%) reported a mild increase in intraepithelial lymphocytes (IELs), 31 (6%) were diagnosed with other conditions, and 430 (86%) were morphologically normal. 285 (57%) patients were not tested for coeliac antibodies, 190 patients (38%) tested negatively and 25 (5%) had a positive serology. Of the 25 with confirmed coeliac histology 21 patients had positive serology, 3 had none and 1 tested negatively (IgA deficient). 2 cases had positive serology and normal histology; 1 was a known coeliac on a gluten-free diet, the other had a mild increase in IELs and may represent early coeliac disease.

Conclusions: 1. Positive serology is a strong predictor of coeliac disease; It may be positive before histological changes, and is especially important in cases where the IEL count is raised. 2. Routine use of coeliac serology could reduce the number of morphologically normal biopsies assessed. 3. A combination of histology and serology is most specific for a diagnosis of coeliac disease.

**P24****Crypt Cell Carcinoma Of The Appendix: A Series Of 6 Cases Of A Rare Appendiceal Neoplasm**Ⓟ SNK Kalimuthu<sup>1</sup>; KS Sheahan<sup>2</sup>; SB Bakhiet<sup>1</sup>; AF Fabre<sup>1</sup><sup>1</sup>St Vincent's University Hospital, Dublin, Ireland; <sup>2</sup>St University Hospital, Dublin, Ireland

Appendiceal neoplasms with mixed neuroendocrine and glandular features are rare, and have been variously designated as adenocarcinoma, mixed adenocarcinoma and more recently referred to as crypt cell carcinomas (CCC)/goblet cell carcinoids.

We report a retrospective study of 6 cases of CCCs of the appendix during 1991-2010. It includes 3 women and 3 men, age range 45 – 82 years. The most common clinical presentation was acute bowel obstruction (4/6). One patient had a previous appendicectomy and presented with a recurrent ovarian mass. Using the staging parameters of the UICC TNM system for appendiceal carcinoma, we found 4 cases to be pT4 and 2 cases to be pT3. Histologically, all cases were well differentiated CCCs with small clusters or large sheets of goblet cells with minimal cytological atypia (differing from signet ring cell adenocarcinomas). Pools of extracellular mucin were observed in 3/6 cases. The immunoprofile of CCCs categorise them as appendiceal carcinomas rather than a variant of carcinoid, as all were strongly positive for CK20 and CDX2 and only focally positive or negative for synaptophysin, chromogranin and/or CD56. Proliferation index assessed by Ki-67 immunohistochemical stain (performed in 5 cases) show a high index, ranging between 6 – 56%.

The pathological stage of the current series is advanced, commonly presenting with nodal disease (N1) on surgical resections. CCCs are rare appendiceal neoplasms with an unpredictable behaviour and warrant life-long surveillance for disease recurrence, even after satisfactory surgical resection.

## P25

### Neonatal Haemochromatosis — A Rare Cause for Fetal Hydrops Post Mortem Case Report

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Neonatal haemochromatosis is a rare condition. There are only a few cases in the literature which present with neonatal hydrops, placental oedema and oligohydramnios.

Baby M was delivered by caesarean section at 30 weeks gestation due to severe maternal pre-eclampsia toxemia. Baby M died at 20 hours after little autonomous respiratory effort and maximum ventilator support. At autopsy external examination revealed a 2kg (>98th centile for gestation), severely hydropic baby with distorted facial features and jaundice. Internal examination revealed bloody ascities, bilateral pleural effusions, a small liver and left liver lobe haematoma. There were also features of intra-uterine stress: thymic involution and adrenal fat deposition. Features of neonatal haemochromatosis were seen histologically; iron deposition in the liver, bile duct epithelium and pancreas. The pancreas showed islet cell hyperplasia and hypertrophy. There was liver necrosis, cholangiopathy and giant cell change. The placenta was large and hydropic with a weight >95th centile. The chorionic villi were large and oedematous with irregular outlines. Neonatal haemochromatosis is clinically and pathologically defined as severe liver disease of intra-uterine onset associated with extra-hepatic siderosis that spares the reticulo-endothelial system. In this case we saw iron within the pancreatic acini. Supporting features include cholangiopathy, giant cell hepatocyte change with hypertrophy and hyperplasia of the pancreatic islet cells. Although there was no cirrhosis, there was fibrous expansion of portal tracts and pericellular fibrosis. If the baby had lived on to term this may have eventually resulted in liver cirrhosis.

The aetiology of this condition remains elusive. No genetic abnormalities were found in this case. There are theories of maternal viral infection and associations with maternal autoantibodies to RO/SS-A and LA/SS-B.

## P26

### Wolf Hirschhorn Syndrome and Beyond

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Wolf Hirschhorn syndrome (WHS) cases show multiple congenital abnormalities resulting from partial deletion of the short arm of chromosome 4. The syndrome encompasses a wide spectrum of clinical signs, with the severity of the expressed phenotype depending on the size and mechanism of the deletion. A minimal critical region, that when deleted will lead to WHS, has been defined as a 165kb segment located in chromosomal band 4p16.3. Potentially important genes within this segment include WHSC1, WHSC2 and LETM1

A minimal phenotype consists of the typical facial appearance, mental retardation, hypotonia and growth retardation. The characteristic facial features in WHS include prominent and wide-spaced eyes, prominent nasal bridge, "Greek warrior helmet", short philtrum and downward-turning corners of the mouth

Other abnormalities in cases of WHS, including microcephaly, midline defects, congenital heart defects and renal abnormalities. However, these are associated with deletions larger than that of the critical region. We present the findings from a neonate with partial monosomy 4p and trisomy 20p showing features similar to the one other case in the literature. The neonate was born at 32 weeks gestation by Caesarean section due to poor foetal growth. The birth-weight was 1247g. Congenital abnormalities evident at birth included facial features characteristic of WHS, cleft palate, low set ears and cloudy corneas. USS of the brain showed bilateral subependymal cysts and heterotopia. Examination of the organs revealed an atrial septal defect, agenesis of the corpus callosum and small dysplastic kidneys with incomplete scant nephrogenic zones. The karyotype was 46,XX, der(4)t(4;20)(p14;p11.2).

Renal agenesis, cystic dysplasia, hypoplasia, oligomeganephronia and vesicoureteric reflux have been described when WHS is deleted beyond the critical region and may be a resource for studying candidate genes for these renal pathologies.

## P27

### Lymphatic Marker Expression Upregulation Correlates with Increased Stage, Unfavourable Histology and Advanced Stage Neuroblastoma

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**PURPOSE:** High-risk and advanced stage neuroblastoma (NB) has a dismal outcome as the majority of patients have lymphatic/ and or haematogenous metastases at diagnosis. To investigate the role of lymphatic endothelial markers D2-40, Prox-1 and LYVE-1 in lymphatic dissemination of NB, we compared their expression with clinicopathological and biological variables.

**METHODS:** Serial sections of 92 NB and 9 ganglioneuromas (GN) were immunostained for D2-40, Prox-1 and LYVE-1 and lymphatic vascular density (LVD) measured using Chalkley point counting. Double-staining for D2-40 and proliferation marker Ki-67, using MIB1, was also performed. Prox-1 expression in neuroblastic cells was quantified.

**SUMMARY OF RESULTS:** Double-staining showed the presence of proliferating lymphatic channels in the peritumoral areas of neuroblastomas. D2-40, Prox-1 and LYVE-1 stained lymph vessels were present in 78%, 51% and 27% of the NBs respectively. D2-40, Prox-1 and LYVE-1-LVD was significantly higher in the abdominal NBs ( $p=0.010$ ,  $p=0.022$ ,  $p=0.038$  respectively). Furthermore, D2-40 and Prox-1 LVD were significantly increased in NBs from children with stage 4 disease ( $p=0.044$ ,  $p=0.034$  respectively). Prox-1 expression in neuroblasts was significantly higher in NB with high mitosis-karyorrhexis index ( $p=0.043$ ), undifferentiated- and poorly-differentiated status ( $p=0.004$ ) and in children with stage 4 disease ( $p=0.033$ ).

**CONCLUSIONS:** Higher LVD, using all three lymphatic markers and Prox-1 neuroblastic tumour cell expression correlated with unfavourable clinicopathological factors.

## P28

### Accidental Childhood Deaths, a Review of Cases from a Specialist Paediatric Centre

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**Purpose of the Study:** Accidental and unintentional injuries account for around 15% of deaths in children >1 year of age in the UK. This study reviews findings from paediatric autopsies in a single specialist centre of cases where accidents lead to the death.

**Methods:** Data from >1,500 consecutively performed paediatric autopsies at one centre were retrospectively recorded into an autopsy database. Cases where the cause of death was accidental and explained were identified and autopsy findings reviewed.

**Summary of Results:** Of 1,516 paediatric post-mortem examinations, 407 (27%) patients were over 12 months of age. Of these, 55 (13%) were identified as having accidental deaths. Ages varied from 1-15 years, with 39 (71%) occurring before 5 years of age. Gender difference was marked from 10 years upwards, with 88% of cases being male. Of the 55 deaths, the most common cause was trauma (17, 31%), with half (9) of these cases being associated with road traffic accidents. Fire related deaths accounted for 14 (25%) cases, 12 (22%) were due to drowning, 10 (18%) were other asphyxial and two were due to iatrogenic causes. Of the 55 cases, 13 were resuscitated and showed secondary post-resuscitation findings (including ventilator-associated pneumonia (9 cases) and ARDS (2 cases)).

**Conclusions:** Referred cases of accidental deaths for autopsy align with National statistics in England and Wales. The autopsy confirmed the cause of death and showed expected findings as well as identifying post-resuscitation changes. The autopsy examination in such cases remains an important tool, particularly in confirming injuries and mechanism of death.

**P29****Intra-alveolar Haemorrhage (IAH) and Co-Sleeping in Sudden Unexpected Deaths in Infancy (SUDI)**Ⓟ ZM Yap<sup>1</sup>; JW Pryce<sup>2</sup>; MA Weber<sup>3</sup>; MT Ashworth<sup>3</sup>; NJ Sebire<sup>2</sup><sup>1</sup>University College London, London, United Kingdom; <sup>2</sup>Institute of Child Health, London, United Kingdom; <sup>3</sup>Great Ormond Street Hospital, London, United Kingdom

**Purpose of the study:** Sudden unexpected death in infancy (SUDI) is defined as the death of an infant 7-365 days that was sudden and unexpected. Previous studies have suggested that SUDI with a history suspicious of possible overlaying / asphyxia have an increased incidence of intra-alveolar haemorrhage (IAH) at autopsy. This study reviews cases of SUDI with regards to frequency of significant IAH in relation to co-sleeping status.

**Methods:** Retrospective analysis of >2,800 consecutively performed post-mortem examinations at a single centre over a 14-year period (1996-2009) was performed. This included analysis of the provided clinical history, including sleeping arrangements. The final cause of death was determined according to objective previously published criteria. Findings of lung histology, as recorded by the pathologist reporting the case at the time, were reviewed.

**Results:** Of 2,841 autopsies, 886 were for SUDI, of which 523 died during sleep and lung histology and sleeping arrangements were well-documented; 272 (52%) were co-sleeping-associated deaths. Of the 523 cases, 259 (50%) had significant acute histological IAH noted by the reporting pathologist. Significantly more of the 272 co-sleeping cases, (156 (57%)) had evidence of IAH, compared to non co-sleeping cases (103 (41%) of 251; comparison of proportions test  $P < 0.001$ ).

**Conclusion:** IAH is more prevalent in co-sleeping associated SUDI compared to cases without co-sleeping, regardless of final cause of death. The interpretation of what represents 'significant' IAH as a discriminator of mode of death however remains uncertain.

**P30****Macroscopic Findings in Autopsies for Sudden Unexpected Death in Infancy (SUDI) in Relation to Cause of Death; Need for Ancillary Investigations**Ⓟ E Minas<sup>1</sup>; JW Pryce<sup>2</sup>; MA Weber<sup>3</sup>; M Malone<sup>3</sup>; NJ Sebire<sup>2</sup><sup>1</sup>University College London, London, United Kingdom; <sup>2</sup>Institute of Child Health, London, United Kingdom; <sup>3</sup>Great Ormond Street Hospital, London, United Kingdom

**Purpose of the study:** A thorough infant autopsy includes review of the clinical history and events prior to commencing the recommended external and internal examinations in cases of sudden unexpected death in infancy (SUDI). This study reviews the internal macroscopic findings from a consecutive series of SUDI autopsies performed in a single specialist centre over a 14 year period (1996 to 2009) to determine in what proportion of cases a cause of death could be determined from the macroscopic findings at the time of autopsy.

**Methods:** Data from >2,750 consecutive paediatric autopsies performed by specialist paediatric pathologists at one centre according to a standard protocol were retrospectively recorded into an autopsy database. SUDI cases were identified and the autopsy findings reviewed. Macroscopic findings were categorised including normal and abnormal appearances and the cause of death.

**Results:** Of 1,526 consecutive infant autopsies, 1,228 were in infants between the ages of 7- 365 days, of which 886 presented as SUDI. Of the 886 cases, 53 (6%) had macroscopic findings at autopsy which determined the definite cause of death. 51 had significant findings in one organ only whilst two cases had multiple organs involved. The heart was involved in 24 (45%) cases, followed by the brain in 19 (36%). The commonest findings were of congenital heart disease and bacterial meningitis.

**Conclusion:** In a large series of SUDI autopsies at a specialist centre, macroscopic findings at the time of autopsy allow determination of cause of death in only a small minority of cases. Ancillary investigations, including histological examination, are required in the majority of SUDI deaths.

**P31****Autopsy findings in Sudden Unexpected Death in Infancy (SUDI) due to Gastrointestinal Pathology**Ⓟ JW Pryce<sup>1</sup>; MA Weber<sup>2</sup>; MT Ashworth<sup>2</sup>; M Malone<sup>2</sup>; NJ Sebire<sup>1</sup><sup>1</sup>Institute of Child Health, London, United Kingdom; <sup>2</sup>Great Ormond Street Hospital, London, United Kingdom

**Purpose of the study:** A cause of death is identified in 30-40% of Sudden Unexpected Deaths in Infancy (SUDI) following autopsy, gastrointestinal (GI) causes representing an unusual group of deaths with this presentation. This study reviews findings from infant autopsies performed at a tertiary centre where an underlying diagnosis of GI pathology as the cause of death was identified.

**Method:** A review of over infant 1,500 autopsies was performed at a tertiary centre. This included analysis of clinical history, preceding symptoms, post-mortem findings and ancillary investigations. Cases were identified of infants in whom GI pathology was the underlying cause of death and these were subsequently reviewed.

**Results:** Of 1,526 autopsies, 15 (1%) were identified as having underlying GI pathology, pertinent to cause of death. This included 5 cases of volvulus, 5 of Necrotising Enterocolitis (NEC) and 3 of intussusception. Of the infants with NEC, 2 were premature, one had IUGR and one had associated congenital anomalies (anal atresia with fistula) respectively. One infant was born at term with no associated risk factors for NEC. Of all 15 cases, 6 (40%) had underlying congenital anomalies of the gastro-intestinal tract, including malrotation, Hirschsprung's disease and tracheo-oesophageal fistula.

7 cases (47% of GI deaths and 8% of SUDI cases) presented as SUDI, including 4 cases of volvulus (2 associated with malrotation), one case of Hirschsprung's, one of intussusception and one case of NEC (with underlying congenital anomalies). Of these sudden deaths, only 3 had preceding symptoms of vomiting. Of the other 4, one was noted to be feeding poorly, one was restless and one had a cold.

**Conclusion:** Underlying GI pathology can rarely present as SUDI and is an uncommon finding in autopsies performed at a tertiary referral centre. Often there are associated congenital anomalies, in particular, malrotation.

**P32****Lung Weights at Autopsy Do Not Allow Identification of Lower Respiratory Tract Infection (LRTI) in Sudden Unexpected Deaths in Infancy (SUDI)**Ⓟ JCH Lau<sup>1</sup>; JW Pryce<sup>2</sup>; MA Weber<sup>3</sup>; MT Ashworth<sup>3</sup>; M Malone<sup>3</sup>; NJ Sebire<sup>2</sup><sup>1</sup>University College London, London, United Kingdom; <sup>2</sup>Institute of Child Health, London, United Kingdom; <sup>3</sup>Great Ormond Street Hospital, London, United Kingdom

**Purpose of the study:** The collection of organ weights remains a traditional part of the autopsy procedure yet the clinical significance of such findings remains uncertain. In part, this is due to the difficulty in determining a 'normal' reference range for comparative analysis. Lower respiratory tract infections (LRTI) remains one of the commonest identifiable causes of death in sudden unexpected death in infancy (SUDI). This study evaluates lung weights in relation to the final cause of death in SUDI to assess the usefulness of lung weight assessment in cause of death determination.

**Methods:** Retrospective analysis of >2,500 consecutively performed paediatric post-mortem examinations at a single centre over a 14-year period (1996-2009). Autopsy cases of liveborn infants (between 0 and 365 days of age) were assessed and combined lung weights were identified and classified based upon macroscopic and histological findings. Using polynomial linear regression models, delta values for lung weights (to account for age) were generated for comparative groups including cases of unexplained SUDI and those with histological evidence of LRTI.

**Results:** Of 1,526 cases of infant death, 886 cases presented as SUDI. Of these, 397 cases were unexplained following a full autopsy including ancillary investigations. Of the 886 cases, 90 had histological evidence of LRTI. Cases of unexplained SUDI (uSUDI) had heavier lungs than the overall group ( $p=0.0001$ ) as did cases of LRTI ( $p=0.02$ ). However, there was no significant difference in lung weights between uSUDI and those with LRTI ( $p=0.34$ ). Lung 'congestion' was reported in 210 (54%) of the cases of uSUDI.

**Conclusion:** Lung weights in SUDI autopsies cannot distinguish between those with and without LRTI. This appears to relate to the presence of 'congestion' in uSUDI, and the inflammatory process in those with pneumonia. Histological sampling is required in all cases to identify LRTI.

**P33****Thymus and Spleen Weight in Sudden Unexpected Death in Infancy (SUDI) in Relation to Cause of Death**P A Warkentin<sup>1</sup>; JW Pryce<sup>2</sup>; MA Weber<sup>3</sup>; M Malone<sup>3</sup>; MT Ashworth<sup>3</sup>; NJ Sebire<sup>2</sup><sup>1</sup>University College London, London, United Kingdom; <sup>2</sup>Institute of Child Health, London, United Kingdom; <sup>3</sup>Great Ormond Street Hospital, London, United Kingdom

**Purpose of the study:** The pathophysiology of unexplained Sudden Unexpected Death in Infancy (SUDI) remains uncertain but recent evidence suggests an infectious aetiology may play some role. Since lymphoid tissue, in particular the thymus and spleen may play an important role in the immune response; we present the largest series of data to date on these organ weights in SUDI in relation to final cause of death.

**Methods:** Data from >1,500 consecutively performed infant autopsies performed by specialist paediatric pathologists at one centre according to a standard protocol were retrospectively recorded into an autopsy database. Cases were separated into unexplained SUDI (uSUDI), accidental deaths and non-accidental injury, systemic sepsis and those with focal histological evidence of infection (such as pneumonia and meningitis). Delta values adjusted for age of thymus and spleen weights were compared between groups.

**Results:** The thymus was heavier in cases of uSUDI, compared to all infants ( $p<0.0001$ ) and those with focal infection ( $p=0.017$ ). Cases with sepsis had heavier thymuses than all cases ( $p<0.0001$ ) and those with focal infection ( $p<0.0001$ ). The spleen was also heavier in cases of uSUDI, compared to all infants ( $p=0.027$ ), but no difference was noted in spleen weight between the other groups including focal infection or sepsis.

**Conclusion:** Cases of uSUDI have statistically significantly heavier thymus and spleen compared to the total infant autopsy population but no consistent difference in weights allows the identification of the subgroup of those with systemic sepsis or focal infection as the mechanism of death.

**P34****Placental Intervillous Haematomas Associated with Fetomaternal Haemorrhage**

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Pregnancy in a 31 year old lady with sickle cell trait was complicated by severe pre-eclampsia and intra-uterine growth restriction, resulting in premature delivery by Caesarian section at 27 weeks. The newborn was anaemic, with excess nucleated red cells, consistent with a response to blood loss or peripheral destruction of red cells. Blood transfusion led to full recovery. Kleihauer test was not done as the mother was Rh pos. Gross examination of the placenta revealed discrete haemorrhagic lesions measuring up to 10 mm. On histology, several haematomas were identified, some being layered intervillous haematomas at the centres of lobules, with adjacent viable villi. Others were centred on the maternal surface and were composed of central areas of haemorrhage with surrounding rims of infarcted villi and intervillous fibrin.

The mother's sickle trait allowed characterisation of the lesions. The hypoxic state of the separated placenta after delivery caused entrapped deoxygenated maternal red cells to sickle, whereas deoxygenated fetal red cells retained their normal morphology. This observation presented an opportunity to study the composition of the vascular lesions, in that it demonstrated which were fetal and which were of maternal origin. It was observed that the intervillous haematomas were composed of normal fetal red cells, but the haemorrhages within infarcts were maternal sickled red cells. There were no fetal nucleated red cells in the placental fetal vessels or in the haemorrhages. These findings suggest that the cause of anaemia could be fetal haemorrhage into the maternal intervillous space.

Fetal haemorrhage can complicate pregnancy, and can contribute to fetal anaemia or demise. It is detectable by Kleihauer test when suspected clinically. This case demonstrates the fetal origin of intervillous haematomas, which when found in placental specimens should raise the possibility of acute fetal haemorrhage.

**P35****The Status of MGMT Protein Expression is a Prognostic Factor For Meningeal Haemangiopericytoma**

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**Purpose:** Meningeal haemangiopericytoma (HPC) have a high tendency to recur and to metastasize outside the central nervous system (CNS). Currently, the use of chemotherapy is ineffective in the treatment of recurrent HPCs. To investigate the prognostic value of the expression status of O<sup>6</sup>-methylguanine DNA methyltransferase (MGMT), and the possible role of certain chemotherapeutic agents for meningeal HPCs, we conducted the current study.

**Methods:** Total twelve cases were obtained from 1992 to 2010. Histological grading is based on new WHO classification of tumours of CNS. Expression status of MGMT protein was assessed by immunohistochemical stain. The percentage and the intensity of staining were semiquantitatively scored from 0 to 4+.

**Results:** There were five men and seven women, with a median age of 37.5 years. Histopathologically, sixty-seven per cent primary tumours belonged to WHO grade II, while 33% belonged to WHO grade III. Immunohistochemically, twenty per cent primary tumours exhibited 3+ to 4+ nuclear staining for MGMT protein. Ten per cent exhibited 2+ staining. Seventy per cent exhibited 0 to 1+ nuclear staining of MGMT protein. Local recurrence occurred in 55% patients. Distant metastasis occurred in 27% patients. The mean of disease-free survival (DFS) was 6.2 and 3.5 years for patients with grade II and III primary tumours, respectively. The mean of DFS was 6.2, 2.5 and 0.3 years for primary tumours with 0 to 1+, 2+, and 3+ to 4+ MGMT staining, respectively.

**Conclusion:** In this study, we confirmed the frequent recurrent and metastatic rate of meningeal HPCs. Primary tumours with higher histological grade and more intensive MGMT staining had shorter DFS. Furthermore, MGMT protein is the key factor in resistance to alkylating agents, such as temozolomide. For the candidate patients for treatment of temozolomide, we suggest one should examine the MGMT expression status of the tumour before chemotherapy.

**P36****Effect of Prolonged Formalin on Immunohistochemical Staining for the Proliferation Marker Ki67**P ER Hitchman<sup>1</sup>; C Hodgkinson<sup>1</sup>; D Roberts<sup>1</sup>; G Ashton<sup>1</sup>; Z Yunus<sup>1</sup>; R Byers<sup>2</sup>; T Ward<sup>1</sup>; C Womack<sup>2</sup>; C Dive<sup>1</sup><sup>1</sup>Paterson Institute for Cancer Research, Manchester, United Kingdom;<sup>2</sup>University of Manchester, Manchester, United Kingdom

Immunohistochemistry remains the gold standard, semi quantitative method to measure tissue biomarkers in situ, but protocols must be standardised for it to be of robust diagnostic, prognostic or predictive value in clinical trials. The length of formalin fixation time is known to affect the ability to detect some tissue biomarkers by IHC and numerous methods have been established to retrieve antigens in formalin fixed tissue. Formalin is the most commonly used fixative that maintains tissue integrity. Here, the impact of formalin fixation time on immunohistochemical detection of the commonly used proliferation marker Ki67 was evaluated. Ki67 IHC is considered to be robust in clinical and research settings but our results showed that formalin fixation for 48 hours or more led to significantly decreased Ki67 staining in both human tumour xenografts and in a clinical leiomyosarcoma specimen. We conclude that standardisation and recording of length of formalin fixation should be taken into consideration when Ki67 measurements are performed and results compared in clinical and research settings.

## P37

### Application of Genie™ Pattern Recognition Software for the Automated Analysis of Immunohistochemical (IHC) Markers in Preclinical Xenograft Models

© M Cumberbatch; N Gray; S Loddick; C Womack

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Automated analysis of xenograft tumour samples currently involves manual annotation of digital slides followed by application of an appropriate image analysis algorithm to the regions of interest. However, some projects comprise large numbers of slides leading to a lengthy manual annotation process. Genie™ (Aperio Technologies Ltd.) is a pattern recognition software tool which can be trained to recognise specific tissues or cell types and then combined with a tuned image analysis algorithm for the automated analysis of digital slides. We have examined here the utility of Genie™ for the automated markup and analysis of pAKT in PC3 and BT474 xenograft samples and for the automated quantitation of androgen receptor in tumour versus stroma in a transgenic model of prostatic cancer, the rat Dunning model. Genie™ classifiers were developed, focusing on recognition of tumour versus necrosis (PC3 and BT474) or tumour versus stroma (Dunning). For PC3 and BT474, the accuracy of automated versus manual markup was examined, together with concordance of image analysis output. For Dunning tumours, the precision of automated recognition of tumour versus stroma was explored.

A high degree of concordance was observed between manual and automated markup, and image analysis output for pAKT expression, in PC3 and BT474 tumours. The classifier developed for structure recognition in the Dunning model identified with a reasonable degree of accuracy tumour versus stroma; however, results were less consistent across the samples due to the more varied morphology of this model. Our data suggest that Genie™ will have utility in the automated annotation and analysis of IHC markers in routine xenograft models. Furthermore, we demonstrate that Genie™ may be valuable in the recognition of tumour versus stroma in Dunning tumours, enabling quantitative assessment of compartment specific IHC markers.

## P38

### KRAS Mutation Assessment between Tumour DNA and Circulating Free DNA in Plasma and Serum Samples

© SR Morgan<sup>1</sup>; E Donald<sup>1</sup>; J Whiteley<sup>1</sup>; J Smith<sup>1</sup>; M Eisenberg<sup>2</sup>; E Kallam<sup>2</sup>; L Kam-Morgan<sup>2</sup>

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Biomarkers that require a tumour sample can impose constraints on clinical utility, particularly in disease settings where obtaining tumour tissue prior to treatment is problematic (e.g. lung cancer). A patient's tumour mutation status has become increasingly important to guide targeted drug therapy, e.g. KRAS in colorectal and non-small cell lung cancers. The development of blood-based biomarkers that accurately reflect the genetic profile of the host tumour is an emerging field. The use of easily obtainable samples such as plasma or serum would be ideal if tumour derived material could be readily extracted and contained the same predictive mutations as the source tumour.

The aim of the study was to correlate KRAS mutations in tumour DNA with tumour-derived cell free or circulating DNA (cfDNA), which may allow biomarker blood tests for detection of cancer and prediction of a likely treatment effect. KRAS mutations were evaluated in a cohort of 71 colorectal cancer cases with matched tumour, serum and plasma. Allele specific PCR tests (ARMS™) were used to detect and quantify tumour, and cfDNA. Mutation detection was compared across the sample types.

KRAS mutation analysis was successful in all colorectal tumour samples, 70/71 plasma samples (98.6%) and 67/71 serum samples (94.4%). Tumour versus plasma sensitivity and specificity was 25.0%, 100% respectively. Tumour versus serum sensitivity and specificity was 15.6%, 100% respectively in this sample set.

In conclusion, cfDNA derived from serum or plasma may be a useful surrogate for mutation detection when a tumour sample is unavailable.

## P39

### Automated Identification of Regions of Interest in Digital Images from Paraffin Sections of Human Non-Small Cell Lung Cancer Using Genie™ Pattern Recognition Software

© C Womack<sup>1</sup>; GD Young<sup>2</sup>; T Johnson<sup>2</sup>; M Cumberbatch<sup>1</sup>; NM Gray<sup>1</sup>

<sup>1</sup>AstraZeneca, Macclesfield, United Kingdom; <sup>2</sup>Flagship Biosciences, Flagstaff, AZ, United States

Despite the increasing speed and utility of digital image recording, marking regions of interest (ROI) for subsequent automated analysis is still relatively time consuming. We have found that Genie™ pattern recognition software (Aperio Technologies Ltd) can be trained to recognise ROI (tumour, necrosis, stroma etc) with reliable and reproducible results in preclinical xenograft samples. This is the first of a series of studies we are undertaking to evaluate Genie™ on human tumour samples.

Fifty non-small cell lung cancer (NSCLC) resection tissue samples were stained with hematoxylin alone and H&E. Whole slide digital images were uploaded into Flagship's Clipper slide database and a small subset were used as trial tissues to generate classifiers for subsequent histology pattern recognition. Images were analyzed using Genie™ software with classifiers for differentiation for different tissue elements, including tumour epithelial cells, stroma, lymphoid infiltrate, and necrosis. Multiple iterations of Genie™ were run and reviewed for sensitivity of tissue type detection.

When compared to visual ROI selection, the sensitivity of Genie™ to identify and annotate the tissue types accurately (tumour, stroma, necrosis and lymphoid tissue) is 85% at best. This is despite adding or removing tissue types from the training montage to try and better refine the solution after each Genie™ run. Results are also dependant on IHC staining intensity.

To increase precision and speed of automated morphological recognition, some degree of manual image mark up is required for NSCLC ROI selection. It is difficult to train Genie™ software to differentiate normal lung morphological features and inflammatory elements from adjacent tumour tissue. A pre-processing manual delineation of ROI is recommended for NSCLC tumors when using this automated tool. Further classifiers will be required for NSCLC morphological subtypes.

## P40

### The Effect of Digital Microscopy on Diagnostic Accuracy and Patient Outcomes in Histopathology: A Systematic Review

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**Background** – Digital pathology (viewing scanned glass slides on a computer screen) is an internationally established educational and research tool, but digital slide technology is now being considered for primary and secondary diagnostic use. Digital pathology promises a number of benefits, both in terms of efficiency and safety, however, the evidence regarding diagnostic accuracy and impact on clinician performance and patient outcomes is not clear. It is therefore important to determine whether the diagnostic information content of digital slides is equivalent to that of glass slides.

**Objective** – To conduct a systematic review to assess the effect of digital microscopy on diagnostic accuracy in histopathology. Additional outcomes such as speed of diagnosis and patient outcomes are also evaluated. The review identifies and reflects on issues (technological, case related and training related) that are associated with effective use of digital slides.

**Methods** – A search was conducted on a number of electronic databases, with no language limitations imposed. We identified crossover trials, multiple reader multiple case studies and validation studies that compared the diagnostic accuracy of digital slides and glass slides. Further studies were identified through hand searching of relevant literature and citation mapping of included studies. Two independent reviewers extracted data and assessed quality of included studies using a recognised assessment tool.

**Results** – An extensive electronic database search yielded a total of 2248 references. Those deemed potentially eligible were retrieved and assessed for inclusion in the review. We consider the implications of the results of the review, including issues for future implementation of digital pathology and promising areas for further research. We reflect on the methods of the included studies and make recommendations for the design of future studies.

## P41

### Tissue MicroArrays, Immunohistochemistry and Informatics: Novel High Throughput Disease Linkage Supporting Decision Making in Oncology Drug Discovery

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Tissue Microarrays (TMA) enable immunohistochemistry (IHC) to deliver high dimensional analyses to link potential drug target to disease. Hundreds of cores of tissue allow high-throughput identification of cellular location and relative amount and distribution of protein in tumour and normal tissue by IHC. We have established a cascade of multitumour, oncology disease specific and disease sub segment TMAs in order to enable a systematic approach to protein expression identification. We describe the informatics platform developed to process the thousands of data points produced.

Delivery of TMA data in a consistent and high throughput manner has been hampered by lack of universal standards, data management tools and analysis software. We have developed an informatics workflow described by standard operating procedures and based on commercial software that incorporates information from TMA maps and tissue metadata including basic histological subtype, grade and stage, with analysis scores generated by-eye and automated systems. Complex analyses looking at pathway markers and classification of disease are visualised with heatmap and clustering tools and bespoke informatics/statistical scripts.

In 2010 we performed nearly 200 TMA IHC biomarker analyses that can be exemplified by androgen receptor IHC expression in a 400 core prostate cancer progression TMA in relation to its localisation in progressive disease and site specific metastasis.

Development and application of informatics tools and infrastructure: increased efficiency through standardisation of analysis of TMAs; centralised archiving of high dimensional IHC information, produced images and data that can be complemented with other forms of analysis data; developed infrastructure being deployed across global research sites and demonstrated that clinical tissue samples can be utilised to address key cancer biology questions regarding target expression.

## P42

### Perforation of a Gastric Peptic Ulcer into the Left Ventricle of the Heart Mimicking Ischaemic Heart Disease: A Case Report

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Gastro-epicardial fistula is a rare condition which is associated with high morbidity and mortality. It can occur as a complication of gastro-oesophageal surgery and in association with oesophageal and gastric malignancies and ruptured peptic ulcers.

We report a case of a 49-year old man who was admitted with chest pain, breathlessness and intermittent back pain. His past medical history included hepatitis C, intravenous drug abuse and oesophago-gastrectomy for a ruptured oesophageal ulcer. The clinical impression was that of acute coronary syndrome; he was prescribed anti-ischaemic medications, and was later discharged home. Several days later he had a sudden onset chest pain and subsequently died.

At autopsy he was found to have perforation of a peptic ulcer of the stomach in a hiatus hernia with erosion of the ulcer into the left ventricle causing myocardial fibrosis. There was no evidence of significant coronary artery disease. Gastro-epicardial fistula should be included in the differential diagnosis of chest pain, mainly in patients with a history of complex gastro-oesophageal disease as early diagnosis can prevent disastrous consequences and death.

## P43

### Pulmonary Carcinoids: A Single Centre 10-Year Retrospective Review

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We conducted a retrospective, single-institutional review of histology specimens of pulmonary carcinoids over a 10-year period, including a qualitative review of specimen reports.

Results: 44 patients were identified (18 male; 26 female), with an age range of 17-81 years. There were 37 therapeutic and 7 diagnostic procedures.

Lymph node sampling was undertaken in 35 cases and was the primary diagnostic procedure in 1 case (mediastinal biopsy).

There were 34 typical and 10 atypical carcinoids (32 central; 12 peripheral). Atypical features assessed were the presence of mitoses and necrosis and Ki67 proliferation rate. Ki67 was recorded in 10 of 44 cases, all within the latter half of the 10-year period.

In the atypical carcinoid group, mitoses were quantitatively analysed in 4 cases. Necrosis was focal in 2 cases.

There was histological confirmation of lymph node metastases in 8 atypical cases and, in 1 of these, metastasis to liver was confirmed.

Using the 2009 TNM staging system, 25 cases were T1N0, 1 T1N1, 8 T2N0, 2 T2N1, 1 T2N1M1, 1 T4N0 and 1 TxA2.

Median follow-up was 41 months (3-127). Recurrent carcinoid developed in 1 typical and 5 atypical carcinoids. The overall survival was 94% for typical carcinoids and 70% for atypical carcinoids.

Conclusion: Identification of atypical histological features in pulmonary carcinoids is critical due to the higher rate of recurrence in these patients, higher mortality rate and higher incidence of lymph node metastases.

## P44

### A study of Fatal Pulmonary Embolism within a defined population on the South Coast of England.

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Pulmonary thromboembolism (PE) is a major cause of morbidity and mortality in hospitalized patients, with PE being the cause of 10% of all hospital deaths. There are 60,000 deaths due to venous thromboembolism (VTE) (pulmonary embolism/deep vein thrombosis) each year in the UK, with 36% of community based incidences linked to a surgical procedure or hospital stay in the preceding 90 days.

However, adequate prophylaxis against VTE during and after hospital stay has the potential to markedly reduce the frequency of VTE related deaths. Despite this, studies show that implementation of prophylaxis is inconsistent with the guidelines, with one study finding that just 60% of eligible patients received VTE prophylaxis.

The primary aim of this study is to ascertain the proportion of patients shown to have fatal PE at post mortem, and those who were not receiving prophylaxis at time of death. The audit also sought to identify individuals at increased risk of fatal PE and therefore candidates for prophylaxis by collating epidemiological variables including age, sex and ethnicity as well as post mortem measurements of BMI and details about the patient's past medical history and medication. In addition the study aims to quantify the rate of fatal PE in the community compared to the hospital setting.

We collected data both prospectively and retrospectively from post mortem examinations undertaken within a defined community between two Coronial districts within the south coast of England between 2009 and 2011. Patients who died of causes other than PE were excluded from the study. Preliminary findings have shown that pharmacological prophylaxis was absent in 92% of cases of fatal PE. 68% of fatal PE cases were female vs. 32% male. 33% of cases had a history of previous PE/DVT. 50% of deaths occurred within hospital, 17% within the emergency department and 33% of deaths were from the community.

Ⓟ = Presenter

**P45****Autopsy Findings within Heart Failure Patients from a Defined Population**Ⓟ JD Shott<sup>1</sup>; A Alimo<sup>1</sup>; B Lockyer<sup>2</sup>; PJ Gallagher<sup>3</sup><sup>1</sup>University of Southampton Medical School, Southampton, United Kingdom; <sup>2</sup>Department of Histopathology, Queen Alexandra Hospital, Portsmouth, United Kingdom; <sup>3</sup>Department of Pathology, Southampton General Hospital, Southampton, United Kingdom

Congestive heart failure presents a significant burden on healthcare services in developed nations. Ageing demographics are expected to account for a 50% rise in congestive heart failure related admissions over the next 2 decades mounting upward spending pressures on already financially constrained health services. Prognosis remains poor with long-term survival worse than for patients diagnosed with bowel and breast cancer.

Heart failure can be difficult to diagnose clinically and identification of pathological lesions associated with heart failure can also be difficult especially in patients who have received appropriate treatment. Review of articles relating to post-mortem findings in patients with congestive heart failure show limited analysis of the frequency of the classical pathological findings in congestive heart failure.

The primary aim of this audit was to record the pulmonary, cardiac, hepatic, splenic and systemic changes which may be seen in patients with evidence of unknown or clinically diagnosed heart failure and to assess the frequency of these pathological findings being seen at post-mortem. This audit also seeks to identify patients most at risk of developing congestive heart failure by collating drug histories, past medical histories and place of death.

We prospectively collected data from post-mortem examinations from a defined population from two Coronial districts along the south coast of England between 2010 and 2011. Patients with no clear evidence of heart failure (determined by either pathological or clinical findings) were excluded from data collection. Preliminary findings show that cardiovascular pathology was evident in 92% of post-mortem cases; pulmonary pathology in 94%; hepatic changes were seen in 79%; splenomegaly in only 26%; and peripheral oedema was noted in 44% of cases. Hypertension, ischaemic heart disease and diabetes were the most common identifiable contributory factors.

**P46****"Macro Round" Teaching — An Under-utilised Teaching Format in Histopathology?**

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Accurate macroscopic description underpins all histopathological examinations. It is vital in the correct staging of some tumours and if not done well it can make microscopic examination very difficult. To underline its importance, there are macroscopic components in the Year 1 assessment and FRCPATH part 2 examination. Despite this, teaching sessions more often concentrate on the development of microscopy skills.

Our department has a monthly consultant-led Macro Round which uses surgical specimens and photographs. Trainees are asked to provide accurate descriptions, formulate an appropriate differential diagnosis and outline their block taking strategy.

We conducted a survey of 12 histopathology trainees (ST1-5) in our department to assess their previous exposure to macroscopic teaching and to explore their attitudes to the Macro Round.

11 trainees responded. They had worked in 23 different departments, predominantly in the South East of England. 5 (21%) of these departments had used macroscopic training methods, outside of day-to-day cut-up. 10 trainees had attended Macro Round teaching in our department with 9 agreeing or strongly agreeing that this was; relevant to their stage of training, interesting and challenging. All trainees agreed or strongly agreed that the training was of high quality. 10 stated they would arrange Macro Rounds when they were consultants.

Good macroscopic description is a key part in the reporting of any histopathology specimen but specific teaching on it is infrequent in the departments within the region. A Macro Round is an interesting and easy session to organise and one that affords valuable learning opportunities in macroscopic description and presentation. We would encourage other trainees to set up this style of teaching in their departments.

**P47****Evaluation of Histopathology Training School Board Year 1 Block Teaching**Ⓟ G Petts<sup>1</sup>; E Byrne<sup>2</sup>; A Green<sup>3</sup>; E O'Hagan<sup>4</sup>; S Cossins<sup>5</sup><sup>1</sup>Thames 2009/10 ST1 Representative, Histopathology Training School Board, London, United Kingdom; <sup>2</sup>Northern 2009/10 ST1 Representative, Histopathology Training School Board, Leeds, United Kingdom; <sup>3</sup>Southern 2009/10 ST1 Representative, Histopathology Training School Board, London, United Kingdom; <sup>4</sup>Midlands 2009/10 ST1 Representative, Histopathology Training School Board, Leicester, United Kingdom; <sup>5</sup>Training Schools Administrator, Histopathology Training School Board, Leeds, United Kingdom

Introduction: Department of Health (DOH) funding, through the Histopathology Training School Board (HTSB), for Year 1 Histopathology training is likely to be reduced in the future and may not support the current level of intensive block teaching. In this situation of reduced funding it was felt necessary to evaluate block teaching in order to provide useful information for future financially unsupported Training Programme Directors regarding trainees' opinions on block teaching. Method: An electronic questionnaire was sent to all Histopathology trainees who had experienced Year 1 DOH funded teaching from 2006-2009. The questionnaire asked qualitative questions regarding the national Bristol block teaching week and regional teaching programmes. Results: 95 trainees responded (37% return). The majority of trainees found both Bristol and regional teaching programmes a valuable experience in terms of theoretical knowledge, practical skills and social networking. When asked to choose either Bristol or regional teaching programmes 50% of non-Thames trainees and 20% of Thames trainees chose Bristol. 70% of non-Thames trainees and 18% of Thames trainees reported that they would attend the Bristol teaching if the funding was to come from their individual study leave budget.

Discussion: The difference between non-Thames and Thames trainees may be a reflection of different teaching programme structure; non-Thames trainees experienced at least two further block teaching weeks whereas Thames trainees received a programme of day release teaching. Training Programme Directors throughout the country may wish to consider the data from this questionnaire when planning their individual training school block teaching needs.

**P48****A Correlation Review of Diagnostic Modalities for Assessing Thyroid Nodules**

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CASE REVIEW: This is a 36 year old female who presented with a thyroid nodule. The patient initially underwent an FNA. This was reported as a Thy5, consistent with papillary carcinoma. The features being hypercellularity, intranuclear grooves, frequent intranuclear inclusions and a coarse chromatin pattern.

At the time of surgery a frozen section was requested. This demonstrated a follicular cystic lesion. There was nuclear crowding and overlapping, the cells had an irregular chromatin pattern with intranuclear inclusions. On the basis of the cytology and frozen section it was felt that this was likely to be a follicular variant of a papillary carcinoma and the patient had a total thyroidectomy.

The paraffin sections confirmed this cystic lesion made up of small thyroid follicles, some containing colloid, again crowded, overlapping nuclei were noted with a few intranuclear inclusions and grooves. Psammoma bodies were not present and typical nuclear clearing "Orphan Annie Eye nuclei" was not prominent. Immunohistochemical staining was performed to confirm the initial cytological diagnosis. Cytokeratin 19 and HMBE were positive the diagnosis of follicular variant of papillary carcinoma was confirmed.

Discussion: This case highlights the difficulties in diagnosing papillary carcinoma, a diagnosis traditionally made on its cytological features. We believe that architectural features and Immunohistochemistry also play important roles in making this diagnosis.

The British Thyroid Association (BTA) advocates surgical management on the basis of a Thy5 alone. The authors wish to emphasise that by taking an MDT approach we should wherever possible adhere to this guidance and encourage our surgical colleagues to do the same. In the current economic climate pathology departments are under pressure to make large financial savings and adding in unnecessary and expensive tests is unhelpful to the departments concerned and the patient.

**P49****An Audit of Pathology Reports of Suspected Renal Cell Carcinoma Specimens**

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The pathologist plays a crucial role in the urological multidisciplinary team by reporting on renal cell carcinoma specimens and providing prognostic information that can be used by the team to determine which patients might benefit from further therapy. It is therefore important that pathologists' reports of the specimens are accurate so that the risk and prognosis associated with the tumour can be determined and an appropriate management plan made early. The Royal College of Pathologists (RCP) set out a dataset for adult renal parenchymal cancer histopathology reporting in November 2006. This dataset lists the core data items that should be included in reports of renal cell carcinoma specimens. A retrospective audit of thirty renal cell carcinoma histopathology reports made in 2009-10 was undertaken at a district general hospital in the North West of England. The reports were audited against the RCP dataset to determine compliance with their reporting standards. Findings show that compliance was 100% with all standards except for sarcomatoid change where only 50% of reports included information about this. In three of these cases (10% of the total) the tumour was grade 4 but evidence of sarcomatoid change was not reported. Good compliance with other items of the RCP dataset is likely due to the use of a standardised proforma which acts as an aide memoir when reporting. We aim to disseminate these findings within the pathology community to improve awareness of the importance of reporting on sarcomatoid change in high grade renal cell carcinoma tumours.

**P50***This abstract has been withdrawn***P51****Multiple Subtypes of Renal Cell Carcinoma in End-stage Kidneys: A Morphological and Immunohistochemical Study of Two Cases**

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End-stage renal disease (ESRD) carries an increased risk of renal cell carcinoma (RCC). Those with acquired cystic disease (ACD) are especially at risk. RCC in end-stage kidneys occurs in younger patients and is more often multifocal and bilateral. It has been reported that the majority of tumours in such kidneys are of two distinct subtypes: ACD-associated RCC and clear cell papillary RCC of end-stage kidneys.

We present two cases in which multiple subtypes of RCC, including ACD-associated tumours, are present in a single nephrectomy specimen.

Case 1: A 41 year-old male with a renal transplant for ESRD had a left native nephrectomy. This contained 6 tumours, including (i) ACD-associated RCC (solid, cystic, papillary and cribriform architecture, with large cells containing eosinophilic or clear cytoplasm with mild nuclear atypia and prominent nucleoli; c-kit positive; focally CK7/vimentin/MOC31 positive; RCC/AMACR negative), (ii) clear cell papillary RCC (papillae lined by clear cells of low nuclear grade; CK7/MOC31 positive; RCC/AMACR/vimentin/c-kit negative), (iii) type I papillary and (iv) conventional clear cell subtypes.

Case 2: A 61 year-old male with a renal transplant for ESRD had a right native nephrectomy. This contained 4 tumours, including (i) ACD-associated (RCC/AMACR/c-kit/MOC31/CD10/Ber-EP4 positive; focally CK7 positive; vimentin negative), (ii) type I papillary and (iii) conventional clear cell subtypes.

The morphology and immunohistochemistry of ACD-associated tumours is characteristic and differs from that of conventional types of RCC. The genetics of the new subtypes also appears to differ from recognised subtypes of RCC. The occurrence of multiple tumour types in one kidney supports the concept that a "field defect" due to the carcinogenic milieu in ACD leads to the production of multiple clones of neoplastic cells.

**P52****11 beta Hydroxysteroid Dehydrogenase Type 2 is a Key Component of Neovascularisation in Renal Carcinoma and Glioma**P S Galbraith<sup>1</sup>; M Gallacher<sup>2</sup>; C Smith<sup>3</sup>; L Christie<sup>2</sup>; S Fleming<sup>1</sup>*<sup>1</sup>University of Dundee, Dundee, United Kingdom; <sup>2</sup>Ninewells Medical School, Dundee, United Kingdom; <sup>3</sup>University of Edinburgh, Edinburgh, United Kingdom*

11 beta hydroxysteroid dehydrogenase type 2 (11HSD2) converts active cortisol to inactive corticosterone to protect mineralocorticoid and glucocorticoid receptors from illicit activation by high levels of circulating glucocorticoids. It has an important role in salt and water regulation in the distal tubule, is important in the maturation of the developing vasculature but may also limit the effectiveness of steroid based therapy.

In a study of expression of 11HSD2 in carcinomas derived from mineralocorticoid responsive tissue we noted 11HSD2 in new blood vessels in some tumours. This study was undertaken to systematically examine for the expression of 11 HSD2 in tumour vasculature during neovascularisation. We used immunocytochemistry on tissue microarrays of renal, ovarian, prostate and colorectal carcinoma and whole section staining of glioblastoma.

We found strong reactivity in pericytes of new blood vessels in 5/5 glioblastomas and 29/30 clear cell carcinomas of kidney. 11HSD2 was found infrequently (<10%) in other renal carcinoma subtypes and in the prostate, ovarian and colorectal carcinomas. RNA was extracted from frozen glioblastoma samples and 11HSD2 specific mRNA identified by rtPCR.

11HSD2 is crucial for normal artery and arteriole formation during development and these data suggest it may be important in protecting tumour neovascularisation from the growth inhibitory effects of endogenous or, importantly, therapeutic glucocorticoids

**P53****Tubulovillous Adenoma of the Bladder associated with Ectopic Colonic Mucosa**

Ⓟ GVS Wathuge; M McCole; ISD Roberts

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Tubulovillous/villous adenomas of bladder are rare benign neoplasms of the urinary tract. They are thus called because they are histologically identical to those common tumours of the gastrointestinal tract. The common sites for urinary tract villous adenomas are bladder and urachus. We report a case where an 86 year-old female patient was found to have an extensive but superficial looking solid/papillary tumour in the bladder.

The biopsy of this tumour showed a tubulovillous adenoma with high grade dysplasia resembling a colonic adenoma with foci suspicious of lamina propria invasion. Subsequently, the whole tumour was resected and submitted for histology which confirmed the previous diagnosis. Together with this resection, a bladder biopsy from a possible diverticulum was also received which showed a fragment of normal-appearing colonic mucosa, indicative of ectopic mucosa rather than glandular metaplasia/cystitis glandularis.

There are two views postulating the possible origin of colonic-type adenomas in the bladder. One suggests that chronic irritation and intestinal metaplasia may later give rise to glandular neoplasia. The other view suggests that cloacal rests may remain in the adult bladder and urachus with the potential to give rise to glandular neoplasms. The presence of well-formed colonic mucosa associated with a tubulovillous adenoma in our case favours the latter view.

Due to their association with invasive malignancies, these lesions must be thoroughly sampled when found. Isolated villous adenomas in the urinary tract have an excellent prognosis. However, those with coexisting infiltrative adenocarcinomas or urothelial carcinomas have a more aggressive course. As such, follow up of patients with adenoma of the bladder with associated invasive carcinoma is recommended.

**P54****MicroRNA-141 Expression in Clear Cell Renal Cell Carcinoma is Linked with Sunitinib Response**

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**Study Purpose:** Sunitinib is the first line targeted therapy for stage IV clear cell renal cell carcinoma (ccRCC) in good and intermediate risk patients according to Memorial Sloan-Kettering Cancer Center criteria. Objective response is reached in  $\pm 40\%$  of patients. MicroRNA's from the miR-200 family are linked with tumour aggressiveness, progression and therapy resistance. Downregulation of microRNA-141, a member of the miR-200 family, is linked with proliferation and invasion through epithelial-to-mesenchymal transition in various types of cancer. We aim to identify whether these epigenetic mechanisms might be linked with sunitinib response.

**Methods:** Fresh-frozen ccRCC tissue samples from a single institution nephrectomy-specimens database of patients who underwent sunitinib treatment between 2006 and 2010 as first-line targeted therapy were included in the study population. Bad responders were considered those patients with progressive disease within 6 months. Patients with progression free survival of more than 1 year were considered good responders. Currently 20 fresh-frozen nephrectomy ccRCC specimens have been analyzed. Fold expression of micro-RNAs was attained by means of real-time qPCR and statistical analysis was performed using a Mann-Whitney U test. Validation by means of in situ hybridization of microRNA-141 was performed on formalin-fixed paraffin embedded ccRCC tissue of the same patients.

**Results:** Expression of microRNA-141 was significantly lower in the bad responders group ( $p=0,0098$ ). In situ hybridization of microRNA-141 shows that bad responders display lower expression of microRNA-141 as compared to good responders.

**Conclusion:** MicroRNA-141 downregulation could play an important role in sunitinib-resistant ccRCC suggesting epithelial-to-mesenchymal transition as an important underlying mechanism. A larger population as well as functional data will be obtained to validate these results.

**P55****Audit of Testicular Tumour Expert Histopathology Referrals**Ⓟ A Merve<sup>1</sup>; A King<sup>2</sup>; S Williams<sup>2</sup>; D Berney<sup>2</sup><sup>1</sup>*Blizard Institute, Barts and the London SMD, London, United Kingdom;*  
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**Introduction:** Testicular pathology is difficult due to rarity and complexity of tumour sub-typing. But the accuracy of the report is paramount as treatment is dependent on histology. The aim of this audit was to review the disagreement rate among the cases referred for expert opinion to North-East London Centre.

**Methods:** 124 cases referred between 2007-2010 from 33 hospitals across the UK were reviewed. Cases were categorised into 'agreement' or 'disagreement' with the initial report. The latter was further subdivided into 'minor' (with no possible effect on patient management) and 'major' (which might have significantly affected treatment). The disagreements were either of tumour 'type' or 'stage'. Where the referrer was undecided on the diagnosis, it was registered as a 'disagreement' if a definitive opinion was reached.

**Results:** There was 'disagreement' in 48 (39%) cases. In 38 (31%) there was major disagreement, 9 (7%) of which were disagreements on vascular or rete testis invasion involving changes in stage between T1 and T2. 29 (23%) of them were significant changes in tumour typing. In 10 (8%) the disagreement would have no effect on patient management. These included 9 over types of germ cell tumour present and 1 with vascular invasion in a T3 tumour.

**Conclusion:** This series included challenging and rare cases referred nationally which may explain the high disagreement rate. This audit emphasises the necessity of continuing specialist referral nationally and for specialist referral for testicular tumours to ensure optimal assessment of the tumour.

**P56****Unusual Morphological Features of Uterine Leiomyomas Treated With Progestogens**

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Uterine leiomyomas are extremely common in surgical pathology practice and in the vast majority there are no issues in diagnosis. Progestogens are widely prescribed drugs for a variety of indications and are often given to women with leiomyomas but the pathological features of leiomyomas treated with progestogens are poorly described. We report the pathological features in 8 cases of uterine leiomyomas in women who had been treated with oral progestogens or a progestogen containing intrauterine device; all cases were received in consultation because the features raised concern for leiomyosarcoma, smooth muscle tumour of uncertain malignant potential (STUMP) or a benign leiomyoma with unusual features. Additionally, we reviewed a series of cases of uterine leiomyomas (n=99) in women who exhibited progestogenic effects in the endometrium. The morphological features in the consult cases, which were widespread and marked and which varied somewhat from case to case, included small and/or large areas of infarct-type necrosis (sometimes mimicking coagulative tumour cell necrosis) with surrounding increased cellularity, mitotic activity, nuclear pyknosis, cytoplasmic eosinophilia, epithelioid morphology, stromal oedema, haemorrhage and myxoid change and infiltration by CD56 positive granulated lymphocytes. Sometimes the features resulted in an almost decidualoid appearance. Similar features were present in minor degree in significant numbers of the additional series of cases. Pathologists should be aware of these progestogen-associated features when reporting uterine leiomyomas since otherwise a diagnosis of leiomyosarcoma or STUMP may be rendered. Useful features in suggesting a benign leiomyoma, in addition to recognition of the morphological features described which in combination are characteristic of progestogens, are the lack of true nuclear atypia and the low mitotic activity away from the abnormal areas.

**P57****A Detailed Immunohistochemical Analysis of Two Cases of Papillary Cystadenoma of the Broad Ligament: an Extremely Rare Neoplasm Characteristic of Patients with Von Hippel-Lindau Disease.**Ⓟ A Brady<sup>1</sup>; WG McCluggage<sup>1</sup>; A Nayar<sup>2</sup>; P Cross<sup>2</sup>; A Patel<sup>2</sup>; R Naik<sup>2</sup>; S Lee<sup>3</sup>; S Kaushik<sup>3</sup>; D Barton<sup>3</sup><sup>1</sup>Royal Victoria Hospital, Belfast, United Kingdom; <sup>2</sup>Queen Elizabeth Hospital, Gateshead, United Kingdom; <sup>3</sup>St George's Hospital, London, United Kingdom

We report two cases of papillary cystadenoma, a rare neoplasm characteristic of patients with Von Hippel-Lindau (VHL) disease, involving the pelvic soft tissues of females and probably arising within the broad ligament. In only one of the women was there a history of VHL disease. The other woman was investigated for VHL disease following the diagnosis of papillary cystadenoma and all tests were negative. There has been debate as to whether papillary cystadenomas in females are of mesonephric (Wolffian) or Mullerian origin and to investigate this we undertook a detailed immunohistochemical analysis. Both tumours were positive with AE1/3, Ber EP4, EMA, CK7, CD10, CA125, CA19.9, calretinin and vimentin. One exhibited focal nuclear staining with WT1 and PAX8. The tumours were negative with oestrogen receptor, progesterone receptor, androgen receptor, CK20, CEA, TTF1, inhibin, RCC marker and hepatocyte nuclear factor 1 beta. Although favouring a mesonephric origin, the immunohistochemical findings are essentially inconclusive and not definitive for either a mesonephric or Mullerian origin. We believe that patients found to have papillary cystadenoma should be investigated for VHL disease if there is no history of this. This is the second reported example of papillary cystadenoma in a female not known to have VHL disease and the first in which investigations have excluded this disease.

**P58****Misplaced Skene's Glands: Glandular Elements In The Cervix, Vagina And Vulva Which Are Variably Prostate Marker Positive And Which Encompass Vaginal Tubulosquamous Polyp And Cervical Ectopic Prostatic Tissue**Ⓟ PJ Kelly<sup>1</sup>; HA McBride<sup>1</sup>; K Kennedy<sup>2</sup>; LE Connolly<sup>1</sup>; WG McCluggage<sup>1</sup><sup>1</sup>Royal Victoria Hospital, Belfast, United Kingdom; <sup>2</sup>Belfast City Hospital, Belfast, United Kingdom

So-called ectopic prostatic tissue in the cervix and vaginal tubulosquamous polyp are rare morphologically similar lesions which may exhibit positive immunohistochemical staining with prostatic markers. It has been suggested that they are related to paraurethral Skene's glands which are the female equivalent of prostatic glands in the male. We report a large series of lesions in patients aged 23 to 81 within the cervix (n=24), vagina (n=10) and vulva (n=2) which we believe to be part of a spectrum of lesions derived from Skene's glands, either eutopic or more commonly misplaced during embryonic development. In all cervical cases, the lesion was predominantly situated in the ectocervix and was an incidental finding in specimens procured for a variety of reasons. In the vagina, the lesions usually presented as polyps or cysts, although occasionally they were an incidental finding. The two vulval cases were incidental findings in punch biopsies. The basic morphological features were of epithelial elements of both glandular and squamous type; in some cases, the glandular elements formed a double cell layer. Uncommon findings included the presence of sebaceous glands in 2 cases (1 cervix, 1 vagina), basaloid formations resembling hair follicle structures in 4 (2 cervix, 2 vagina) and microglandular proliferation resembling nephrogenic adenoma in 1 vaginal case. Prostate specific antigen was positive in 13 of 26 cases and prostatic acid phosphatase in 16 of 26 tested. Six cases were negative with both markers. We propose that these benign lesions in the cervix, vagina and vulva are derived from eutopic or misplaced Skene's glands. Although we recommend retention of the term tubulosquamous polyp for those cases forming vaginal polyps, we consider that these lesions which occur at all sites within the lower female genital tract should be recognised as being of Skene's gland derivation and reported as such.

**P59****Cervical LLETZ Cone Biopsies: How accurate is the histological assessment of depth?**

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Purpose of Study: Colposcopists need to be able to assess the depth of cervical tissue taken by a cone biopsy so that they can achieve adequate excision of ectocervical lesions and counsel women regarding their risk of poor pregnancy outcome. Currently this information is gained from the histology report. Tissue received for histological examination undergoes chemical and physical processing which alters the tissue. Therefore, are histology report dimensions of a cervical cone biopsy a true representation of the actual depth of tissue taken?

Method: Independent data was prospectively collected on the depth of cone biopsies in theatre/outpatients ('fresh tissue depth'), on arrival in the histopathology department (after fixation and prior to dissection – 'macroscopic depth') and from the histology reports and slides.

Summary of Results: 62 cervical LLETZ cone biopsies were included in the study. There was no statistically significant difference when comparing the fresh tissue depth with the macroscopic depth [paired t(60)=0.046, p(0.05)=2.009] or the slide depth [paired t(60)=0.729, p(0.05)=2.009]. There was no significant difference between the study macroscopic depth and the histology report depth [paired t(34)=0.002, p(0.05)=1.691]. Conclusion: The results support the reliance on macroscopic histology reports to guide clinicians on the depth of cone biopsies. Although not statistically significant, interesting trends were seen in the mean tissue depths during the specimens processing (data not included in abstract) which is of interest to Colposcopists and Pathologists.

**P60****A Rare Case of Diffuse Peritoneal Malignant Mesothelioma in a Young Female**Ⓟ Y Alizadeh<sup>1</sup>; P Da Costa<sup>2</sup>; EJ Buxton<sup>1</sup>; N Wilkinson<sup>1</sup><sup>1</sup>St James's University Hospital, Leeds, United Kingdom; <sup>2</sup>Airedale General Hospital, NHS Trust, Airedale, United Kingdom

Peritoneal malignant mesothelioma (PMM) in young female population is extremely rare and histologically and radiologically can mimic the far more common papillary serous carcinoma of the female genital tract. The purpose of this case report is to raise awareness and to avoid misdiagnosis. This is a case report of a 38 year old female patient who presented with abdominal discomfort. The abdominal cross-sectional imaging was performed which demonstrated diffuse peritoneal and left iliac fossa abnormality. The initial left ovarian biopsies showed a well-differentiated papillary neoplasm with psammoma bodies, suggestive of a low-grade papillary serous carcinoma but with equivocal immunohistochemistry. Following the review of the ovarian biopsies at a tertiary centre and discussion of the patient's radiology and histology findings at the MDT meeting, a decision for staging laparotomy was made. The resection specimen was examined and the diagnosis of diffuse well-differentiated PMM was confirmed by immunohistochemistry. On review a previous history of asbestos exposure was established. Conclusion: Papillary PMM is a rare diagnosis and can closely mimic low-grade papillary serous carcinoma of the female genital tract. Early histological diagnosis may alter prognosis and subsequent treatment. In this case report we discuss the diagnostic pitfalls and review the literature.

**P61****Inverted Transitional Papilloma of the Cervix and Vagina: Report of Two Cases of an Extremely Rare Lesion.**Ⓟ CL Hennell<sup>1</sup>; WG McCluggage<sup>1</sup>; J Jamison<sup>2</sup>; M Wells<sup>3</sup><sup>1</sup>Department of Pathology, Royal Group of Hospitals, Belfast, United Kingdom; <sup>2</sup>Antrim Hospital, Antrim, United Kingdom; <sup>3</sup>Sheffield Teaching Hospital, Sheffield, United Kingdom

We report two cases of inverted transitional papilloma of the lower female genital tract, occurring in the cervix and upper vagina of 60 and 50 year old women respectively. Microscopically, the features were similar to those of the corresponding tumour of the urinary bladder with interconnecting solid sheets of bland transitional epithelium with an inverted growth pattern. There were small foci of squamous and mucinous differentiation in the cervical case. Linear array human papilloma virus (HPV) genotyping revealed HPV type 42 in the cervical case. Inverted transitional papilloma in the lower female genital tract is extremely rare with, as far as we are aware, only two previously reported cases in the cervix and none in the vagina. Our results suggest that these neoplasms when occurring in the lower female genital tract may be associated with low risk HPV.

**P62****Clinico-pathological Spectrum of Primary Ovarian Malignant Mixed Mullerian Tumours (OMMMT) from a Tertiary-care Oncology Centre and Correlation with Outcome Variables**

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Purpose of the study: OMMMTs are extremely rare. We aimed to analyse the clinico-pathological characteristics of OMMMT and assess the factors associated with treatment outcome and survival.

Methods: Consecutive cases of OMMMT diagnosed and managed at our institute from 2004-2010 were included. The histology was reviewed and clinical details and follow-up was obtained from hospital medical records in all cases.

Summary of results: A total of 27 cases were included. Median age at diagnosis was 51 years (range, 33-70 years). The mean pre-operative serum CA 125 levels was 5125.2 U/ml (range, 29.6–34851 U/ml). Twenty cases presented as advanced FIGO stage (III/IV). Histology revealed biphasic tumours with 37% epithelial-dominant (ED) and 44% stromal-dominant (SD) with the rest showing equal epithelial and stromal components. The most frequent epithelial and stromal components were endometrioid carcinoma (37%) and rhabdomyosarcoma (29%), respectively. Germ cell/yolk-sac tumour elements were demonstrated in 3 cases. Clusters of intra- and extra-cellular spheroid hyaline-globules amidst sarcomatous zones were striking as "archipelago in a sea of spindle cells" in 60% cases. Upfront cytoreductive surgery was performed in 18 cases whereas 7 patients received neo-adjuvant chemotherapy followed by surgery. Median follow-up was 15 months (range, 3-40 months). The median recurrence-free survival in SD tumours was 10.5 months in comparison to 13 months in ED cases. On Kaplan-Meier survival estimates, stromal-dominant, suboptimal debulking and advanced stage exhibited trends of worse outcome.

Conclusions: Ovarian MMT are rare malignancies. Advanced stage, suboptimal cytoreduction and stromal-dominant tumours may portend worse outcome. Also, hyaline globules amidst sarcomatous areas are an under-recognised feature which may serve as a diagnostic clue in a small biopsy.

**P63****Gamna-Gandy Bodies Associated with Corpora Albicantia**Ⓟ YA Bury<sup>1</sup>; T Chalhoub<sup>2</sup>; AM Ralte<sup>1</sup><sup>1</sup>Cellular Pathology, Royal Victoria Infirmary, Newcastle Upon Tyne, United Kingdom; <sup>2</sup>Women's Services, Royal Victoria Infirmary, Newcastle Upon Tyne, United Kingdom

Gamna-Gandy bodies are nodules of fibrosis containing deposits of iron and calcium encrusted on connective tissues and elastic fibers. They are most commonly observed in congestive splenomegaly. Extrasplenic Gamna-Gandy bodies are rare. No published record of this occurring in the ovary is available in English literature. A case of a 44-year old lady who presented with pelvic pain of 1 year duration is reported here. Imaging revealed an ovarian mass with solid and cystic elements, possibly a mature teratoma. Microscopy showed capsular adhesions, corpora albicantia and haemorrhagic cystic follicles. The corpora albicantia were associated with aggregates of grey-brown refractile structures with a 'fungal filament-like' configuration, showing tinctorial features of elastic fibres. Stellate nodules of yellowish-brown structures containing iron and calcium were also seen adjacent to these nodules.

As far as we are aware, this is the first case report in English literature of Gamna Gandy Bodies in the ovary associated with corpora albicantia. These nodules are thought to result from organization of small haemorrhages. Although haemorrhage is fairly common in the ovary, it is unclear why this entity is so rarely observed in this organ. Recent literature suggests that Gamna-Gandy bodies are more commonly observed on MRI T2 weighted scans producing a hyperdensity. Although we are not aware of a radiological report of Gamna-Gandy bodies in the ovary, an increasing proportion of the population undergo radiological investigations, and we expect that Gamna-Gandy bodies in the ovary will be identified more commonly, leading to surgical removal of suspicious ovarian masses. We would like to raise awareness of this pathology in the ovary to avoid misdiagnosis and prevent over treatment.

**P64****Analysis of Monocarboxylate Transporters 1 and 4 as Biomarkers for Prognosis after Radiotherapy**Ⓟ AL Chadwick<sup>1</sup>; C Womack<sup>2</sup>; G Watkins<sup>3</sup>; BM Bola<sup>1</sup>; N Slevin<sup>4</sup>; J Homer<sup>3</sup>; P Smith<sup>5</sup>; S Critchlow<sup>6</sup>; CM West<sup>3</sup>; S Wedge<sup>6</sup>; IJ Stratford<sup>1</sup><sup>1</sup>School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, United Kingdom; <sup>2</sup>Oncology Clinical Development, AstraZeneca Pharmaceuticals, Macclesfield, United Kingdom; <sup>3</sup>School of Cancer & Enabling Sciences, The University of Manchester, Manchester, United Kingdom; <sup>4</sup>Christie Hospital, Manchester Cancer Research, Manchester, United Kingdom; <sup>5</sup>Bioscience, AstraZeneca Pharmaceuticals, Macclesfield, United Kingdom; <sup>6</sup>Cancer Bioscience, AstraZeneca Pharmaceuticals, Macclesfield, United Kingdom

Hypoxia contributes significantly to tumour progression and rates of disease-free and overall survival. Hypoxic tumour cells utilize the glycolytic pathway for survival, producing vast quantities of lactate. Monocarboxylate Transporters (MCTs) 1 and 4 are key transporters of lactate. MCT1 may transport lactate in a bidirectional manner, whereas MCT4 is responsible for lactate efflux. Efflux of lactate enables sustained high glycolytic rates, maintaining a stable intra-cellular pH. The aim of this research is to carry out the first study evaluating tumour MCT1 and 4 expression as potential biomarkers of prognosis in patients with head and neck squamous cell carcinoma (HNSCC) undergoing radiotherapy. 125 histologically confirmed SCC pre-treatment diagnostic oropharyngeal cancer biopsies (tonsil or posterior third of the tongue) were collected retrospectively from diagnostic archives. The biopsies were analyzed immunohistochemically to evaluate MCT1 and 4 membrane expression. MCT expression was assessed in a double blind manner using a semi-quantitative scoring system. Scores were analyzed for possible correlations with clinicopathological data relating to outcome 5 years post diagnosis, where all patients had received radiotherapy to the primary site. A univariate analysis comparing high (top 25% of scores) vs low MCT expression (lower 75%) showed that MCT4, but not MCT1, is a significant adverse prognostic factor for radiotherapy outcome. High MCT4 expression correlates with poor loco-regional control ( $p = 0.017$ ), reduced cancer-specific survival ( $p = 0.02$ ) and reduced overall survival ( $p = 0.055$ ). In a multivariate analysis high MCT4 expression retained prognostic significance for poor loco-regional control ( $p = 0.007$ ). MCT4 should be explored further as a novel target and biomarker for prognosis and prediction of benefit from hypoxia-modifying therapy in patients undergoing radiotherapy.

**P65****Diagnostic Head and Neck Biopsies – An Audit of the Value of Levels**

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Diagnostic Head and Neck biopsies have a crucial role in patient management and should be reported in a timely and accurately manner. Analysis of data from our laboratory information system (LIMS) showed that only 71% of samples were being reported in 7 days.

As part of a vertical audit, which had been carried out to follow a biopsy from tissue sampling at the clinic to authorization of histology report, we analyzed the number of levels needed for diagnosis with a view to improving our turnaround time.

40 consecutive Head and Neck diagnostic biopsies were identified using the LIMS. We recorded the specimen dimensions and the number of initial and additional levels. Each case was reviewed with a consultant histopathologist with special interest in Head and Neck pathology to determine which level was diagnostic, whether extra levels were needed for the diagnosis and the reasons for this.

28/40 samples had been cut and stained at 3 levels and 1/40 at 2 levels. In 27.5% (11/40) of cases further levels had been requested. In 77.5% (31/40) of biopsies no more than 2 levels were required for diagnosis. In 9/40 cases the first 2 levels were not diagnostic mainly due to (a) poor orientation resulting in cross-cutting (4/9) and (b) the need for deeper levels in larger biopsies ( $\geq 4.0\text{mm}$ ) to demonstrate more epithelium and stroma (4/9).

Our recommendations were that these biopsies should have 2 initial levels and that larger biopsies should be bisected prior to embedding. A reaudit of 32 cases has shown that in 84.4% (27/32) of cases no more than 2 levels were required for diagnosis and only 15.6% (5/32) of cases required further levels. Thus the measures introduced have not resulted in a compensatory increase in requests for further levels and have contributed to a reduction in laboratory workload. This has contributed to an increase in the proportion of diagnostic Head and Neck biopsies reported in 7 days (>80%).

**P66****Hyaline Vascular Castleman's Disease Involving the Biliary Tract**

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Purpose of study : Castleman's disease(CD) of hyaline vascular subtype is an uncommon lesion which most frequently occurs in the mediastinum. We report a case of CD, hyaline vascular subtype involving the biliary tract with obstruction.

Methods : A 43 year old man presented with a 5 week history of abdominal and back pain with biliary obstructive symptoms. He was jaundiced with persistently elevated LFTs. Radiological investigation revealed a stricture in the extrahepatic biliary tract with lymphadenopathy in the gastrohepatic ligament. The clinical impression at the time was of sclerosing cholangitis with bile duct cholangiocarcinoma. Surgical resection of the gallbladder, cystic duct, common bile duct together with the porta hepatis was performed. Summary of results : Histology revealed a follicular lymphoid hyperplastic process exhibiting prominent central hyaline vascular proliferation with hyalinization and 'onion skinning' of lymphocytes. Immunohistochemistry supported the histologic diagnosis of CD of hyaline vascular subtype. There was no evidence of disease elsewhere and the patient was disease free after a 6 year follow-up.

Conclusions : Our case describes the hyaline vascular subtype of CD, a relatively rare disease occurring in a previously undescribed location. Surgery is the primary treatment of choice in unifocal cases, emphasizing the importance of an accurate histopathological diagnosis as clinical and radiological findings are of limited value.

**P67****Carcinoma Head of the Pancreas Masquerading as Hepatocellular Carcinoma: A Case Report**Ⓟ AE Omonisi<sup>1</sup>; OO Olaofe<sup>1</sup>; GO Omoniyi-Esan<sup>2</sup>; AO Adisa<sup>2</sup>; BJ Olasode<sup>2</sup><sup>1</sup>*Obafemi Awolowo University Teaching Hospitals Complex, ILE-IFE, Nigeria;*<sup>2</sup>*Obafemi Awolowo University, ILE-IFE, Nigeria*

**Purpose of the Study:** To highlight the usefulness of postmortem examinations in diagnosing cases of misdiagnosis.

**Method:** A comprehensive review of the case note of this patient, autopsy findings and appropriate literature was done.

**Summary of Results:** A 70 year old trader who presented with upper abdominal swelling of 4 months and yellowish discolouration of the eyes. There was history of weight loss and she smoked 5 sticks per week for 20 years. Physical examination revealed an elderly woman that was moderately pale, severely jaundiced. Examination of the abdomen revealed an epigastric mass which measured 16x10cm, hard, craggy and tender. The liver span was 12cm. Investigations done were; PCV 21%, total bilirubin 516 micro mol/L bicarbonate of 21 micro mol/L, potassium 3.1 mmol/L, sodium 126 mmol/L, Urea 17.5 mmol/L. Serum hepatitis B Antigen was positive and ultrasound done revealed a pancreatic tumour. A diagnosis of hepatocellular carcinoma was made. Autopsy findings revealed a pancreas which weighed 900g, it contained an ill-defined mass in the head of the pancreas with local involvement of peripancreatic tissues. Serial sections of the pancreatic substance revealed a tumour at the head of the pancreas. This tumour obstructs the distal common bile duct as it coursed through the head of the pancreas with marked distension of the biliary tree. The liver weighed 1980g. The capsular surface was rough and showed multiple variably sized tumour nodules displaying umbilication. There were multiple metastatic tumour masses in the lungs. Histology of the pancreatic tissue revealed a well differentiated pancreatic adenocarcinoma, mucin secreting type. While that of the liver and lungs revealed metastatic adenocarcinoma.

**Conclusions:** This case typifies the importance of conducting an autopsy because things are not always what they seem to be. Therefore, high index of suspicions should be the rule when managing a patient.

**P68****Occurrence and Clinicopathological Relevance of Prognostic Markers in Hepatocellular Carcinoma.**Ⓟ O Govaere<sup>1</sup>; A Katoonizadeh<sup>1</sup>; M Komuta<sup>1</sup>; C Janssen<sup>1</sup>; F de Luca<sup>2</sup>; S Vander Borgh<sup>1</sup>; C Verslype<sup>1</sup>; R Aerts<sup>1</sup>; B Topal<sup>1</sup>; F Nevens<sup>1</sup>; J Pirenne<sup>1</sup>; VJ Desmet<sup>1</sup>; M Pinzani<sup>2</sup>; T Roskams<sup>1</sup><sup>1</sup>*University Hospitals Leuven, Leuven, Belgium;* <sup>2</sup>*Università degli Studi di Firenze, Firenze, Italy*

The heterogeneous nature of hepatocellular carcinomas (HCCs) poses a variable clinical outcome which impairs the prognosis for the patient. Currently several markers linked with overall poor survival are being advocated to stratify HCCs, including keratin(K) 19, Epithelial cell adhesion molecule(EpCAM) and  $\alpha$ -fetoprotein(AFP). Although these markers have been used to describe subtypes of HCCs, none of these markers have been simultaneously validated on a large series of HCCs. The incidence of K19, EpCAM, and AFP expression was obtained from 411 FFPE liver biopsies(n=411) from 242 patients with HCC and semi-quantitatively assessed by means of immunohistochemistry with a cut-off value of five percent. Statistical analysis was performed to correlate marker expression to clinicopathological parameters including tumour size, -differentiation, microvascular invasion and metastasis. Out of the 411 HCCs 12 percent showed K19 positivity(n=49), 17 percent EpCAM positivity (n=68), and 7 percent AFP positivity(n=30). K19 expression was significantly correlated with an increased tumour size(p=0.03), decreased tumour differentiation (p=0.0001), metastasis (p=0.0005), and microvascular invasion(p=0.0001). Although 73 percent of the K19 positive HCCs showed EpCAM expression, EpCAM expression itself was not significantly correlated with the clinicopathological parameters. In contrast, AFP expression was significantly correlated with decreased tumour differentiation(p=0.003) and microvascular invasion(p=0.001).

Correlation to histopathological parameters indicated that both K19 and AFP can be used to signify a more malignant subtype of HCC. However the incidence of AFP in HCC is much lower which implies that K19 is a more relevant marker. In the future these markers can be decisive in establishing guidelines for patient treatment and follow up.

**P69****Bile Canalicular Protein Expression is Altered in Chemotherapy-induced Sinusoidal Obstruction Syndrome (SOS)**P A Koshy<sup>1</sup>; A Knisely<sup>2</sup>; SM Robinson<sup>1</sup>; S White<sup>1</sup>; AD Burt<sup>1</sup><sup>1</sup>Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom; <sup>2</sup>Institute of Liver Studies, King's College Hospital, London, United Kingdom

Oxaliplatin is used as a neoadjuvant therapy in the treatment of colorectal liver metastases. Several groups have demonstrated that this agent can cause sinusoidal obstruction syndrome (SOS) which is associated with a poorer post-surgical outcome. SOS is characterised by sinusoidal dilatation and atrophy of perivenular hepatocytes and with nodular regenerative hyperplasia. The precise nature of liver cell injury is uncertain; the purpose of this paper was to investigate changes at the canalicular domain of hepatocytes in oxaliplatin-induced SOS.

Resected liver tissue was available from 50 patients with metastatic colorectal cancer that had received neoadjuvant chemotherapy: (i) 5FU/capecitabine (n=12); (ii) oxaliplatin alone (n=17); (iii) irinotecan alone (n=13); oxaliplatin and irinotecan (n=5). Significant SOS (at least grade 2) was seen in 53% of those receiving oxaliplatin alone and in 15% of those with irinotecan alone but not in any of the two remaining groups. Immunohistochemistry was performed on sections from a subset of cases from the oxaliplatin alone group and the 5FU/capecitabine group for the following canalicular proteins: BSEP; CD10; CD13; CD66; GGT; MDR3; MRP2.

In cases with SOS, there was either loss or reduction in the expression of CD10 and CD66 but no apparent change in the expression of the transporter proteins; the down regulation of the former molecules was seen in areas of atrophy and there was a correlation between the extent of loss and severity of the sinusoidal changes. We speculate that the canalicular alterations may be the result of local ischaemia although the mechanism for the apparent selective loss is unclear. Nevertheless, this may be of functional significance: post operative bilirubin and alkaline phosphatase levels were higher in patients with SOS than those without (p=0.006 and p=0009).

**P70****The Pathology of Flupirtine-induced Liver Injury: Histological and Clinical Study of 6 Cases**P F Puls<sup>1</sup>; C Agne<sup>2</sup>; M Koch<sup>3</sup>; K Rifai<sup>2</sup>; MP Manns<sup>2</sup>; J Borlak<sup>4</sup>; HH Kreipe<sup>5</sup><sup>1</sup>University Hospital Hannover, Hannover, Germany; <sup>2</sup>Department of Hepatology, Gastroenterology and Endocrinology, University Hospital Hannover, Hannover, Germany; <sup>3</sup>Institute of Pathology, Charite University Hospital, Berlin, Berlin, Germany; <sup>4</sup>Fraunhofer Institute of Toxicology and Experimental Medicine, Centre for Drug Research and Medical Biotechnology, Hannover, Germany; <sup>5</sup>Institute of Pathology, University Hospitals Hannover, Hannover, Germany

Flupirtine, a non-opioid analgesic, has been reported to cause liver injury of idiosyncratic type in rare instances. The aim was to characterize the histopathological features of flupirtine induced liver injury, which have not been reported so far. Liver biopsies of five patients with flupirtine induced liver injury and the liver explant of one patient requiring liver transplantation were reassessed. In addition clinical presentation and course were reviewed and clinical follow up was performed. Extensive perivenular necrosis with associated pigmented ceroid-laden macrophages and a mild to moderate lymphocytic infiltrate was a common feature in all cases. Four of six patients showed severe impairment of liver function, transplantation was required in one case. Histological extent of liver necrosis corresponded well to serum aminotransferase levels. An accidental reexposure of one patient resulted in a plasma cell rich hepatitis with perivenular necrosis. This series suggests that flupirtine can cause substantial liver injury, which produces a characteristic morphological picture. Clinical and histological features suggest a drug-induced and immune-mediated toxicity.

**P71***This abstract has been withdrawn***P72****T-cell Large Granular Lymphocytic Proliferations; How Well Do Histology and Flow Cytometry Correlate?**P E Byrne<sup>1</sup>; R Morilla<sup>2</sup>; NM Killeen<sup>3</sup>; E Matutes<sup>2</sup>; KN Naresh<sup>4</sup><sup>1</sup>Department of Histopathology, Hammersmith Imperial College Healthcare NHS Trust, London, United Kingdom; <sup>2</sup>Section of Haemato-Oncology, Institute of Cancer Research, London, United Kingdom; <sup>3</sup>Department of Haematology, Hammersmith Hospital Campus, Imperial College Healthcare NHS Trust, London, United Kingdom; <sup>4</sup>Department of Histopathology, Hammersmith Hospital Campus, Imperial College Healthcare NHS Trust, London, United Kingdom

**Introduction:** T-cell large granular lymphocyte (T-LGL) leukaemia is a rare lymphoproliferative disorder that generally has indolent behavior. Though the roles of peripheral blood, bone marrow aspirate and flow-cytometry are well-defined in the diagnosis of T-LGL leukaemia, the contribution of bone marrow trephine biopsy (BMTB) has yet to be established.

**Aim:** To compare BMTB investigations with flow-cytometry in patients with suspected T-LGL leukaemia.

**Methods:** BMTB, flow-cytometry and T-cell clonality reports, from January 2003 to December 2010, from patients suspected to have T-LGL proliferations on either flow-cytometry or BMTB were reviewed. Flow-cytometry panels included antibodies to CD2, CD3, CD4 CD8, CD5, CD7, CD 56 and CD57. Immunohistochemical panels on BMTB included CD3, CD5, CD4, CD8, CD56, CD57 and perforin/granzyme B.

**Results:** A total of 15 cases were studied. In 3 cases the BMTB was inadequate and in 1 case the flow-cytometry sample was suboptimal. Of the remaining 11 cases: a) In 7 cases both the BMTB and flow-cytometry reported T-LGL proliferation, of these 5 cases were tested for T-cell receptor gene rearrangements and 3 showed a clonal T-cell population. b) In 2 cases BMTB suggested LGL proliferation which was not confirmed on flow-cytometry, a clonal T-cell population was seen in 1 of these cases. c) In 2 cases, flow-cytometry suggested LGL proliferation, while the BMTB did not. In 1 of these cases the T-cell clone was small and the other case represented a patient with acute myeloid leukaemia on chemotherapy.

**Conclusion:** BMTB and flow-cytometry correlated in 64% of cases (7/11). This study supports the need to perform flow-cytometry, BMTB and T-cell clonality to aid in the diagnosis of T-LGL leukaemia and highlights the complementary nature of these three investigations.

**P73****In-situ Mantle Cell Lymphoma**

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**Introduction:** Mantle cell lymphoma (MCL) is a rare, aggressive B cell non-Hodgkin lymphoma composed of small lymphoid cells. It is associated with a translocation between chromosomes 11 and 14 that results in increased expression of cyclin D1, which regulates cell cycle progression.

**Case History:** A 69 year old male smoker presented with increasing shortness of breath. A mediastinoscopy was performed and lymph node biopsy taken. The differential diagnoses at the time included bronchogenic cancer, lymphoma and tuberculosis.

**Histology:** The lymph node biopsies showed small follicles, some of which appeared primary and others having small, reactive germinal centres with mild to moderate expansion of the mantle zones.

**Immunohistochemistry:** A proportion of the primary follicles and the expanded mantle zones surrounding reactive germinal centres contained cells which were positive for CD20, CD5, IgM, IgD and cyclin D1 and negative for CD10, there was also a suggestion of lambda light chain restriction in these areas. Ki-67 expression was <5% in the cells.

**Diagnosis:** In-situ MCL.

**Discussion:** Although very rare, In-situ MCL may easily be misdiagnosed as a reactive process due to the perseverance of normal architecture. Mantle zone expansion or a monotonous population of cells within the mantle zone should arouse suspicion. Cyclin D1 immunohistochemistry is invaluable in these cases. The biology of in-situ MCL and therapeutic implications are unclear at the present time.

**P74****Two Rare Manifestations of Haematological Malignancies**

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**PURPOSE OF STUDY:** To report two rare presentations of haematological malignancy: 1) A solitary cutaneous lesion as the first and only presentation of Hodgkin lymphoma and 2) Extramedullary haematopoiesis in a patient with myelofibrosis presenting as pleural effusion.

**METHODS:** Case notes and pathological specimens of both the cases were reviewed. A literature search was done.

**SUMMARY OF THE RESULTS:** The first patient, an 83-year-old lady presented with a slowly growing lesion on the forehead. No lymphadenopathy was seen clinically or radiologically. Skin biopsy showed morphological features of nodular sclerositis Hodgkin lymphoma which was confirmed by immunohistochemistry. Truly localised cutaneous disease was confirmed by PET scan and the excellent response to chemotherapy and ongoing remission suggest an indolent course.

Whilst cutaneous involvement by Hodgkin lymphoma is rare, but well described, it is highly unusual for it to present as a solitary cutaneous lesion with no evidence of disseminated disease. The majority of reported cases of cutaneous Hodgkin lymphoma occur as a manifestation of stage IV disease. The second patient, a 60-year-old man presented with cough, breathlessness and a left pleural effusion revealed on CT thorax. He had a history of myeloproliferative disease. Video assisted thoracoscopy was performed and biopsies taken confirmed extramedullary haematopoietic tissue in the pleura.

**CONCLUSIONS** These cases highlight two very unusual clinical manifestations of haematological malignancies. 1. Solitary cutaneous Hodgkin's lymphoma is exceedingly rare but one must be aware of this possibility. 2. Extramedullary haematopoiesis causing pleural effusion is very occasionally observed but needs to be considered in patients with haematological diseases.

**P75****Intraoperative Flow Cytometry Diagnosis of Follicular Lymphoma During a Renal Transplantation Procedure**

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Intra-operative pathological diagnosis relies on rapid assessment of H&E stained frozen sections (FS). Ancillary diagnostic tests are not feasible due to time constraints. We present a case in which flow cytometry (FC) crucially complemented FS diagnosis.

A 68-year woman underwent a live related donor renal transplantation for end stage focal segmental glomerulosclerosis. During the procedure a large right iliac lymph node (LN) was noted compressing the ureter and causing hydronephrosis. The donor kidney from patient's daughter had already been removed. FS of the LN revealed a monomorphic follicular proliferation suspicious of follicular lymphoma (FL). As the features were not diagnostic, following an advice of a haematopathologist, an urgent FC analysis on disaggregated cells from the LN was completed within 30 minutes. FC revealed a B-cell clone of germinal centre immunophenotype, confirming the diagnosis of FL. This was later corroborated on paraffin sections. An intra-operative consultation between the surgeon, haematopathologist and haematologist concluded that FL would pose a low risk for disease progression under immunosuppression provided additional lymphoma specific therapy is administered. The transplant procedure was completed with uneventful postoperative recovery. A modified immunosuppression regimen without Tacrolimus was administered also including Rituximab. Two months post intervention the patient is alive and well with no rejection and with stable FL.

To the best of our knowledge intraoperative use of FC has not been reported in diagnosis of lymphoma and has rarely been applied for other malignancies. This technique gives an opportunity for rapid immunophenotyping of solid tissue samples in emergency circumstances such as FS. Our case also highlights the importance of multidisciplinary and subspecialist expert opinion in handling difficult FSs.

**P76****A Mouse Model for Osseous Heteroplasia**J Peters<sup>1</sup>; K Vowell<sup>1</sup>; L Jones<sup>1</sup>; Ⓟ M Warren<sup>2</sup>; M Cheeseman<sup>1</sup>*<sup>1</sup>Mammalian Genetics Unit, MRC Harwell, Oxfordshire, United Kingdom; <sup>2</sup>Pathology Diagnostics Ltd, Cambridge, United Kingdom*

In humans, loss of function mutations in the imprinted gene *GNAS1* give rise to pseudohypoparathyroidism type 1A (PHP1a) with PTH resistance when maternally inherited, and pseudopseudohypoparathyroidism (PPHP) when paternally inherited. Both can be associated with dermal ossification which on paternal inheritance can lead to progressive osseous heteroplasia (POH). In this condition, ectopic bone formation in the dermis and subcutaneous fat progresses to extend into deep connective tissue and skeletal muscle.

In the mouse, oedematous-small (Oed-Sml) is a loss of function mutation in *Gnas*. When maternally inherited it gives the Oed phenotype characterized in adults by a reduced metabolic rate and susceptibility to obesity. Paternal inheritance gives rise to the Sml phenotype where adults have increased metabolic rates and are resistant to high fat diets. In this study we investigated the radiological and pathological changes associated with heterotopic ossification in adult Oed and Sml mice up to 15-months-old. Oed mice are strongly resistant to PTH and Sml mice are partially resistant. Both Oed and Sml mice have hypocalcaemia, reduced bone mineral density and males and females develop dermal ectopic ossification. The incidence of heterotopic ossification is >84% and while the number and cumulative area of skin lesions increase in severity with age, heterotopic ossification does not affect deeper tissue. 12-32% of mice have a second skin phenotype characterized by pedunculated or sessile fibromatous masses on sparsely haired skin of the tail and feet. Thus the Oed-Sml mouse mutant is a model for dermal osseous heteroplasia but is not truly 'progressive' (POH).

**P77****Extra-gastrointestinal Stromal Tumours: A Clinico-pathological and Immunohistochemical Analysis of Forty-four Cases at a Single Tertiary-care Oncology Centre**

P MM Bal; M Deshpande; K Deodhar; S Arya; S Shrikhande; M Mallath; B Rekhi; NA Jambhekar; M Ramadwar

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Purpose of the study: Extra-gastrointestinal stromal tumours (EGISTs) are mesenchymal neoplasms identical to their gastrointestinal (GI) counterparts, albeit without evidence of GI attachment. We analysed the clinico-pathological and immunohistochemical spectrum of EGISTs. Methods: All consecutive intra-abdominal gastrointestinal stromal tumours (GISTs) with no gross or histological evidence of attachment to GI tract were reviewed and diagnosis confirmed according to WHO classification. Metastatic/recurrent GIST, other specific mesenchymal neoplasms and cases with inadequate histological material were excluded. Clinical details and follow-up was obtained from hospital medical records.

Summary of Results: Of the total 543 GISTs, 44 cases (including 23 consultation cases) were identified as EGIST. Age ranged from 23-80 years and male to female ratio was 2.6:1. Mean tumour size was 12.6 cm. The commonest site of tumour localisation was retroperitoneum (n=15), followed by mesentery (n=12), omentum (n=8), pelvic cavity (n=7), rectovaginal septum (n=1) and prostate (n=1). Tumours formed either a solitary (n=29) or multiple masses (n=15). Tumour cells exhibited spindle (66%), epithelioid (28%) or mixed morphology (6%). Spindle-type predominated at all sites except in the mesentery. Tumours expressed c-Kit (100%), CD34 (40%), bcl-2 (55%), smooth muscle antigen (14%) and S-100 (5%) while none expressed desmin. Follow-up information was available in 19 cases (range, 4-69 months; median, 13 months). Six cases recurred while 8 patients developed metastasis. Conclusions: EGISTs are neoplasms with identical histological and immunohistochemical characteristics as conventional GISTs. However, their origin remains conjectural. Inclusion of EGIST in the differential diagnoses of mesenchymal intra-abdominal neoplasms is prudent to avoid diagnostic and treatment errors.

**P78****Five Year Audit of Skin Immunofluorescence Reports: The Mater Hospital Experience**P MR Downes<sup>1</sup>; NJ Mulligan<sup>2</sup>*<sup>1</sup>Department of Histopathology, Mater Misericordiae University Hospital, Dublin, Ireland; <sup>2</sup>Mater Misericordiae University Hospital, Dublin, Ireland*

Purpose: We performed a retrospective audit of all in-house skin direct immunofluorescence (DIF) reports between 2005-2009. The aim was threefold, to assess the correlation of clinical impression and H&E histology with DIF results and determine the false negative and positive DIF rates, secondly to assess the value of DIF according to diagnostic category and finally to develop a workflow to minimise inappropriate requests. Methods: The immunology records were searched for all skin biopsies performed between 2005 and 2009. The corresponding histology reports for these specimens were also accessed. The cases were divided into four diagnostic categories based on the clinical indication for the biopsy: blistering, autoimmune, vasculitic disease and those with an inappropriate indication were designated to the category 'other'. The data was audited using agreed dataset criteria: sex, age, clinical indication, histology result and DIF result. The data was analysed in Excel spreadsheet format. False positive and negative DIF rates were recorded. Results: We identified 320 cases in the review period: blistering (n=114), autoimmune (n=63), vasculitic disease (n=59) and 'other' (n=84). Clinical/histological correlation varied from 83% in the vasculitic group to 48% in the blistering group. Overall, the false negative DIF rate was 30% (52% in vasculitis category) and the false positive rate was 0.02%. 26% of cases were inappropriate referrals for DIF ('other' category). Conclusions: We concluded that routine DIF for vasculitis is mostly unnecessary and recommend that assessment of all skin DIF requests be performed by a pathologist prior to analysis to minimise inappropriate resource usage.

**P79****Case Report of an Unusual Skin Tumour Mimicking Basal Cell Carcinoma**

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Adamantinoid trichoblastoma (also known as cutaneous lymphadenoma) is an unusual cutaneous neoplasm which typically arises on the head and neck of young to middle-aged patients. We report a case of an adamantinoid trichoblastoma from the forehead of a 30 year old Mexican lady, initially reported as a basal cell carcinoma of infiltrative subtype. Clinically, she had a lightly pigmented nodule on her left forehead, which had been slowly increasing in size over the past seven years. The patient underwent a skin punch biopsy, which showed an unencapsulated dermal lesion composed of irregular epithelial islands embedded within a fibrous stroma. A key feature of adamantinoid trichoblastoma is the characteristic biphasic appearance of the epithelial islands with peripheral palisading of basaloid cells and a central area composed of larger pale cells with a florid lymphocytic infiltrate. The differential diagnosis includes infiltrative or clear cell-type basal cell carcinoma, trichoepithelioma, clear cell syringoma, and lymphoepithelioma-like carcinoma of the skin. We present the clinical, histological, and immunohistochemical findings of this rare tumour. In addition, we provide a review of the literature and summarize key points helpful in distinguishing the tumour from other histologically similar cutaneous lesions.

**Presenters'  
Index**

*Presenter's name  
followed by  
Abstract number(s)*

<b>A</b>	Abdel-Fatah, TMA ..... O3	<b>H</b>	Hav, M ..... O8, O15	Pryce, JW ..... O34, P31
Ahmed, M ..... O24	Hennell, CL ..... P61	Herrington, CS ..... S4	Puls, F ..... P70	<b>Q</b>
Al-Ghamdi, S ..... O28	Hitchman, ER ..... P36	Ho-Yen, C ..... P1	Quaglia, A ..... S19	Quinn, AM ..... O32, P23
Alimo, A ..... P44	Hutchins, G ..... O20	Ibrahem, S ..... PL2	<b>R</b>	Radhi, JM ..... P18
Alizadeh, Y ..... P60	Ironsides, AJ ..... P7	Jacob, A ..... P26	Rahman, MAU ..... P75	Rao, AS ..... O37
Allen, MD ..... O2	Jasani, B ..... P9	Jubb, AM ..... S22	Rao, P ..... P10	Rao, P ..... P10
Anaspure, RJ ..... P74	Jubba, AM ..... S22	Kelly, PJ ..... P58	Remmeling, M ..... O33	Richman, SD ..... O12
Arends, MJ ..... PL6	<b>K</b>	Kindle, KB ..... O14	Rickaby, W ..... P34	Rickaby, WR ..... P79
Athanasou, NA ..... O38	Kloppel, G ..... S27	Komuta, MK ..... O7	Rickaby, WR ..... P79	Roberts, ISD ..... O9, S30
<b>B</b>	Koshy, A ..... P69	<b>L</b>	Robinson, GD ..... P17	<b>S</b>
Baker, EA ..... P4	Langer, R ..... O11	Lantuejoul, S ..... S16	Salmon, I ..... S12	Sempoux, C ..... S8
Bal, MM ..... P77	Lau, JCH ..... P32	Lau, JCH ..... P32	Sheahan, K ..... S9	Shepherd, NA ..... O13
Bateman, AC ..... S7	Le Brenne, AC ..... P19	Le Quesne, J ..... P2	Sheppard, MN ..... O31	Shott, JD ..... P45
Beran, G ..... P41	Lerut, E ..... S31	Liebmman, R ..... O1	Shott, JD ..... P45	Sundaresan, V ..... O4, O5
Berkers, JHM ..... P54	Lievelde, MCS ..... O36	Lloyd, KL ..... P25, P46	<b>T</b>	Thorgeirsson, S ..... S21
Berney, DM ..... S28	Lloyd, KL ..... P25, P46	<b>M</b>	Thunnissen, E ..... S15	Timens, W ..... S14
Bosman, FT ..... S23	Marbaix, E ..... S3	McCluggage, WG ..... S2	Timmers, LM ..... O16	Timmer, LM ..... O16
Boyd, C ..... P56	McCluggage, WG ..... S2	McNicol, AM ..... S25	Titiloye, NA ..... P11	Tursini, MS ..... P28
Brady, A ..... P57	McNicol, AM ..... S25	McVeigh, G ..... O30	<b>V</b>	Van Leenders, GJL ..... S29
Brougham, K ..... P48	McVeigh, G ..... O30	Mellor, MS ..... P49	van Nederveen, FH ..... S26	van Nederveen, FH ..... S26
Browning, L ..... P51	Mellor, MS ..... P49	Menon, S ..... P62	Van Vlierberghe, H ..... S18	Vergheese, ET ..... PL5
Bury, YA ..... P63	Merve, A ..... P55	Minas, E ..... P30	<b>W</b>	Warkentin, A ..... P33
Byrne, E ..... P72, P73	Minas, E ..... P30	Moore, L ..... P42	Warren, M ..... P76	Warren, M ..... P76
<b>C</b>	Morgan, SR ..... P38	<b>N</b>	Warren, MV ..... P15	Wathuge, GVS ..... P53
Carvalho, B ..... O21	N Kalimuthu, SNK ..... P24, P66	Nagy, A ..... P65	Wellings, R ..... P12	Wells, M ..... S5
Chadwick, AL ..... P64	Nicholson, AG ..... S6, S13	<b>O</b>	West, NP ..... O17	West, NP ..... O17
Chang, IW ..... P35	<b>O</b>	O'Mahony, OH ..... P16	Williams, BJ ..... P40	Williams, BJ ..... P40
Clarke, LPM ..... P43	O'Mahony, OH ..... P16	Omonisi, AE ..... O23, P13, P67	Williams, ED ..... S24	Williams, ED ..... S24
Collis, SA ..... P5, P6	Omonisi, AE ..... O23, P13, P67	Onwu, N ..... PL3	Womack, C ..... P3, P20, P39	Womack, C ..... P3, P20, P39
Collis, SA ..... P5, P6	Onwu, N ..... PL3	<b>P</b>	<b>Y</b>	Yap, ZM ..... P29
Cumberbatch, M ..... P37	Pelekianou, V ..... O10	Petts, G ..... P47, P59	<b>Z</b>	Zucman-Rossi, J ..... S20
Cuvelier, CA ..... S32	Piets, G ..... P47, P59	Piot, P ..... S17		
<b>D</b>	Piot, P ..... S17	Poulsom, R ..... PL4		
De Smet, R ..... O22	Poulsom, R ..... PL4			
Delvenne, PH ..... S1				
D'Haene, N ..... O35				
Downes, MR ..... P78				
Dungwa, JV ..... P27				
<b>E</b>				
East, M ..... O18				
Elewaut, D ..... S11				
Emami, EMA ..... P21				
Ewington, LJ ..... O29				
<b>F</b>				
Fadhil, WM ..... O19, O27				
Fijneman, RJA ..... O25				
<b>G</b>				
Galbraith, S ..... P52				
Gallacher, MA ..... P14				
Geboes, K ..... S10				
Going, JJ ..... O6, P8, P22				
Goos, JAC ..... O26				
Govaere, O ..... P68, PL1				