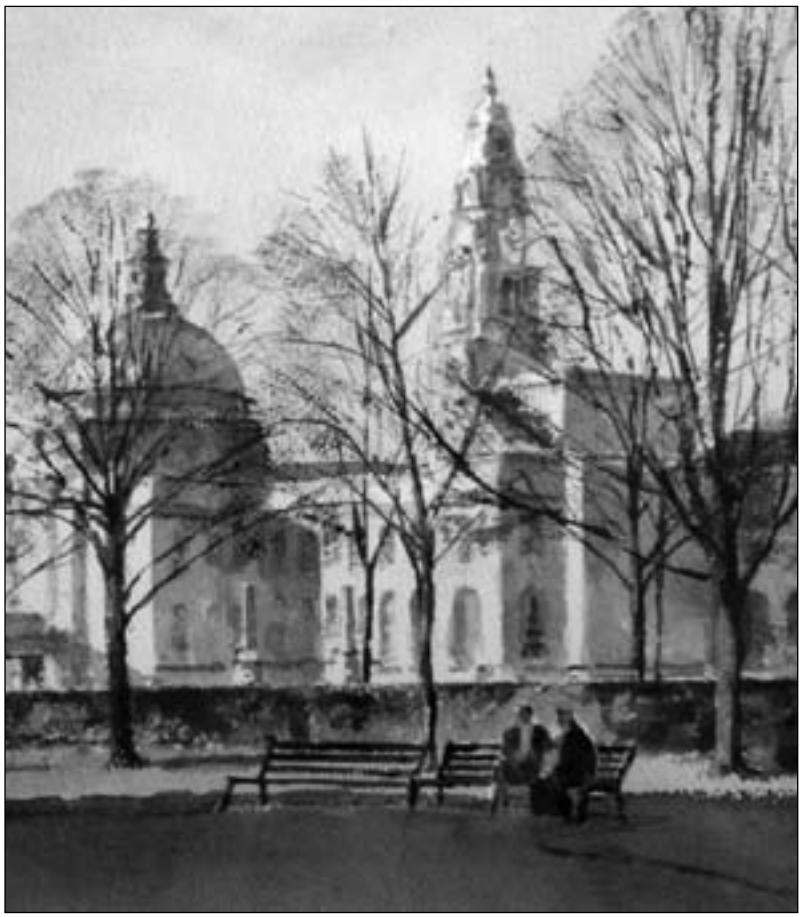
CARDIFF PATHOLOGY 2009



30 June – 3 July 2009

Fifth 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 Cardiff University

Venue
The Mercure Holland House Hotel and Spa, Newport Road, Cardiff CF24 0DD, UK

There will also be Companion Meetings with the Association of Clinical Electron Microscopists, Liver EQA, Renal EQA, UK NEQAS for Cellular Pathology and UK NEQAS for ICC & ISH

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

Pathological Society
Understanding Disease

Programme Contents

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PROGRAMME ACKNOWLEDGEMENTS

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and the Pathological Society of Great Britain & Ireland

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CARDIFF PATHOLOGY 2009

Programme Summary
(Quick Reference)

Tuesday
30 June 2009

08.00 [Reception]
Registration and Coffee

09.00–17.00 [Shetland Room – 2nd floor]
Slide Seminar Competition Case Viewing: ***Iatrogenic pathology***

09.00–12.45 [Balmoral 1]
Symposium: ***Genomic instability in health and disease***

10.30–11.00 [Balmoral 2 & Reception]
Coffee

12.45–13.00 [Balmoral 1]
Welcome Address
Prof S Tomlinson, CBE, Provost, Cardiff University

13.00–14.00 [Restaurant – 1st floor]
Lunch *Dessert and Coffee:* [Balmoral 2 & Reception]

13.30–14.30 [Argyll Room – 2nd floor]
Meet the Experts: ***Lymphoma Diagnosis and Classification – WHO and beyond***

14.00–15.00 [Balmoral 2 & Reception]
Poster Viewing and Trade Stands

15.00–17.00
[Argyll Room – 2nd floor]
Symposium: ***Airborne mineral particles and lung disease***

15.00–17.00
[Balmoral 1]
Oral Presentations

15.00–17.00
[Caernarfon Suite – 1st floor]
Oral Presentations

17.00
Buses depart for public lecture

17.30–18.30 [Reardon Smith Lecture Theatre, Park Place]
Public Lecture
Professor Sir Martin Evans, Nobel Laureate, Cardiff University School of Biosciences

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18.30–20.00 [National Museum of Wales, Grand Hall & Impressionist Galleries] — *adjacent to Reardon Smith LT*
Welcome Reception
Sponsored by: School of Medicine, Cardiff University

07.30 [Reception]
Registration and Coffee

07.45–09.00 [Argyll Room – 2nd floor]
Breakfast Meeting for Trainees*: *Cervical cytology in 2009: recent advances and what you need to know for the FRCPath*
***** *Breakfast will be provided outside the lecture theatre*

09.00–17.00 [Shetland Room – 2nd floor]
Slide Seminar Competition Case Viewing: *Iatrogenic pathology*

09.00–12.00 [Balmoral 1]
Symposium: *Dissecting colorectal cancer – molecules to macroscopy*

10.15–10.45 [Balmoral 2 & Reception]
Coffee

10.00–15.30 [Caernarfon Suite – 1st floor]
UK NEQAS for Cellular Pathology Technique 2009 Annual Meeting

11.20–11.50 [Balmoral 2 & Reception]
Coffee

12.00–12.45 [Balmoral 1]
Pathological Society 29th CL Oakley Lecture
Dr A Ibrahim, Cambridge

13.00–14.00 [Restaurant – 1st floor]
Lunch *Dessert and Coffee:* [Balmoral 2 & Reception]

13.00–14.00 [Argyll Room – 2nd floor]
Liver EQA Meeting

14.00–15.00 [Balmoral 2 & Reception]
Poster Viewing and Trade Stands

15.00–17.00 [Balmoral 1]
Plenary Oral Presentations

15.30–16.00 [Balmoral 2 & Reception]
Tea

17.00–18.00 [Balmoral 1]
British Division of the IAP: George Cunningham Lecture
Prof GT Williams, Cardiff University

18.00–19.30 [Balmoral 2 & Reception]
Formal Chairman's Poster Rounds *(All categories)*
and Refreshments
Sponsored by: Environmental Lung Disease Research Group, Department of Pathology, Cardiff

07.45 [Reception]
Registration and Coffee

08.30–10.00 [Caernarfon Suite – 1st floor]
Oral Presentations

10.00–10.30 [Caernarfon Suite – 1st floor]
Renal Pathology Group

09.00–17.00 [Shetland Room – 2nd floor]
Slide Seminar Competition Case Viewing: *Iatrogenic pathology*

09.30–12.00 [Argyll Room – 2nd floor]
Slide Seminar Discussion: *Iatrogenic pathology*

09.00–09.30 [Balmoral 1]
Historical Presentations

09.30–13.00 [Balmoral 1]
Oral Presentations

09.20–10.30 [Caerphilly Room – 3rd floor]
Association of Clinical Electron Microscopists Annual General Meeting [ACEM]

10.30–11.00 [Balmoral 2 & Reception]
Coffee *(for ALL morning sessions)*

11.00–13.00 [Caernarfon Suite – 1st floor]
Joint UK Renal Pathology Group / ACEM Session

13.00–14.00 [Restaurant – 1st floor]
Lunch *Dessert and Coffee:* [Balmoral 2 & Reception]

13.30–14.30 [Argyll Room – 2nd floor]
Pathological Society Annual Business Meeting

14.00–15.00 [Caernarfon Suite – 1st floor]
Renal EQA Meeting

14.00–14.30 [Balmoral 2 & Reception]
Poster Viewing and Trade Stands

14.30–17.00
[Balmoral 1]
Symposium:
UK NEQAS for ICC & ISH:
Trends in diagnostic immunocytochemistry

14.30–17.00
[Argyll Room – 2nd floor]
Trainees' Symposium:
A beginner's guide to pathology research

14.00–17.00
[Caerphilly Room – 3rd floor]
Association of Clinical Electron Microscopists meeting
—continued

15.30–16.00 [Balmoral 2 & Reception]
Tea *(for ALL afternoon sessions)*

17.00–18.00 [Balmoral 1]
Pathological Society's 6th Doniach Lecture
Prof BA Gusterson, University of Glasgow

19.30–23.00 [Assembly Room, City Hall, Cardiff]
Conference Dinner

08.15 [Reception]
Registration and Coffee

09.00–12.15 [Caernarfon Suite – 1st floor]
Symposium: ***Prostate cancer: the present and future for histopathology***

10.30–11.00 [Outside Caernarfon Suite – 1st floor]
Coffee

Packed lunches are available to take away

COMPANION MEETINGS

Wednesday 1 July

10.00–15.30 UK NEQAS for Cellular Pathology Technique **[Caernarfon Suite – 1st floor]**
13.00–14.00 Liver EQA **[Argyll Room – 2nd floor]**

Thursday 2 July

09.20–17.00 Association of Clinical Electron Microscopists **[Caerphilly Room – 3rd floor]**
10.00–15.00 Renal Pathology Group, incorporating Joint session with ACEM **[Caernarfon Suite – 1st floor]**

KEYNOTE AND NAMED LECTURES

Tuesday 30 June

12.10–12.45 Keynote Lecture: *Defective biological responses to DNA damage and human disease*
Prof E Freidberg, Texas **[Balmoral 1]**
17.30–18.30 Public Lecture: *Inheritance from teratocarcinomas*
Prof Sir Martin Evans, Cardiff **[Reardon Smith Lecture Theatre]**

Wednesday 1 July

12.00–13.00 CL Oakley Lecture: *DNA methylation in the natural progression and early detection of colorectal neoplasia*
Dr A Ibrahim, Cambridge **[Balmoral 1]**
17.00–18.00 George Cunningham Lecture: *Elephant traps in gastrointestinal surgical pathology*
Prof GT Williams, Cardiff **[Balmoral 1]**

Thursday 2 July

17.00–18.00 Doniach Lecture: *Normal biology and new insights into breast cancer*
Prof BA Gusterson, Glasgow **[Balmoral 1]**

ORAL COMMUNICATIONS

Sessions will be held as follows:

Tuesday 30 June	15.00–17.00	**[Balmoral 1 & Caernarfon Suite – 1st floor]**
Thursday 2 July	09.00–13.00	**[Balmoral 1]**
	08.30–10.00	**[Caernarfon Suite – 1st floor]**

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

The six highest-ranked submitted oral abstracts will be presented on Wednesday 1 July 15.00–17.00. **[Balmoral 1]**

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

Posters Size:
Poster boards will be size 1m x 1m. Please do not exceed these dimensions. Velcro will be provided.

Viewing:

Tuesday 30 June	14.00–15.00	**[Balmoral 2]**
Wednesday 1 July	14.00–15.00	**[Balmoral 2]**
Thursday 2 July	14.00–14.30	**[Balmoral 2]**

Formal Poster Viewing and Chairman's Rounds and Drinks Reception:

Wednesday 1 July 18.00–19.30 **[Balmoral 2]**

Sponsored by: Environmental Lung Disease Research Group, Department of Pathology, Cardiff

Prizes:
Poster round chairs will be circulating on Wednesday 1 July to select the winners of the Pathological Society's Sir Alastair Currie Prize and second and third poster prizes. Winners will be announced at the Conference Dinner on 2 July.

Note to presenters:
Ideally, posters should be in place by Tuesday 30 June, **09.00 hrs** and removed by Thursday 2 July, 17.00 hrs.

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 & REVIEW SESSION – *Iatrogenic pathology*

Viewing:

Microscopes	**[Shetland Room – 2nd Floor]**
Virtual slides	i–PATH stand **[Reception – Trade exhibition area]**

Slides and/or virtual slide images will be available for viewing on:

Tuesday 30 June	09.00–17.00
Wednesday 1 July	09.00–17.00
Thursday 2 July	09.00–17.00

Competition:
There will be a slide competition using slide images, which will be available during the above dates/times. Entry for the competition will close on Wednesday at 1700.

Prize:
A case of champagne. The winner will be announced at the Conference Dinner on Thursday 2 July. *At the discretion of the winner, by tradition, this is shared amongst those present at the dinner!*

Discussion Session:
Thursday 2 July 09.30–12.00

SYMPOSIA

Tuesday 30 June
09.00–12.45 *Genomic instability in health and disease* **[Balmoral 1]**
15.00–17.00 *Airborne mineral particles and lung disease* **[Argyll Room – 2nd floor]**

Wednesday 1 July
09.00–12.00 *Dissecting colorectal cancer – molecules to macroscopy* **[Balmoral 1]**

Thursday 2 July
14.30–17.00 UK NEQAS for ICC & ISH: *Trends in diagnostic immunocytochemistry* **[Balmoral 1]**

Friday 3 July
09.00–12.00 *Prostate cancer: the present and future for histopathology*
[Caernarfon Suite – 1st floor]

TRAINEES PROGRAMME

Tuesday 30 June
13.30–14.30 Meet the Experts:
Lymphoma diagnosis and classification – WHO and beyond **[Argyll Room – 2nd floor]**

Wednesday 1 July
07.45–09.00 Breakfast meeting:
Cervical cytology in 2009: recent advances and what you need to know for the FRCPath **[Argyll Room – 2nd floor]**

Thursday 2 July
14.30–17.00 Symposium:
A beginner's guide to pathology research **[Argyll Room – 2nd floor]**

CONTINUING PROFESSIONAL DEVELOPMENT (CPD)

This Meeting has been approved by the Royal College of Pathologists for the purpose of Continuing Professional Development.

Credits can be accrued as follows:

Tuesday	7 credits (full-day)	3 credits (half-day)
Wednesday	8 credits (full-day)	4 credits (half-day)
Thursday	7 credits (full-day)	3 credits (half-day)
Friday	3 credits (full-day)	

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

TRADE EXHIBITION

Delegates are encouraged to visit the Trade Exhibition and are requested to support the companies represented there. **[Reception]**

Fees and Registration

EARLY BIRD REGISTRATION FEES UNTIL MIDNIGHT ON MONDAY 1 JUNE 2009				
Delegate Type	**Fee Categories**	**Per Day or Part Day**	**Whole Meeting**	**Conference Dinner**
BDIAP or Pathological Society Members	Ordinary Members, Consultant and/or equivalent position	£ 100	£ 290	£ 55
BDIAP or Pathological Society Concessionary Members	Biomedical Scientists; Honorary or Senior Members; PhD Students; Post-Doctoral Fellows, Technicians and Trainees	£ 30	£ 85	£ 55
Undergraduate Students ❇		£ 30	£ 85	£ 55
Non-Members	Consultant and/or equivalent position	£ 150	**Not Available**	£ 55
Non-Members Concessionary ❇	Biomedical Scientists; PhD Students; Post-Doctoral Fellows, Technicians and Trainees	£ 45	**Not Available**	£ 55

LATE REGISTRATION FEES FROM MIDNIGHT (00.01 hr) ON TUESDAY 2 JUNE 2009				
Delegate Type	**Fee Categories**	**Per Day or Part Day**	**Whole Meeting**	**Conference Dinner**
BDIAP or Pathological Society Members	Ordinary Members, Consultant and/or equivalent position	£ 150	**Not Available**	£ 55
BDIAP or Pathological Society Concessionary Members	Biomedical Scientists; Honorary or Senior Members; PhD Students; Post-Doctoral Fellows, Technicians and Trainees	£ 45	**Not Available**	£ 55
Undergraduate Students ❇		£ 45	**Not Available**	£ 55
Non-Members	Consultant and/or equivalent position	£ 225	**Not Available**	£ 55
Non-Members Concessionary ❇	Biomedical Scientists; PhD Students; Post-Doctoral Fellows, Technicians and Trainees	£ 75	**Not Available**	£ 55

REGISTRATION

Registration is ONLY available on-line via: http://asp.artegis.com/CardiffPath09

REFRESHMENTS

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

❇ CONCESSIONS

Delegates from categories:

Undergraduate Students
Non-Members Concessionary

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

ADVANCE REGISTRATION

Advance registration will close on **Monday 22 June 2009**. Thereafter delegates may only register on-site on arrival at the meeting.

CANCELLATIONS

Please note that we are unable to refund registration fees for cancellations received after **Monday 15 June 2009.**

ENQUIRIES

Before the Meeting enquiries should be addressed to:

Pathological Society
2 Carlton House Terrace, London, SW1Y 5AF, UK.
Tel: +44 (0)20 7976 1260
Fax: +44 (0)20 930 2981
Email: admin@pathsoc.org

or

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

VENUE LOCATION

The Mercure Holland House Hotel and Spa Cardiff, 24–26 Newport Road, Cardiff CF24 0DD, UK.
For information on-line please see:
http://www.mercure.com/gb/hotel-6622-mercure-holland-house-hotel-and-spa-cardiff/index.shtml

DELEGATE ENROLMENT (AT THE MEETING)

Enrolment at the Delegate Reception Desk will take place from:

Monday 29 June	15.00–18.00
Tuesday 30 June	from 08.00
Wednesday 1 July	from 07.30
Thursday 2 July	from 07.45
Friday 3 July	from 08.15

PRESENTATION CHECKING AND PREVIEW

This will be available in: **[Inverness Room – 2nd Floor]**

ORAL PRESENTATIONS/LECTURES

Presenters must register for the meeting in advance.

Presentation format:

- Powerpoint Only
- Must be PC compatible
- Must be on memory sticks only

Presenters must attend their designated lecture theatre 30 minutes before their session commences.

INTERNET ACCESS

This will be available in: **[Kinross Room – 2nd Floor]**

MESSAGES

During the Meeting, messages for delegates may be left at the following telephone number:

07818 640887

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

REFRESHMENTS

Unless stated otherwise in the programme all refreshments will be served in:

[Restaurant – 1st floor]
[Balmoral 2 & Reception]

BADGES

Delegates are requested to wear their badges at all times.

COATS & BAGS

Secure facilities will be provided for coats and bags.

TRAVELLING TO CARDIFF

For information and maps visit: www.path.org.uk
www.visitcardiff.com/How-to-get-here.html

SOCIAL ACTIVITIES

Tuesday 30 June

Welcome Reception. ***Sponsored by: School of Medicine, Cardiff University.***
To be held at the National Museum of Wales, Grand Hall and Impressionist Galleries. For location information see: http://www.museumwales.ac.uk/en/cardiff/hire/
Reserve your free ticket when registering on-line.

Wednesday 1 July

Evening Poster Round and Drinks Reception.
Sponsored by: Environmental Lung Disease Research Group, Department of Pathology, Cardiff

Thursday 2 July

Conference Dinner.
To be held at the Assembly Room, City Hall, Cardiff.
For location information see: http://www.cardiffcityhall.com/CH_assembly_e.htm
Tickets are £55. Please reserve your ticket when registering on-line – places are limited.

LOCAL PLACES OF INTEREST

For more information please see: http://www.visitcardiff.com/

FURTHER INFORMATION

Details of the Meeting are also available on: http://www.path.org.uk/
Any further information or amendments to this Programme will be posted on the above web pages.

DISCLAIMER

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

FUTURE MEETINGS

British Division of the IAP

2009
November 27–28
London
The Autopsy

2010
Spring
Cork
Upper GI Pathology

October 10–15
São Paolo
IAP International Congress

November 26–27
London
Head and Neck Pathology

2011
November 25–26
London
Topic to be advised

2012
September 30 – October 5
Cape Town
IAP International Congress

Pathological Society of Great Britain & Ireland

2009
September 1–4
Manchester
3rd Summer School – Pathologists teaching pathologists to teach pathology

2010
January 7–8
Imperial College, Kensington Campus
Winter Meeting including Trainees' Programme

June 29 – July 2
St Andrews
Summer Meeting

2011
January 6–7
Cambridge
Winter Meeting including Trainees' Programme

2012

JOINT MEETINGS

of the British Division of the IAP and the Pathological Society

2011
May 10–13
Ghent
Ghent Pathology 2011

TUESDAY 30 JUNE

From 08.00 — **Reception**

REGISTRATION AND COFFEE

09.00 – 17.00 — **Shetland Room – 2nd Floor**

SLIDE SEMINAR COMPETITION VIEWING: ***Iatrogenic pathology***

09.00 – 12.45 — **Balmoral 1**

SYMPOSIUM: *Genomic instability in health and disease*
Chair: Prof R Waters, Cardiff University Medical School

09.00–09.30 **[S1]** ***An introduction to genomic instability and chromosome structure***
Prof R Waters, Cardiff University

09.30–10.00 ***Examining DNA damage and repair throughout the entire human genome at high resolution: implications for diagnostics and therapeutics***
Dr S Reed, Cardiff University

10.00–10.30 **[S2]** ***Replication of damaged DNA and cancer protection***
Prof A Lehmann, University of Sussex, Genome Damage and Stability Centre

10.30–11.00 **COFFEE** [Balmoral 2 & Reception]

11.00–11.30 **[S3]** ***Telomeres, genome stability and human disease***
Dr D Baird, Cardiff University

11.30–12.00 **[S4]** ***Clinical aspects of human genomic instability syndromes: common cancer predisposition***
Prof G Evans, St Mary's Hospital, Manchester

12.00–12.45 **KEYNOTE LECTURE**
[S5] ***Defective biological responses to DNA damage and human disease***
Prof E Friedberg, University of Texas, Southwestern Medical Centre

12.45 – 13.00 — **Balmoral 1**

12.45–13.00 **WELCOME ADDRESS**
Chair: Prof GT Williams, Cardiff University
Prof S Tomlinson, CBE, Provost, Cardiff University

13.00 – 14.00 — **Restaurant – 1st Floor**

LUNCH
Dessert and coffee will be served in [Balmoral 2 & Reception]

13.30 – 14.30 — **Argyll Room – 2nd Floor**

MEET THE EXPERTS
Chair: Dr A Christian, University Hospital of Wales, Cardiff

[S6] ***Lymphoma diagnosis and classification – WHO and beyond***
Dr S Dojcinov, University Hospital of Wales, Cardiff

Lunch will be provided for participants in the lecture theatre

14.00 – 15.00 — **Balmoral 2 & Reception**

POSTER VIEWING AND TRADE EXHIBITION

▶ 15.00 – 17.00 Balmoral 1

ORAL COMMUNICATIONS: ***Technical Advances; Cellular/Molecular; Gastrointestinal; Hepatobiliary/Pancreas***

Chair: Prof M Pignatelli, University of Bristol
Prof NA Shepherd, Cheltenham General Hospital

15.00 **[O1]** ***A comparative study of quantitative immunohistochemistry and quantum dot immunohistochemistry for mutation carrier identification in Lynch Syndrome***
E Barrow, RJ Byers, DGR Evans, J Hill, **{P}** RFT McMahon

15.15 **[O2]** ***Assessment of longitudinal and intratumoral heterogeneity of KRAS and BRAF mutation status in patients with advanced colorectal cancer***
{P} SD Richman, P Chambers, S Grant, C Daly, MT Seymour, P Quirke

15.30 **[O3]** ***The effect of complete mesocolic excision with central vascular ligation for colonic carcinoma***
{P} N West, W Hohenberger, P Quirke

15.45 **[O4]** ***A role for the adenomatous polyposis coli protein in mitotic spindle alignment in gut epithelium***
{P} AJ Quyn, FA Carey, RJ Steele, IS Nathke

16.00 **[O5]** ***Tracing clonal expansion in the human colon using methylation patterns and mitochondrial DNA***
{P} TA Graham, A Humphries, SAC McDonald, SJ Leedham, NA Wright

16.15 **[O6]** ***The clonal origins of dysplasia arising from metaplasia in the human stomach***
{P} SAC McDonald, L Gutierrez-Gonzalez, M Rodriguez-Justo, SJ Leedham, MR Novelli, I Mitchell, DL Stoker, JAZ Jankowski, NA Wright

16.30 **[O7]** ***Prognostic significance of histopathologic tumour regression after neoadjuvant chemotherapy in esophageal adenocarcinomas***
{P} R Langer, K Ott, M Feith, F Lordick, JR Siewert, H Hoefler, K Becker

16.45 **[O8]** ***The histogenesis of regenerative nodules in human liver cirrhosis***
{P} WR Lin, V Wright, AP Dhillon, MR Alison

▶ 15.00 – 17.00 Caernarfon Suite – 1st Floor

ORAL COMMUNICATIONS: ***Cellular/Molecular; Osteoarticular/Soft Tissue; Education & Audit; Lymphoreticular***

Chair: Dr C O'Brien, ABMU NHS Trust, Swansea
Dr RJ Byers, University of Manchester

15.00 **[O9]** ***Grouping of ovarian cancer by phosphoprotein pathway profiling: A novel approach to therapeutic response prediction***
{P} D Faratian, I Um, A Graham, AR Williams, SP Langdon, DJ Harrison

15.15 **[O10]** ***Is SEPT9 a p53 regulated gene?***
{P} KA McKee, PA Hall, SEH Russell

15.30 **[O11]** ***Interleukin 1 signalling pathways in the intervertebral disc***
DM Barrott, K Kennedy, K Tahar, **{P}** CL Le Maitre

15.45 **[O12]** ***Activation of receptor tyrosine kinases and PKC theta in non skull base chordoma***
{P} ASEM Shalaby, N Presneau, B Idowu, AM Flanagan

16.00 **[O13]** ***p53 mutation and loss have different effects on tumourigenesis in a novel mouse model of rhabdomyosarcoma***
{P} B Doyle, JA Wilkins, DW Delaney, W Kolch, OJ Sansom

TUESDAY 30 JUNE *—continued*

16.15 **[O14]** ***Peer group audit of lymphoma reporting practice in the east of Scotland***
{P} PW Johnston, GD Smith, JR Goodlad, WB Al-Qsuos, T Doig, LY Christie, AM Lessells, AS Krajewski, NM Kernohan, ME McKean, TJ Palmer, M Rahilly, DA Levison

16.30 **[O15]** ***The significance of MiR-34a as a part of the TP53 network in diffuse large B-Cell lymphoma***
{P} DM Azim, KP West, JH Pringle

16.45 **[O16]** ***Genomic profiles of gastrointestinal diffuse large B-cell lymphoma***
{P} G Dong, E Chanudet, RA Hamoudi, YW Chen, SS Chuang, H Ye, H Liu, Z Gao, G Srivastara, MQ Du

▸ 15.00 – 17.00 — Argyll Room – 2nd Floor

SYMPOSIUM: ***Airborne mineral particles and lung disease***
Chair: Dr R Attanoos, University Hospital, Llandough
Dr A Gibbs, University Hospital,Llandough

15.00–15.30 **[S7]** ***Airborne mineral particles, properties, deposition patterns in the lung and disease***
Prof F Pooley, Cardiff University, Medical Microscopy Sciences

15.30–16.00 **[S37]** ***Atmospheric particles and lung disease***
Prof R Maynard, Health Protection Agency

16.00–16.30 ***Mineral particle induced pulmonary non neoplastic disease***
Dr A Gibbs, University Hospital, Llandough

16.30–17.00 ***Mineral particle induced pulmonary neoplastic disease***
Dr R Attanoos, University Hospital, Llandough

▸ 17.30 – 18.30 — Reardon Smith Lecture Theatre – Park Place

17.00 Buses depart for the Public Lecture

17.30–18.30 **PUBLIC LECTURE:** ***Inheritance from teratocarcinomas***
Chair: Prof B Jasani, Cardiff University
Speaker: Prof Sir Martin Evans, Nobel Laureate, Cardiff University School of Biosciences

▸ 18.30 – 20.00 — Grand Hall & Impressionist Galleries · National Museum of Wales

The Grand Hall is adjacent to the Reardon Smith Lecture Theatre

WELCOME RECEPTION
Sponsored by: School of Medicine, Cardiff University

WEDNESDAY 1 JULY

From 07.30 — **Reception**

REGISTRATION AND COFFEE

07.45 – 09.00 — **Argyll Room – 2nd Floor**

TRAINEES' BREAKFAST* MEETING: ***Cervical cytology in 2009: recent advances and what you need to know for the FRC Path***
Chair: Dr L Browning, Oxford University
Dr KE Robertson, University of Dundee

08.00–08.30 ***Role of HPV testing and the impact of the HPV vaccine on the cervical screening programme***
Prof D Jenkins, GlaxoSmithKline, Belgium and Nottingham University

08.30–09.00 ***Other new advances and changes in cervical cytology***
Dr K Denton, Southmead Hospital, Bristol

***** *Breakfast will be provided outside the lecture theatre*

09.00 – 17.00 — **Shetland Room – 2nd Floor**

SLIDE SEMINAR COMPETITION VIEWING: ***Iatrogenic pathology***

09.00 – 12.00 — **Balmoral 1**

SYMPOSIUM: ***Dissecting colorectal cancer – molecules to macroscopy***
Chair: Prof GT Williams, Cardiff University

09.00–09.25 **[S8]** ***Pathways in colorectal carcinogenesis***
Dr MJ Arends, University of Cambridge

09.25–09.50 ***Finding new genes***
Prof J Sampson, Cardiff University School of Medicine

09.50–10.15 ***Learning from transgenic models***
Prof AR Clarke, Cardiff University, School of Biosciences

10.15–10.45 **COFFEE** [Balmoral 2 & Reception]

10.45–11.10 **[S9]** ***Getting the most from a resection specimen***
Dr I Nagtegaal, University Medical Centre St Radboud, Nijmegen, The Netherlands

11.10–11.35 ***Coping with unusual polyps and cancers***
Prof M Novelli, University College, London

11.35–12.00 **[S10]** ***Pathology-guided colorectal cancer treatment***
Prof TS Maughan, Cardiff University / CRC Cymru / WCTU / Velindre Hospital

12.00 – 13.00 — **Balmoral 1**

PATHOLOGICAL SOCIETY OF GREAT BRITAIN & IRELAND'S 29th CL OAKLEY LECTURE
Chair: Prof I Ellis, City Hospital, University of Nottingham

[S11] ***DNA methylation in the natural progression and early detection of colorectal neoplasia***
Dr A Ibrahim, University of Cambridge, Addenbrooke's Hospital

WEDNESDAY 1 JULY *—continued*

13.00 – 14.00 — Restaurant – 1st Floor

LUNCH
Dessert and coffee will be served in [Balmoral 2 & Reception]

13.00 – 14.00 — Argyll Room – 2nd Floor

LIVER EQA MEETING

14.00 – 15.00 — Balmoral 2 & Reception

POSTER VIEWING AND TRADE EXHIBITION

15.00 – 17.00 — Balmoral 1

PLENARY ORAL SESSION
Chair: Prof IO Ellis, University of Nottingham
Dr BF Warren, John Radcliffe Hospital, Oxford

15.00 **[PL1]** ***Mucinous and neuroendocrine carcinomas: Distinct molecular entities? A transcriptomic analysis***
{P} B Weigelt, FC Geyer, B Kreike, JS Reis-Filho

15.15 **[PL2]** ***Mechanisms of ERβ regulation in breast cancer***
{P} H Al-Nakhle, PA Burns, M Cummings, AM Hanby, TA Hughes, MD Parker, L Smith, AM Shaaban, V Speirs

15.30–16.00 **TEA** [Balmoral 2 & Reception]

16.00 **[PL3]** ***CD24 confers a stem cell phenotype and enhances migration and invasion in colorectal cancer***
{P} MA Ahmed, D Jackson, R Seth, M Ilyas

16.15 **[PL4]** ***Accelerated disc degeneration in the intervertebral discs of IL-1Ra knockout mice***
DM Barrott, LA Roome, FA Maharus, MJH Nicklin, **{P}** CL Le Maitre

16.30 **[PL5]** ***The role of the tumour suppressor p53 in invasion in an inducible mouse model of intestinal tumourigenesis***
{P} B Doyle, JA Wilkins, W Kolch, OJ Sansom

16.45 **[PL6]** ***RNA-i inhibition of PRKC-ζ_{vb} expression down-regulates the aggressive phenotype of human prostate cancer cells***
S Yao, A Bee, C Beesley, CM Gosden, YQ Ke, **{P}** CS Foster

17.00 – 18.00 — Balmoral 1

THE BRITISH DIVISION OF THE IAP'S 3rd GEORGE CUNNINGHAM LECTURE
Chair: Prof NA Shepherd, Cheltenham General Hospital

Elephant traps in gastrointestinal surgical pathology
Prof GT Williams, Cardiff University

▶ 18.00 – 19.30 Balmoral 2 & Reception

FORMAL POSTER ROUNDS AND DRINKS RECEPTION

Sponsored by: Environmental Lung Disease Research Group, Department of Pathology, Cardiff

Category	Poster Numbers	Chairs
Autopsy & Forensic	P01 – P09	Prof SB Lucas & Dr S Leadbeatter
Breast 1	P10 – P28 ⋆	Dr N Dallimore & Prof RA Walker
Breast 2	P29 – P47	Dr C O'Brien & Dr V Speirs
Cardiovascular/Pulmonary	P48 – P61	Dr A Gibbs & Dr R Attanoos
Cellular/Molecular	P62 – P65	Prof B Jasani & Prof M Ilyas
Experimental Tumour Pathology	P62 – P69	
Technical Advances	P70 – P73	
Education & Audit	P74 – P90	Dr PJ Gallagher & Dr DFR Griffiths
Endocrine	P91 – P93	Dr S Dojcinov & Dr RW Simpson
Head & Neck	P94 – P99	
Lymphoreticular	P100 – P104	
Gastrointestinal	P105 – P125	Dr RFT McMahon & Dr M Morgan
Hepatobiliary/Pancreas	P126 – P128	
Genitourinary/Renal	P129 – P146	Dr ISD Roberts & Dr M Varma
Gynaecological	P147 – P157	Dr A Boyde & Prof WG McCluggage
Neonatal/Paediatric	P158 – P162	Dr J Neal & Dr G Vujanic
Neuropathology/Ophthalmic	P163 – P165 ⋆	
Osteoarticular/Soft Tissue	P166 – P171	
Skin	P172 – P184	Dr S Howarth & Dr A Robson

⋆ Withdrawn abstracts: P23, P24, P164

WEDNESDAY 1 JULY *—continued*

▸ 10.00 – 15.30 **Caernarfon Suite – 1st Floor**

UK NEQAS FOR CELLULAR PATHOLOGY TECHNIQUE
2009 ANNUAL MEETING

10.00–10.20 ***Introduction and Annual Report***
Mr D Evans, Scheme Organiser, UKNEQAS CPT

10.20–10.50 **[S12]** ***"So when I am an Accredited Specialist Expert …"***
Mrs S Dicken, Walsall Hospitals NHS Trust

10.50–11.20 **[S13]** ***Cancer causing lipids***
Prof P Murray, University of Birmingham

11.20–11.50 **COFFEE** [Balmoral 2 & Reception]

11.50–12.00 **[S14]** ***Bone marrow trephine biopsies – time for a national technical EQA?***
Dr A Ramsay, University College, London

12.00–12.30 **[S15]** ***Pathology: the patients' champion in bowel cancer***
Dr N West, Leeds Institute of Molecular Medicine, St James's University Hospital, Leeds

12.30–13.00 ***User satisfaction survey***
Miss J Evans, Quality Manager, UKNEQAS CPT

13.00–14.00 **LUNCH** [Restaurant – 1st floor]
Dessert and coffee will be served in [Balmoral 2 & Reception]

14.00–14.30 **[S16]** ***Report of pilot EQA in muscle histochemical techniques***
Mrs J Vickers, Royal Victoria Infirmary, Newcastle-upon-Tyne

14.30–15.00 **[S17]** ***Report of pilot EQA in Osteoarticular histology***
Mr J Smith, Royal Victoria Infirmary, Newcastle-upon-Tyne

15.00–15.30 Speaker to be confirmed

15.30 **CLOSE**

The organisers would like to thank the following for their sponsorship of this session:
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THURSDAY 2 JULY

From 07.45 — **Reception**

REGISTRATION AND COFFEE

08.30 – 10.00 — **Caernarfon Suite – 1st Floor**

ORAL COMMUNICATIONS: ***Cardiovascular/Pulmonary; Autopsy & Forensic; Genitourinary/Renal***
Chair: Dr DFR Griffiths, Cardiff University
Dr MN Sheppard, Royal Brompton Hospital, London

08.30 **[O29]** ***Lung mineral fibre analysis from a National Referral Centre of 402 cases and >4000 fibres – the Cardiff Experience in 2006***
{P} A Christian, FD Pooley, R Attanoos, AR Gibbs

08.45 **[O30]** ***The role of cytologic evaluation of pleural fluid in the diagnosis of malignant mesothelioma***
{P} EA Rakha, S Patel, K Abdulla, M Abdulkader, Z Chaudry, IN Soomro

09.00 **[O31]** ***Accuracy of post-mortem imaging in diagnosing cause of death in adults: A study of 100 coronial autopsies***
{P} ISD Roberts, R Benamore, EW Benbow, J Harris, A Jackson, SH Lee, T Patankar, Z Traill

09.15 **[O32]** ***Predicting the cause of death based on the available clinical history***
{P} NSA Husani, D Farah, PJ Gallagher, B Lockyear

09.30 **[O33]** ***Hsp-27 expression in prostate cancers: A predictive biomarker of aggressive disease and a potential therapeutic target***
{P} C Foster, A Dodson, L Ambroisine, G Fisher, P Scardino, V Reuter, J Cuzick, C Cooper, D Berney

09.45 **[O34]** ***Clinical measurement of prognostic gene signatures in prostate cancer using immunohistochemistry and real-time Poly(A) PCR***
A Pedersen, M Oliveira-Cunha, H Denley, L McWilliam, P Taylor, R Swindell, I Macintyre, **{P}** R Byers

09.00 – 09.30 — **Balmoral 1**

HISTORICAL PRESENTATIONS
Chair: Prof B Jasani, Cardiff University

09.00–09.15 **[S18]** ***Lister: Pathologist***
Prof Sir RN MacSween, Glasgow

09.15–09.30 **[S19]** ***Was Homer a pathologist?***
Dr R Marshall, Peninsula Medical School, Royal Cornwall Hospital

09.30 – 13.00 — **Balmoral 1**

ORAL COMMUNICATIONS: ***Education & Audit; Technical Advances; Breast; Cellular/Molecular***
Chair: Prof B Jasani, Cardiff University
Dr R Attanoos, University Hospital, Llandough

09.30 **[O17]** ***Foundation programme year two (F2) rotations in histopathology – quantitative and qualitative analysis***
{P} PW Johnston

09.45 **[O18]** ***High resolution, next generation sequencing from formalin fixed paraffin embedded archival material***
{P} P Chambers, J Morgan, K Southward, P Quirke, GR Taylor

THURSDAY 2 JULY *—continued*

10.00 **[O19]** ***Identification of molecular pathways regulated by gene copy number aberrations in basal-like, HER2 and luminal breast cancers***
{P} R Natrajan, B Weigelt, A Mackay, A Ashworth, JS Reis-Filho

10.15 **[O20]** ***Systems biology reveals new strategies for personalising cancer medicine and confirms PTEN's role in resistance to trastuzumab***
{P} D Faratian, A Goltsov, G Lebedeva, S Moodie, P Mullen, C Kay, I Um, SP Langdon, I Goryanin, DJ Harrison

10.30–11.00 **COFFEE** [Balmoral 2 & Reception]

09.30 – 13.00 *continued* **Balmoral 1**

ORAL COMMUNICATIONS: ***Breast***
Chair: Dr JS Reis-Filho, Institute of Cancer Research, London
Dr DW Williams, ABMU NHS Trust, Swansea

11.00 **[O21]** ***High resolution array Comparative Genomic Hybridization (aCGH) of breast carcinoma identifies Mouse Double Minutes 4 (Mdm4) as one of the early genetic changes in breast cancer development: Mdm4 is a new independent prognostic and predictive marker***
{P} T Abdel-Fatah, D Powe, M Lambros, J Reis-Filho, I Ellis

11.15 **[O22]** ***Microenvironmental changes in DCIS: myoepithelial cells exhibit a switch from suppressor to promoter***
{P} MM Dawoud, D Jones, K Hodivala-Dilke, S Dreger, C Chelala, JL Jones

11.30 **[O23]** ***Expression of oestrogen receptor ß phosphorylated at serine 105 in primary breast cancer***
W Hamilton-Burke, M Cummings, CA Green, DL Holliday, S Pollock, K Horgan, AM Shaaban, **{P}** V Speirs

11.45 **[O24]** ***Integrative genomic and transcriptomic profiling of triple negative breast carcinomas***
{P} MB Lambros, HM Horlings, R Natrajan, R Vatcheva, KK Shiu, SM Rodriguez-Pinilla, A Mackay, M Van Kouwenghove, J Palacios, A Ashworth, MJ Van De Vijver, JS Reis-Filho

12.00 **[O25]** ***The effects of letrozole and anastrozole in different molecular phenotypes of breast cancer: results from a randomised trial***
{P} SJ Aitken, L Williams, L Renshaw, H Caldwell, J Murray, O Young, JS Thomas, DB Evans, DJ Harrison, JM Dixon, D Faratian

12.15 **[O26]** ***Microarray CGH analysis reveals genetic heterogeneity between distinct components of metaplastic breast carcinomas***
{P} FC Geyer, D De Biase, B Weigelt, MB Lambros, A Mackay, K Fenwick, N Tamber, A Ashworth, JS Reis-Filho

12.30 **[O27]** ***The need for a biological grading system and its relationship to the current Nottingham Histological Grading System (NGS)***
{P} T Abdel-Fatah, D Powe, G Ball, J Reis-Filho, I Ellis

12.45 **[O28]** ***Basal-like and triple negative breast cancer frequently occur in Nigerian women***
J Agboola, N Wanangwa, EA Rakha, AA Banjo, S El-Sheikh, EC Paish, SL Watts, IO Ellis, **{P}** AR Green

09.30 – 12.00 — **Argyll Room – 2nd Floor**

SLIDE SEMINAR DISCUSSION: ***Iatrogenic pathology***
Moderator: Dr S Howarth, Cardiff University
Contributors: Cardiff pathologists – Dr A Boyde, Dr S Dojcinov, Dr Douglas-Jones, Dr DFR Griffiths, Dr S Howarth, Dr P Kitching, Dr A Lammie, Dr K May, Dr M Morgan, Dr M Varma

10.30–11.00 **COFFEE** [Balmoral 2 & Reception]

13.00 – 14.00 — **Restaurant – 1st Floor**

LUNCH
Dessert and coffee will be served in [Balmoral 2 & Reception]

13.30 – 14.30 — **Argyll Room – 2nd Floor**

PATHOLOGICAL SOCIETY OF GREAT BRITAIN & IRELAND ANNUAL BUSINESS MEETING
Members only (Agendas have been sent to Members)

14.00 – 14.30 — **Balmoral 2 & Reception**

POSTER VIEWING AND TRADE EXHIBITION

14.30 – 17.00 — **Balmoral 1**

SYMPOSIUM: UK NEQAS FOR ICC & ISH: ***Trends in diagnostic immunocytochemistry***
Chair: Prof B Jasani, Cardiff University
Mr K Miller, UK NEQAS, University College, London

14.30–15.00 **[S26]** ***Molecular morphology: employing Quantifiable Internal Reference Standards***
Prof C Taylor, University of South California, Keck School of Medicine, Los Angeles

15.00–15.30 ***Modern approaches to the diagnosis of tumour of unknown origin***
Prof D Dabbs, Magee-Womens Hospital, University of Pittsburgh, USA

15.30–16.00 **TEA** [Balmoral 2 & Reception]

16.00–16.30 **[S36]** ***The advent and impact of novel prognostic and predictive markers***
Prof R Osamura, Tokai University, Japan

16.30–17.00 **[S27]** ***Tissue proteomics: A way forward to quantitative biomarker analysis***
Prof Dr K-F Becker, Technical University of Munich, Germany

14.30 – 17.00 — **Argyll Room – 2nd Floor**

TRAINEES' SYMPOSIUM: ***A beginner's guide to pathology research***
Chair: Dr A Jubb, Oxford Radcliffe Hospitals
Dr A Treacy, Connolly Hospital, Dublin

14.30–15.00 ***How to apply for a research grant***
Prof S Fleming, University of Dundee

15.00–15.30 ***How to write a paper***
Prof M Wells, University of Sheffield

15.30–16.00 **TEA** [Balmoral 2 & Reception]

THURSDAY 2 JULY *—continued*

16.00–16.30 **[S28]** ***The Human Tissue Act and research***
Prof PN Furness, University Hospitals of Leicester

16.30–17.00 **[S29]** ***Ethics in research***
Prof PN Furness, University Hospitals of Leicester

▸ 17.00 – 18.00 **Balmoral 1**

PATHOLOGICAL SOCIETY OF GREAT BRITAIN & IRELAND'S 7th DONIACH LECTURE
Chair: Prof DA Levison, President, Pathological Society of Great Britain & Ireland

[S30] ***Normal biology and new insights into breast cancer***
Prof BA Gusterson, University of Glasgow

▸ 19.30 – 23.00 **Assembly Room · City Hall · Cardiff**

CONFERENCE DINNER

▶ 10.00 – 15.00 Caernarfon Suite – 1st Floor

RENAL PATHOLOGY GROUP

10.00–10.30 **[S20]** ***International consensus classification of IgA nephropathy***
Dr ISD Roberts, Oxford Radcliffe Hospitals

10.30–11.00 **COFFEE** [Balmoral 2 & Reception]

11.00–13.00 **JOINT UK RENAL PATHOLOGY GROUP / ACEM SESSION**

11.00–11.50 ***The subpodocyte space: implications for glomerular physiology and pathology***
Dr C Neal, University of Bristol

12.00–12.50 **[S21]** ***When should a renal pathologist request electron microscopy? – The evidence***
Prof G Herrera, NEPHROCOR, Arizona, USA

12.50–13.00 **GROUP PHOTOGRAPH**

13.00–14.00 **LUNCH** [Restaurant – 1st floor]
Dessert and coffee will be served in [Balmoral 2 & Reception]

14.00–15.00 **RENAL EQA**

THURSDAY 2 JULY *—continued*

▸ 09.20 – 17.00 **Caerphilly Room – 3rd Floor**

ASSOCIATION OF CLINICAL ELECTRON MICROSCOPISTS
12th ANNUAL SCIENTIFIC MEETING

09.20–09.55 Chair: Dr J Hobot, Cardiff University
[S22] ***Application of electron microscopy within drug discovery***
Miss A Bigley, Astra Zeneca, Macclesfield

10.00–10.30 Chair: Mr B Wagner, Northern General Hospital, Sheffield
[S23] ***Advances in clinical electron microscopy, 1963–2000: A personal view***
Dr R Griffin, University of the West of England, Bristol

10.30–11.00 **COFFEE** [Balmoral 2 & Reception]

▸ 11.00 – 13.00 **Caernarfon Suite – 1st Floor**

JOINT UK RENAL PATHOLOGY GROUP
ACEM SESSION

11.00–11.50 Chair: Dr ISD Roberts, Oxford Radcliffe Hospitals
The subpodocyte space: implications for glomerular physiology and pathology
Dr C Neal, University of Bristol

12.00–12.50 Chair: Mr B Wagner, Northern General Hospital, Sheffield
[S21] ***When should a renal pathologist request electron microscopy? – The evidence***
Prof G Herrera, Bostwick Laboratories, Arizona, USA

12.50–13.00 **GROUP PHOTOGRAPH**

13.00–14.00 **LUNCH**
Dessert and coffee will be served in [Balmoral 2 & Reception]

▸ 14.00 – 17.00 **Caerphilly Room – 3rd Floor**

ASSOCIATION OF CLINICAL ELECTRON MICROSCOPISTS
12th ANNUAL SCIENTIFIC MEETING – *continued*
Chair: Mr B Wagner, Northern General Hospital, Sheffield

14.00–14.15 ***Technical EM – EQA feedback***
Ms T de Haro, Leicester Royal Infirmary

14.20–14.40 **[S24]** ***IBMS Diploma in Ultrastructural pathology and Certificate in Electron Microscopy: Portfolio and exam feedback from first cohort***
Ms P Tarpey, Manchester Royal Infirmary

14.45–15.25 **[S25]** ***EM technical EQA – the Australian experience***
Mr J Stirling, Principal Medical Scientist, Adelaide, Australia

15.30–16.00 **TEA** [Balmoral 2 & Reception]

16.00–17.00 Chair: Mr T Ryder, Charing Cross Hospital, London
ACEM ANNUAL GENERAL MEETING
Open to non-members

FRIDAY 3 JULY

From 08.15 — **Reception**

REGISTRATION AND COFFEE

09.00 – 12.20 — **Caernarfon Suite – 1st Floor**

SYMPOSIUM: ***Prostate cancer: the present and future for histopathology***
Chair: Dr M Varma, University Hospital of Wales, Cardiff

09.00–09.30 **[S31]** ***Prostate cancer: from screening the masses to tailored treatment for the individual***
Prof M Mason, Cardiff University, Velindre Hospital

09.30–10.00 **[S32]** ***Quality control of the diagnostic process: the pivotal role of histopathology***
Dr DFR Griffiths, Cardiff University, School of Medicine

10.00–10.30 **[S33]** ***Processing and reporting the radical prostatectomy specimen***
Dr L Egevad, Karolinska University Hospital, Stockholm, Sweden

10.30–11.00 **COFFEE** [Outside Caernarfon Suite – 1st floor]

11.00–11.30 **[S34]** ***The histological assessment of the prostate biopsy***
Dr M Varma, University Hospital of Wales, Cardiff

11.30–12.00 **[S35]** ***Morphological and molecular techniques for identifying the tigers in the cattery: current status and future directions***
Dr D Berney, Barts & The London School of Medicine & Dentistry

12.00–12.15 **CLOSE OF MEETING**

LUNCH
Packed lunches are available to take away

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Abstracts

Oral

O1

A comparative study of quantitative immunohistochemistry and quantum dot immunohistochemistry for mutation carrier identification in Lynch Syndrome

E Barrow[1], RJ Byers[2], DGR Evans[3], J Hill[1], **RFT McMahon[4]**
[1]Department of Surgery, MRI, [2]Cancer Studies, University of Manchester [3]Clinical Genetics, Central Manchester Foundation Trust, [4]Medical School, University of Manchester

Lynch Syndrome is caused by mutations in DNA mismatch repair (MMR) genes. Mutation carrier identification is desirable and immunohistochemical (IHC) staining of the MMR proteins is used to aid clinical diagnosis; concerns remain regarding sensitivity. Semiconductor quantum dots (QDs) are novel, near-ideal fluorescent labels that can be used for multiplex staining. This study compares semi-quantitative IHC with quantitative DAB IHC and quantitative QD IHC.

Tissues from 51 mutation carriers and 17 controls were stained with DAB against MLH1 and MSH2. Multiplex QD immunofluorescent staining was performed against MLH1, MSH2 and smooth muscle actin. Semi-quantitative measurements of staining intensity and percentage positivity were recorded on scales of 0-3 and 0-4 respectively, then multiplied for a score of 0-12 per slide. DAB and QD staining intensity were measured by multispectral analysis and ROC curves of staining performance for the identification of mutation carriers calculated.

For semi-quantitative DAB IHC; the area under the MLH1 ROC curve was 0.981 and under the MSH2 ROC curve 0.899. For quantitative DAB IHC; the area under the MLH1 ROC curve was 0.872 and under the MSH2 ROC curve 0.832. For quantitative QD IHC; the area under the MLH1 ROC curve was 0.812 and under the MSH2 ROC curve 0.598.

Despite the advantages of QD staining, it is of lower utility than DAB IHC for the identification of MMR mutation carriers. Automated DAB IHC staining and quantitative slide analysis may enable high throughput IHC.

O2

Assessment of longitudinal and intratumoral heterogeneity of KRAS and BRAF mutation status in patients with advanced colorectal cancer

SD Richman[1], P Chambers[1], S Grant[1], C Daly[1], MT Seymour[1], P Quirke[1]
[1]Leeds Institute of Molecular Medicine

Recent advances in chemotherapeutic treatments for aCRC have seen the introduction of drugs targeting the epidermal growth factor receptor (EFGr) and mutation status of KRAS is a predictive biomarker of response to such drugs. Testing the mutation status is normally carried out on only one formalin-fixed, paraffin-embedded tumour block and treatment decision is based upon the outcome of this single test. We have investigated the question of KRAS and BRAF mutation status heterogeneity, longitudinally (primary tumour versus metastatic lymph node versus secondary tumour) and at the intratumoral level (several separate tumour blocks from each patient).

Blocks obtained from consenting patients in both the MRC FOCUS and PICCOLO aCRC clinical trials were tested for KRAS codons 12/13 and 61 and BRAF codon 600 mutations by pyrosequencing.

RESULTS:

(a) Intratumoural study

Codon analysed	Total no. cases assessed	No. of tumours displaying homogeneity	No. of tumours displaying heterogeneity
KRAS codon 12 &13	18	17	1*
KRAS codon 61	18	18	0
BRAF codon 600	18	17	1

*2 synchronous tumours in 1 patient

(b) Longitudinal study

Codon analysed	No. of complete triplets (primary, lymph node, secondary)	Homogenous	Heterogeneous
KRAS codons 12 &13	18	16	2
KRAS codon 61	16	16	0
BRAF codon 600	18	18	0

SUMMARY: In the intratumoral study 1/18 (5.5%) displayed heterogeneity. In the longitudinal study, 2 tumours (11%) displayed heterogeneity suggesting that a single block will suffice in most cases.

O3

The effect of complete mesocolic excision with central vascular ligation for colonic carcinoma

N West[1], W Hohenberger[2], P Quirke[1]
[1]Pathology & Tumour Biology, Leeds Institute of Molecular Medicine, Leeds, UK, [2]Department of Surgery, University Hospital of Erlangen, Erlangen, Germany

There is wide variation in outcomes between different centres for patients undergoing surgical resection of colonic adenocarcinoma, which may be partially related to the quality of surgery and the extent of mesenteric resection. We have previously shown a 15% 5-year survival advantage in mesocolic plane surgery compared to resections on the muscularis propria. Additionally, institutions offering complete mesocolic excision (CME) and central vascular ligation close to the aorta have reported higher 5-year survivals of up to 89%.

We collected the pathology reports and specimen photographs of 49 primary resections for colonic adenocarcinoma performed at an institution routinely offering CME and compared these to 40 standard specimens from another institution. Tissue morphometry was used to calculate the amount of tissue resected and the plane of surgery was graded by two independent assessors.

CME removed more tissue between the tumour and the major vascular resection margin (130mm vs. 87mm, p<0•0001). The specimens were longer (332mm vs. 237mm, p<0•0001) with a greater area of mesentery resected (19936mm^2 vs. 11389mm^2, p<0•0001) and greater lymph node yield (33 vs. 19, p<0•0001). CME surgery was meticulous with 92% of mesenteric resections in the mesocolic plane compared to just 40% with standard surgery (agreement in 77.5% cases, weighted κ=0•455).

CME surgery with central vascular ligation for colonic adenocarcinoma removes more tissue between the tumour and the vascular resection margin resulting in a maximal lymph node harvest. This, in addition to the better quality of surgery, may partly explain the differences in survival.

O4

A role for the adenomatous polyposis coli protein in mitotic spindle alignment in gut epithelium

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Truncation mutations in the adenomatous polyposis coli (APC) gene are common to sporadic and familial colorectal tumours. In addition to its role in regulating availability of beta-catenin to stimulate the activity of TCF-type transcription factors, the APC protein is an important regulator of cytoskeletal proteins which are crucial for cell division. An inherent asymmetry in dividing cells in gut epithelium has been proposed suggesting that selective segregation of genetic material could be part of a mechanism ensuring protection of stem cell DNA. Asymmetric division requires polarised alignment of mitotic spindles, which in turn is dependent on cytoskeletal proteins.

Our aim was to investigate whether the cell division apparatus is preferentially oriented in gut epithelium consistent with asymmetric division and whether APC plays a role in this process.

We measured orientation of mitotic spindles in intact wholemount sections from mice heterozygous for APC (Min) and wild type littermate controls and also in normal and adenomatous human biopsies using multi-photon immunfluorescence microscopy. We determined the angles of mitotic spindles in three-dimensions free of potential artefacts introduced by sectioning.

We found that cells undergoing mitosis in the stem cell zone of murine and human intestinal crypts are preferentially orientated perpendicular to the apical surface (p<0.005). In Min mice and in human adenomas this preference is lost and spindle orientation is random.

Our data suggests that intestinal stem cells divide asymmetrically and that APC contributes to normal spindle orientation and may thus play a role in asymmetric cell division.

O5

Tracing clonal expansion in the human colon using methylation patterns and mitochondrial DNA

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Methylation of non-expressed genes have been used as clonal markers to study stem cell dynamics in human colonic crypts. It has been shown that mitochondrial DNA (mtDNA) mutations that result in cytochrome c oxidase (CCO)-deficiency, are a reliable marker which can be used to identify patches of related crypts and mutated sub-clones within crypts. We have combined these markers to determine whether methylation patterns record the shared ancestry of crypts and to investigate clonal expansion within a crypt.

Enzyme histochemistry was used to identify wholly and partially CCO deficient crypts. Subsequent sequencing of the mtDNA genome from cells from these crypts confirmed clonality. Mutated clones from partially mutated crypts were mapped using bespoke image analysis software. Methylation patterns of each clone or crypt were determined using bisulphite sequencing. Results were interpreted using a mathematical model of stem cell division and crypt fission.

Crypts related by mtDNA mutations tended to have methylation patterns that were as dissimilar to one another as the methylation patterns from unrelated crypts. Mathematical modeling suggested that methylation patterns diverge rapidly in the two daughter crypts following crypt fission. Intra-cryptal mutated stem cell clones tended to have a single methylation pattern, whereas non-mutated intra-cryptal regions showed diverse methylation patterns.

Methylation patterns do not confirm the shared ancestry of adjacent crypts that are clonal for the same mtDNA mutation. Homogeneous methylation patterns in intra-cryptal stem cell clones confirm methylation is useful for studying human stem cell niche dynamics.

O6

The clonal origins of dysplasia arising from metaplasia in the human stomach

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BACKGROUND: Intestinal metaplasia (IM) of the human stomach has been associated with gastric adenocarcinoma (GA). However, while there have been studies describing the mutation load within GA, there is little evidence to elucidate its genetic origins from metaplasia. Here we define the clonal nature of metaplastic crypts within the human stomach and demonstrate the genetic relationship these have with associated dysplasia.
METHODS AND RESULTS: It has been shown that mitochondrial DNA (mtDNA) mutations that result in cytochrome c oxidase (CCO)-deficiency, are a reliable marker of clonal expansion. We sequenced the entire mtDNA genome from each cell within CCO-deficient crypts. We show that each cell from a CCO-deficient metaplastic crypt contained the same mtDNA mutation (G7588A) but neighbouring CCO-positive crypts were wild-type. Therefore such crypts are clonal.

To determine the genetic relationship between metaplasia and dysplasia we also laser-captured crypts along a strip of gastric mucosa that contained both metaplastic and dysplastic crypts. Initial screening of one of our patients revealed a truncating APC mutation (G4682 insertion). When individual crypts were studied we found that 50% of dysplastic crypts were APC-mutated, interestingly, there were also a few neighbouring metaplastic crypts that also contained the same mutation, indicating the dysplasia arose from a field of metaplasia.
CONCLUSIONS: Here we have presented evidence to show that IM crypts are clonal. We also demonstrated the clonal expansion into a large field of dysplasia of an APC mutation seen in metaplasia, confirming the metaplastic origins of GA.

O7

Prognostic significance of histopathologic tumour regression after neoadjuvant chemotherapy in esophageal adenocarcinomas

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Histomorphologic findings in 92 surgical resection specimens of locally advanced esophageal adenocarcinomas after neoadjuvant cisplatin-based chemotherapy (CTX) were evaluated. Tumour response to neoadjuvant CTX was determined using a system encompassing three tumour regression grades (TRGs) based on the estimation of the percentage of residual tumour tissue in relation to the macroscopically identifiable previous tumour bed.

Seven patients (7.6%) had complete tumour regression (TRG1), 48 patients (52.2%) had subtotal or partial tumour regression (TRG2 = 1-50% residual tumour) and 37 patients (40.2%) had minimal or no regression (TRG3 = >50% residual tumour).

Correlation of the tumour TRGs with corresponding clinicopathological characteristics revealed an association between TRG and post-treatment complete tumour resection status (UICC R0 status; $p=0.016$), tumour category (UICC pT-category; $p<0.001$), and absence of either lymph node metastases ($p=0.001$) or lymphangiosis carcinomatosa ($p<0.001$). Survival analysis demonstrated a significant prognostic relevance of the applied TRG-system in univariate ($p<0.001$) and in multivariate analysis as single independent factor ($p=0.024$).

We conclude that the effect of preoperative CTX in esophageal adenocarcinomas can be assessed by determination of histological tumour regression, providing highly valuable prognostic information, which even may exceed the prognostic impact of the current TNM classification for these tumours. We strongly recommend the implementation of a standardized tumour regression grading system in pathologic reports of esophageal adenocarcinomas treated by neoadjuvant CTX

O8

The histogenesis of regenerative nodules in human liver cirrhosis

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Regenerative nodules (RNs) surrounded by fibrous tissue are a defining feature of liver cirrhosis. RNs are generally considered to result from hepatocyte hyperplasia; however, the histogenesis of RNs is unclear. RNs could result from entrapment of 'old' hepatocytes by connective tissue, but we hypothesize that they could equally well arise from hepatic progenitor cells (HPCs) that are activated in ductular reactions (DRs), which are often prominent in the fibrous septa that surround RNs.

Fourteen cases of liver cirrhosis with different aetiologies (7 HBV; 4 alcohol; 2 alcohol/HCV; 1 NASH) were analyzed by immunohistochemical and histochemical techniques to identify cells in RNs and DRs deficient in cytochrome c oxidase (COX), a mitochondrial DNA (mtDNA) encoded enzyme. Ten of 14 cases had COX deficiencies, including all HBV-related cases. In total, 1,035 RNs were analyzed, of which 785/1035 (75.85%) were homogeneously COX-positive, 220/1035 (21.26%) were completely COX-negative and 30/1035 (2.89%) were mixed. Based upon our previous mtDNA sequencing results which indicated that patches of COX-negative hepatocytes are invariably clonally-derived, together with the scarcity (<3%) of 'mixed' RNs, these results strongly suggest that some RNs are monoclonal in origin. Furthermore, COX-negative DRs were commonly found in close association with COX-negative RNs, and mtDNA sequencing will ascertain if indeed some RNs have their origin in DR derived HPCs. This study highlights how non-pathogenic mutations in mtDNA can be used to solve fundamental questions regarding liver regeneration and organ remodeling.

O9

Grouping of ovarian cancer by phosphoprotein pathway profiling: A novel approach to therapeutic response prediction

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PURPOSE: Advances in predicting responses to therapies in ovarian cancer have not matched progress seen in other solid-organ tumours: ovarian cancer remains a poor-prognosis disease. There has been a trend in therapeutics away from targeting individual molecules to whole biological pathways. The aim of this study was to quantitatively measure the activation state of druggable oncogenic pathways by generating a phosphoprotein profile in cancer tissues, in order to predict therapeutic response.
METHODS: We analysed the expression of ten phosphoproteins within eight signalling pathways (PI3K, MAPK, β-catenin, STAT, NFκB, ER, cell cycle, DNA damage response), proliferation (phospho-histone H3 and Ki67) and apoptosis (caspase 3) in 168 epithelial ovarian cancers using HistoRx AQUA quantitative image analysis. Data were analysed by K-means clustering to determine new biological groups.
RESULTS: Three clusters with distinct phosphoprotein profiles were identified, which significantly differed with respect to proliferation and apoptosis. One cluster had a profile of DNA-damage response (high pBRCA1 and pHistone H2A.X, low p-p53) from which we predicted relative resistance to platinum-based therapy in multivariate analysis (HR=1.40; 95% CI 1.06–1.84; p=0.015). Furthermore, the expression patterns of the other pathways analysed within this study suggest novel therapeutic regimens, such as combination PI3K-inhibitor and platinum/taxane therapy.
CONCLUSIONS: Phosphoprotein profiling is a novel way to classify ovarian cancers which may be readily applied to tissue samples in the clinic, predict responses to existing therapies, and generate testable hypotheses for new therapeutic approaches.

O10

Is SEPT9 a p53 regulated gene?

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The complexity of SEPT9 genomics and resultant transcripts has led us to consider the regulation of this gene. Bioinformatic analysis revealed many potential transcription factor binding sites including numerous putative p53 responsive elements within a 3kb region upstream of the transcription start site of SEPT9_v4* while such sites are infrequent proximal to other SEPT9 transcripts. This transcript can be translated by cap independent mechanisms and is one of two transcripts that encode the SEPT9_i4 isoform (see Hum Mol Gen 2007;16:742-752). We hypothesised that some, but not all, SEPT9 transcripts would be stress responsive via a p53 dependant pathway. We used a range of cells with wild type p53 and an isogenic pair of lines with and without p53 to investigate the cellular physiology of SEPT9 after genotoxic and non genotoxic stress. A range of cellular stresses including DNA damage induce p53 protein expression and concomitant induction of SEPT9_v4* mRNA and SEPT9_i4. In contrast, the levels of other SEPT9 transcripts and proteins show no significant change. In isogenic p53 null cells there is no induction of SEPT9_v4* mRNA or SEPT9_i4. Reconstitution of the p53 pathway in p53 null cells restores induction of SEPT9_i4 protein under conditions of cellular stress. Chromatin immunoprecipitation experiments have confirmed that the bioinformatically observed p53 responsive elements do indeed bind p53 protein. Taken together these data indicate that there are differential responses of SEPT9 transcripts to cellular stress mediated, at least in part, by the p53 pathway.

O11

Interleukin 1 signalling pathways in the intervertebral disc

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The intervertebral disc (IVD) is an important component of the spinal column forming the 'shock absorbers' between each vertebrae allowing bending, flexion and torsion of the spine. Work to date has shown that the chondrocyte-like cells express and respond to IL-1 in an autocrine fashion. IL-1 appears to be crucial in the regulation of matrix synthesis and degradation, and appears to be key in the processes of disc degeneration. However to date few studies have investigated the signalling pathways activated by IL-1 in IVD cells.

Nucleus pulposus cells derived from bovine caudal discs were stimulated with 0 or 10ng/ml IL-1 for 10, 20, 30, 40, 50, 60, 180 and 360 minutes in triplicate. Phosphorylated ERK 1 and 2, p38 MAPK and Akt were then investigated using Phosflow flow cytometry (BD Biosciences).

Phosphorylated ERK 1 and 2 was increased in IL-1 treated cells compared to untreated cells following 10-30min stimulation, thereafter levels returned to baseline. Phosphorylated Akt demonstrated a twin activation profile with an initial activation following 10-20minutes a second peak of activation after 50-60minute stimulation. Surprisingly no increased expression of phosphorylated p38 MAPK was seen at any time point.

This study has shown that both ERK and Akt are involved in the signalling pathways activated by IL-1 in nucleus pulposus cells. This could lead to therapeutic targets to inhibit the pathogenic pathways stimulated by IL-1 in the IVD.

O12

Activation of receptor tyrosine kinases and PKC theta in non skull base chordoma

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Chordoma is a rare malignant bone tumour with frequent recurrences and has considerable metastatic potential. Surgery frequently does not result in cure. Chemotherapy and radiotherapy are largely ineffective.
AIM: to investigate the role of a number of protein kinases in the pathogenesis of chordoma.
METHODS: A tissue microarray (TMA) of 50 non-skull based chordomas was examined for expression of a number of receptor tyrosine kinases (RTK) and signal transduction kinases using immunohistochemistry. Inter-phase fluorescent in situ hybridization (FISH) was performed to look for amplification of EGFR and c-MET. Human phospho-RTK arrays were also employed to investigate RTK activation in UCH-1, a chordoma cell line, and in three selected chordomas with available protein lysate.
RESULTS: Immunohistochemictry revealed that chordomas showed expression of epidermal growth factor receptor (EGFR) (66%), CD117 (93%), L1 (46%), DOG-1 (25%), nestin (8%) and protein kinase C (PKC) theta (68%) but were negative for ErbB2. FISH analysis failed to reveal amplification of EGFR or c-MET. The phospho-RTK array data showed strong phophorylation of EGFR in the chordoma cell line, UCH-1, and the three chordomas analysed. There was also significant phosphorylation of ErbB2, HGFR, Mer, Tie-2 and EphB2.
CONCLUSION: Chordomas show activation of a limited number of RTKs providing direction for further studies to determine if specific inhibitors to these molecules could be valuable in the clinical management of this disease.

O13

p53 mutation and loss have different effects on tumourigenesis in a novel mouse model of rhabdomyosarcoma

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BACKGROUND: Pleomorphic rhabdomyosarcoma is the most common subtype seen in adults and has a poor prognosis. Therefore, animal models of this disease would be desirable. In this study we describe a novel animal model of pleomorphic rhabdomyosarcoma and use it to compare the effect of p53 loss versus p53 mutation.
DESIGN: We used the Cre LoxP system to generate mice which express KRas V12 and either loss of p53 (p53flox) or expression the p53R172H mutation (equivalent to the common human R175H mutation).
Mice were aged until they developed tumours which were examined by histology and immunohistochemistry.
RESULT: 4 cohorts of mice were studied $p53^{flox/+}$, $p53^{flox/R172H}$, $p53^{flox/flox}$ and $p53^{+/R172H}$. All 4 cohorts expressed the oncogenic KRas mutation. $p53^{flox/R172H}$, $p53^{flox/flox}$ and $p53^{+/R172H}$ mice developed tumours, predominantly on the limbs but also within the abdominal cavity. Histologically these tumours showed rhabdoid differentiation, with cross-striations and strap-shaped myoblasts. Immunohistochemistry demonstrated positivity for desmin and myogenin. Time to tumour onset was similar in the $p53^{flox/flox}$ and $p53^{flox/R172H}$ groups (median 49 and 51 days respectively) but was somewhat longer in the $p53^{+/R172H}$ group (median 62 days). $p53^{flox/+}$ mice had a significantly longer survival time ($p<0.001$) and did not develop rhabdomyosarcoma.
CONCLUSION: In this study we show a novel animal model for pleomorphic rhabdomyosarcoma which may be useful in the development of novel treatment strategies. We also demonstrate that p53 mutation is more important than its loss in the development of rhabdomyosarcoma in this model.

O14

Peer group audit of lymphoma reporting practice in the east of Scotland

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Maintaining consistency and accuracy of diagnosis in Histopathology is a continuing challenge relevant to patient safety. EQA is often used to measure individual performance in this respect, although, unlike audit, it does not directly assess actual practice. A relatively high error rate is well documented in lymphoma diagnosis but no EQA scheme currently exists in this field. Little is published on the results of audit. Here, we present the results of external peer review of primary diagnosis in 360 cases of lymphoma within the five institutions that constitute the East of Scotland Lymphoma Group.

There was a high level of concordance between primary and reviewing pathologists, with recorded variation in opinion of 4%. The main areas of disagreement were in grading follicular lymphomas (grade 3a versus 3b) and in subclassification of low grade B-NHLs. Disagreements on classification of high grade B-NHLs largely lay in the interface between diffuse large B-cell lymphoma and follicular lymphoma. Hodgkin lymphoma brought 100% consensus. A specific area of concern was that of interpretation of small needle biopsies where the tendency to disagreement was highest.

This study demonstrates the East of Scotland Lymphoma Group, an arrangement we prefer over centralised reporting, provides high consistency. The findings provide evidence that systematic audit is a reliable mechanism for ensuring and maintaining diagnostic quality in lymphoma diagnosis. As it examines real practice, we believe it is likely to be superior to EQA as a driver of standards in this difficult area.

O15

The significance of MiR-34a as a part of the TP53 network in diffuse large B-Cell lymphoma

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Diffuse large B-cell lymphoma (DLBCL), the most frequent adult lymphoma worldwide is characterized by heterogeneous clinical, immunophenotypic and genetic features. TP53 gene mutations are less frequent in DLBCL than solid tumours but are associated with poor prognosis and drug resistance. Cases with wildtype TP53 may use alternative mechanisms to inhibit this pathway. miR34a is a recently discovered marker of TP53 activity regulating cell cycle and apoptosis genes.

This study has assessed the role of miR34a in DLBCL and 62 cases were investigated, 13 representing cases transformed from follicular lymphoma or relapsed cases. Protein levels of TP53, p21, HDM2, phosphospecific TP53 at serine392, Bcl6, Bcl2 and MIB1 were assessed by immunohistochemistry. TP53 exons 5-9 were screened for mutations by SSCP-sequencing. Expression levels of miR34a were assessed using stem-loop RTPCR.

A significant inverse correlation was found between TP53 protein and miR34a (-0.248, $p<0.05$). There was also a strong association between TP53 missense mutations and low levels of miR34a ($p<0.01$). No correlation was found between miR34a and phosphospecific p53, MIB1, Bcl2 or Bcl6. However, a strong direct correlation with p21 (0.504, $p<0.01$) and HDM2 (0.43, $p<0.01$) was found confirming functional TP53 activity. There was also a significant correlation between cases that have transformed relapsed cases and low expression of p21 or miR34a ($p<0.05$). Therefore expression of miR34a in DLBCL is associated with wildtypeTP53 activity and less aggressive disease highlighting the role of miR34a as important marker of functional TP53.

O16

Genomic profiles of gastrointestinal diffuse large B-cell lymphoma

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Diffuse large B-cell lymphoma (DLBCL) is biologically and clinically heterogeneous. A significant proportion of DLBCL occur in the gastrointestinal tract. Despite the recent advances in the molecular biology and genetics of nodal DLBCL, the molecular genetics underlying the development of gastrointestinal DLBCL is unknown. A total of 59 DLBCL from the stomach (38) and intestine (21) were investigated by 1Mb resolution array comparative genomic hybridisation (array-CGH). The BCL2, BCL6, MYC and CCND1 associated chromosome translocations were studied by interphase FISH. CD10, Bcl-6 and MUM1 immunohistochemistry were performed to sub-classify DLBCL into germinal centre B-cell like (GC) and non-GC subgroups. In general, there was a considerable overlap in the CGH profiles between gastric and intestinal DLBCL. The most frequent genomic imbalances were gain/amplification of 2p15.1-16.1 (22%), 3q26.1-31 (24%), 7q21.3-22.1 (20%), 9q34.3 (20%), 11q23.1-23 (22%), 18q21.3-23.3 (22%), trisomy 19 (19%) and loss of 14q32.33 (24%). There were no significant differences in the frequencies of these genomic gains and losses between DLBCL with and without BCL2, BCL6, MYC and CCND1 associated chromosome translocations, nor between GC and non-GC subgroups. Nonetheless, gains of 11q23.1-23.3, 18q21.2-23 and trisomies 7, 18 and 19 were significantly more frequent in gastric than intestinal DLBCL ($p<0.05$). Array-CGH identified frequent genomic copy number changes in gastrointestinal DLBCL. These genomic profiles are broadly similar to those seen in nodal DLBCL.

O17

Foundation programme year two (F2) rotations in histopathology – quantitative and qualitative analysis

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This study examines the activity and perceptions of the 15 F2s in Histopathology in Aberdeen, August 2006 - December 2009. Only one specifically sought the placement. Foundation Programme generic objectives were supplemented by others specific for Histopathology. F2s were expected to participate in all departmental activities, functioning as new specialty trainees. End of block interviews provided qualitative data from which themes emerged.

Each F2 performed cut-ups, with supervision as required. The median number of independent cuts was 9 (range 6 – 12). F2s reported cases under supervision following the usual training model. The median number of cases reported was 342 (range 127 – 476).

F2s (unexpectedly) enjoyed the placement. The experience provided valuable insights into understanding of disease and its relevance to and application in clinical situations. The eagerness to teach displayed by consultants, trainees and BMSs received positive comment. F2s were impressed by the variety of work and opportunities presented for learning. Many were given new insights into their own abilities in previously untested areas. They expressed increased understanding of the relationship of histopathologists to patient care and how to utilise this. Although their learning objectives seemed challenging initially, each felt they had achieved well.

F2s increase the consultant teaching load but also provide other Histopathology trainees chances to teach pathology. Their exposure to Histopathology may be valuable for recruitment with 6 of 15 applying for specialty training (4 were offered posts, 3 accepted). Placements in Histopathology may benefit both the specialty and F2s' training.

O18

High resolution, next generation sequencing from formalin fixed paraffin embedded archival material

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Current generation DNA sequencers have limited sequencing capacity and whilst formalin fixed paraffin embedded tissue can be sequenced, conventional methods are not quantitative. Next generation DNA sequencing allows the generation of 2.3 Gbases of sequence data per week or can be used to look at single lengths of DNA at extremely high resolution but have not yet beed applied to archival material. We have investigated whether next generation sequencing is possible using such material and what resolution is achievable. DNA was extracted from formalin fixed paraffin embedded tissue samples of colorectal cancer using proteinase K and a phenol:choloroform extraction. An 80bp amplimer encoding KRAS codons 12 and 13 and an 86bp amplimer encoding KRAS codon 61 were amplified and prepared for sequencing. The amplimers were ligated to each other, circularised and large molecular weight DNA generated by rolling circle amplification with phi29 polymerase. This DNA was randomly fragmented, end repaired and had adapters ligated prior to next generation sequencing. It was run on an Illumina GAII next generation analyser. The DNA sequence derived from the sequencer was analysed by NextGene Software. It was found possible to generate sequence data on 700,000 individual sequences present within the cancer. Noise was minimal. Such technology will allow the deep sequencing of tumours from paraffin embedded tumour tissues to look for the evolution of small clones and quantitate their relative size as well as opening up the possibility of large scale multiplexing of samples on such machines.

O19

Identification of molecular pathways regulated by gene copy number aberrations in basal-like, HER2 and luminal breast cancers

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We hypothesised that breast cancer clinical behaviour may be driven by genes whose expression is regulated by gene copy number aberrations. To address this question, we analysed a series of 55 microdissected grade III invasive ductal carcinomas using high-resolution microarray CGH and mRNA expression arrays. We identified 5460 genes whose expression correlates with copy number and 557 genes that are significantly overexpressed when amplified. Significance analysis of microarrays (SAM) comparisons based on copy number regulated genes between basal-like, HER2 and luminal tumours revealed that 1453 genes were differentially expressed between the molecular subtypes. Ingenuity Pathway Analysis of this gene list revealed a significant enrichment for genes involved in G1/S cell cycle progression, protein ubiquitination and the role of BRCA1 in DNA damage control. Furthermore, by overlaying aCGH and expression data for each subgroup separately we identified 27, 128 and 302 genes consistently overexpressed when amplified in basal-like, HER2 and luminal cancers, respectively. Ingenuity Pathway Analysis of these genes highlighted the biological differences between these tumours. Basal-like tumours were characterised by enrichment of G1/S cell cycle checkpoint regulation and protein ubiquitination pathways, HER2 tumours by oestrogen and neuregulin signalling pathways, and luminal tumours by RAR signalling. Our results provide strong circumstantial evidence in support of the hypothesis that breast cancer behaviour may be determined by the pattern and type of genetic aberrations in tumours and highlight regulatory pathways specific to basal-like, HER2 and luminal cancers.

O20

Systems biology reveals new strategies for personalising cancer medicine and confirms PTEN's role in resistance to trastuzumab

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Resistance to targeted cancer therapies such as trastuzumab is a frequent clinical problem, not solely because of insufficient expression of HER2 receptor, but also because of the overriding activation states of cell signalling pathways. Systems biology approaches lend themselves to rapid in silico testing of resistance factors. In this study we developed a new kinetic model which could be interrogated to predict resistance to receptor tyrosine kinase (RTK)-inhibitor therapies, and directly tested predictions in vitro and in clinical samples. The new mathematical model included RTK-inhibitor antibody binding, HER2/HER3 dimerisation and inhibition, AKT/MAPK crosstalk, and the regulatory properties of PTEN. The model was parameterised using quantitative phosphoprotein expression data from cancer cell lines using reverse-phase protein microarrays. Quantitative PTEN protein expression was found to be the key determinant of resistance to anti-HER2 therapy in silico, which was predictive of unseen experiments in vitro using the PTEN inhibitor bp(V). When measured in cancer cell lines, PTEN expression predicts sensitivity to anti-HER2 therapy; furthermore, this quantitative measurement is more predictive of response (RR = 3.0; 95% CI 1.6-5.5, $p<0.0001$) than other pathway components taken in isolation and in multivariate analysis in 122 breast cancers treated with trastuzumab. For the first time, a systems biology approach has successfully been used to stratify patients for personalised therapy in cancer, and is further compelling evidence that PTEN, appropriately measured in the clinical setting, refines clinical decision-making in patients treated with anti-HER2 therapies.

O21

High resolution array Comparative Genomic Hybridization (aCGH) of breast carcinoma identifies Mouse Double Minutes 4 (Mdm4) as one of the early genetic changes in breast cancer development: Mdm4 is a new independent prognostic and predictive marker

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Genome-wide aCGH identified recurrent amplification/gain of 1q from 202,752,134 to 202,862,753 in 86% and 7% of low (LGBC) and high (HGBC) grade breast cancers, respectively. MDM4 gene maps to this locus. We hypothesised that it may be a candidate oncogene and tested this hypothesis by determining its association with clinical outcome and biological features in BC.

MDM4-mRNA expression levels were assessed in 2 independent sets of gene expression arrays. Protein expression levels were assessed using immunohistochemistry in series of 1081 BCs with long term follow up and series of 140 cases of LGBCs with matched precursor lesions and normal breast tissue.

MDM4 mRNA expression levels significantly correlated with copy number (Pearson's correlation=0.55, p=0.0001) and this gene is overexpressed when amplified (Mann-Whitney U test p =0.0018). Mdm4 was overexpressed in 17% of BC and was associated with low grade, ER+ and absence of p53, ATM and BRCA1 loss. In cases showing coexistent precursors with invasive component, MDM4 expression was identical in both lesions. On multivariate analysis that included NPI, MDM4-overexpression was an independent prognostic marker for patients survival outcomes [HR, 0.4; p<0.0001]. In high risk patients who had received systemic adjuvant therapy, MDM4-overexpression predicted better response to both hormone- [HR, 2.7; p<0.0001] and chemo-therapies [HR, 6.7; p=0.008]. Our results demonstrate that MDM4 is an independent prognostic and predictor of BC providing new avenues for therapeutic intervention.

O22

Microenvironmental changes in DCIS: myoepithelial cells exhibit a switch from suppressor to promoter

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Mechanism of transition of ductal carcinoma in-situ (DCIS) to invasive cancer is poorly understood but recently changes in the microenvironment have been implicated.

Normal myoepithelial cells (MECs) have a broad tumour suppressor function but they exhibit changes in DCIS.

Immuno-LCM was used to isolate MECs from normal and DCIS breast tissues followed by whole genome expression profiling using Affymetrix HGU-133 plus2.0 arrays. The data were analysed by Bioconductor packages and a cut off point of ≥4.5 fold change. Ingenuity Pathways software analysis showed clustering of many of the altered genes in cancer, cell death and cell-cell signalling networks. Validation of a panel of genes using QRT-PCR and immunohistochemistry (IHC) revealed a good correlation rate with the array (71.4%). Most dramatic was up-regulation of Fibronectin-1 (FN1) in DCIS MECs. IHC for FN1 on normal (n=88) and DCIS cases with and without associated invasion (n=87) confirmed a strong correlation between FN1 protein expression by MECs and DCIS (p<0.0001). Other key alterations include up-regulation of Integrin β3 and the recently characterised Nephronectin, with down-regulation of PTHLH, FGFR2, ADAMTS5, TGFBR3, and CAV2. In-vitro analysis using MEC cell lines demonstrate that these changes may abrogate the suppressor function of myoepithelial cells.

These data support the hypothesis that there is switch in MEC function from suppressor to potential promoter activity that can influence the progression of in-situ to invasive disease and may lead to novel predictive and therapeutic targets.

O23

Expression of oestrogen receptor β phosphorylated at serine 105 in primary breast cancer

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Oestrogen receptor (ER) α predicts response to hormonal therapy in breast cancer. The role of ERβ is less well understood. ER activities can be modulated by post-translational modifications including phosphorylation and phosphorylated ERα has been correlated with patient outcome. Using immunohistochemistry, we investigated whether ERβ specifically phosphorylated at Serine 105 (P-S105-ERβ) was expressed in breast cancer and examined its relationship with disease-free and overall survival. Immunohistochemical analysis of P-S105-ERβ in a 424-case TMA revealed mainly nuclear expression which could be abolished by phosphatase pre-incubation, indicating antibody specificity. Allred scores ranged from 0-8 (median 6). Distinct nuclear speckling was observed in 45% of cases. P-S105-ERβ correlated with ERβ1 and ERβ2 expression and P-S105-ERβ (Allred score ≥ 2) was associated with better survival. P-S105-ERβ was also expressed in MCF-7 cells and in response to 17β-estradiol (E2), levels were raised within 30 min, and sustained for 24 hours. ERβ1 expression was unaffected by this treatment. Nuclear speckling was also observed and was markedly increased at 24 hours following E2 but not Tamoxifen. This is the first time to our knowledge that the expression of P-S105-ERβ has been investigated in breast cancer. Its association with improved survival suggest P-S105-ERβ might be a useful additional prognostic marker in breast cancer.

O24

Integrative genomic and transcriptomic profiling of triple negative breast carcinomas

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Triple negative breast cancers (TNBCs) comprise a heterogeneous group of tumours defined by the lack of ER, PR and HER2 expression. As a group, TNBCs have a relatively poor prognosis and cannot be targeted with currently available tailored therapies. There is evidence to suggest that genes whose expression correlate with copy number and are consistently overexpressed when amplified are likely to be biological drivers and may be exploited as potential therapeutic targets. To identify potential therapeutic targets, 50 TNBCs were subjected to high resolution tiling path microarray-based comparative genomic hybridisation; out of these cases, 40 were also subjected to genome-wide microarray-based mRNA expression analysis. TNBC showed a high level of genetic instability with an average 44.5% of the whole genome harbouring copy number alterations, ranging from 9%-78%. Tumours were classified as sawtooth in 52% cases, firestorm in 20% and simplex in 28%. Recurrent regions of amplification included multiple regions on 1q and 8q, 3q25.1, 10p14, 10q26.13, 13q34, 15q26.3, 19p13.12 and 19q12-19q13.11. Integration of aCGH and expression data identified 2951 genes whose expression was copy number regulated, of which 138 were significantly overexpressed when amplified, including MCL1, FGFR2, BUB3, RAB20, TUBGCP3, PTK2, PKN1, NOTCH3 and C19orf2. These amplified and overexpressed genes are likely to be amplicon drivers and may constitute potential therapeutic targets for TNBCs. Functional validation of these genes is warranted.

O25

The effects of letrozole and anastrozole in different molecular phenotypes of breast cancer: results from a randomised trial.

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Changes in Ki67 occur within 14 days of starting treatment with aromatase inhibitors (AIs), and these have been shown to predict outcome. The biological effects of AIs on different molecular phenotypes, particularly those not associated with endocrine responsiveness, are unknown.

Thirty-four postmenopausal women with breast cancer classified as ER negative/poor (Allred 2-5) on biopsy were randomised to receive 14 days preoperative letrozole (n=20) or anastrozole (n=14). Paired biopsy tissues were available for all patients. Tumours were defined as basal-like (BL), luminal (L), HER2 (HER2) or other (O) by immunohistochemistry for HER2, ER, PR, CK5/6 and EGFR, and proliferation by %Ki67. Results are presented as means (SEM). Values were transformed on a log scale; analysis is by ANOVA.

Proliferation was reduced in 32/34 tumours.

	BL	L	HER2
Number with decreased Ki67	13/13	9/10	8/9
Pre-treatment mean %Ki67	48 (10.3)	34 (9.4)	46 (8.7)
Post-treatment mean %Ki67	31 (7.6)	20 (6.6)	36 (6.7)
%mean reduction	46	61	25
p-value	0.009	0.0006	0.27

The mean decrease in ER-low tumours was 62% (p=0.0001), and 36% (p=0.007) in ER-negative tumours. There was no significant difference in effect between drugs.

AIs significantly reduce proliferation in BL and L, but not HER2 cancers. The therapeutic effects of AIs in BL cancers must act via ERα-independent pathways. These data suggest that AIs may be beneficial in BL cancers.

O26

Microarray CGH analysis reveals genetic heterogeneity between distinct components of metaplastic breast carcinomas

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It has been suggested that breast cancer may be composed of multiple populations of sub-modal clones harbouring the same initiating genetic lesions followed by the acquisition of divergent genetic hits. We analysed the genome-wide genetic features of distinct components of metaplastic breast carcinomas (MBCs) to determine whether the morphological diversity of these components would be underpinned by divergent genetic aberrations. The distinct components of five MBCs were microdissected and subjected to microarray comparative genomic hybridisation using a 32K tiling path bacterial artificial chromosome array platform. Representative sections of each case were subjected to immunohistochemistry with antibodies against oestrogen (ER) and progesterone (PR) receptors, HER2, epidermal growth factor receptor (EGFR), cytokeratins (CKs) 5/6 and 14. The components of three carcinomas with heterologous elements displayed remarkably similar immunohistochemical and genetic profiles. In contrast, the components of a biphasic spindle cell carcinoma lacked ER and PR and expressed basal markers; while HER2 overexpression (2+) was limited to the epithelial component. Both components of this case harboured similar gains and losses and amplification of 9p23 and 17q11 (HER2); however, each component displayed divergent focal amplifications. In an adenosquamous carcinoma, the lobular component was positive for ER and PR, and negative for HER2 and basal markers; whereas the squamous component lacked ER, PR and HER2 but expressed basal markers. Only the squamous component harboured amplification of 7p11 (EGFR) and displayed overexpression of EGFR. Our results provide evidence that in some MBCs, morphological diversity may be underpinned by distinct genetic aberrations.

O27

The need for a biological grading system and its relationship to the current Nottingham Histological Grading System (NGS)

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In this study, we hypothesised the interaction between mitotic index; MI and Bcl2, could accurately discriminate between low and high-grade breast cancer (BC) and provide a more objective and clinically valuable measure of tumour grade with prognostic significance for patients with moderately differentiated cancer.

A series of 1585 invasive BC with long term follow up were immunohistochemically profiled for apoptosis regulators and others. Mitotic index was assessed according to NGS: M1; <10 mitoses, M2; 10 to 18 mitoses and M3; > 18 mitoses. Subsequently, BC were classified according to combined MI/Bcl2 profile and compared to NGS.

In multivariate Cox regression models including validated prognostic factors, the MI/Bcl2 profile not only remained significantly associated with patients' outcomes but performed better than lymph node status and tumour size. Incorporation of the MI/Bcl2 profile into NPI, accurately reclassified twice as many patients into excellent (EPG) or poor prognostic groups (PPG), improving decision-making for which patients should be given systemic adjuvant therapy. Patients with M1/Bcl2± and M2/Bcl2+ (NGS G1 like) produced a better response to hormone therapy than those with M2-3/Bcl2- and M3/Bcl2+ (NGS G3 like) (HR 3.4; p<0.0001).

In conclusion biological grading achieved through mitosis and Bcl2 expression reclassified the majority (70%) of patients with equivocal NGS G2 into two groups NGS G1 like with low risk versus NGS G3 like with high risk of recurrence, improving prognosis and therapeutic planning and supporting the genetic pathway model of tumour grade origin.

O28

Basal-like and triple negative breast cancer frequently occur in Nigerian women

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Although breast cancer incidence is lower in African-American women compared to White-American, breast cancer is a common disease in African countries such as Nigeria. Nigerian women have a higher risk for early-onset, high-grade, node-positive disease with a high mortality rate from breast cancer. Similar features have characterized hereditary and basal-like breast cancer, prompting speculation that risk factors could be genetically transmitted and the molecular portrait of these tumours are different to those of western women. In this study, we assessed the immunoprofile of breast cancer from Nigerian women compared with age-matched UK control group using 12 biomarkers of known relevance in breast cancer.

Our results confirm that Nigerian women presented with breast cancer are more frequently premenopausal and their tumours are usually larger size, higher grade, lymph node and vascular invasion positive compared with the UK age-match cohort. Nigerian breast cancer showed association with triple-negative and basal-like classes of tumours and are less frequently of luminal-like class. Univariate analysis showed association between breast cancer in Nigerian women and ER, PgR, CK7/8 and E-cadherin negativity, p53 and MUC1 positivity but no association was found with HER2 expression. Nigerian women showed poorer outcome after development of breast cancer compared with UK women.

This study demonstrate that there are genetic and molecular differences between African and Western women breast cancer which cannot be explained only by age. Breast cancer in Nigerian patients tends to be aggressive with a dismal outcome.

O29

Lung mineral fibre analysis from a National Referral Centre of 402 cases and >4000 fibres – the Cardiff Experience in 2006

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BACKGROUND: Asbestos exposure is a well-recognised cause of lung fibrosis, cancer and mesothelioma. Risk estimates are based on anecdotal assessments and airborne fibre measurements by phase contrast light microscopy. Hygeinists measure fibres >5µm in length and <3µm diameter down to the optical microscopy limit of 0.25µm diameter. Fibre analysis of lung tissues by electron microscopy remains the only objective means of determining respirable fibres at the site of tissue injury.
STUDY AIMS: To assess the sensitivity of airborne fibre measurements by determining the respirable bioactive fraction of asbestos in the lung.
METHOD: Fibre characteristics were quantified by transmission electron microscopy and energy dispersive x-ray analysis on digested lung tissue. Analysis was performed on 402 cases received in 2006.
RESULTS: The median turnaround time was 33 days. Results are shown in the table. The majority of fibres were <5µm length (non regulated). Fibres >0.75µm diameter were rarely detected (non respirable).

	Number of Fibres	Bioactive Fibres >5µm length (%)	PCLM Detected Fibres (%)	EM Detected Fibres >5µm length and <0.25µm diameter (%)
Amosite	1874	42.5	16	26.7
Crocidolite	1403	40	4.2	35
Chrysotile	1177	19.3	0	19.3
Tremolite	46	56.5	32.6	17.4

CONCLUSION: PCLM assessment of airborne asbestos exposures are relatively insensitive, failing to detect the majority of respirable fibres. The study shows that significant numbers of bioactive fibres are not optically visible. This implies that there exists considerable difficulties in making risk estimates from anecdotal exposure assessments of historical occupational cohorts.

O30

The role of cytologic evaluation of pleural fluid in the diagnosis of malignant mesothelioma

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Pleural malignant mesothelioma (MM), which is an aggressive neoplasm with a high mortality, frequently manifests initially as pleural effusions. The sensitivity of cytologic examination for its diagnosis varies widely in literature and most of the figures are from earlier studies with conventional cytologic preparations. The objective of this study was to provide the current evidence on the role of cytologic examination of pleural fluid in the diagnosis of MM. We reviewed the cytologic findings in pleural effusions of large series of histologically confirmed MM (234 cases) diagnosed in our institution between 2001 and 2008. Of all cases, 154 (66%) had cytologic material examined. A specific diagnosis of MM was rendered or suspected in 51.3% (79 patients). The lowest sensitivity (26.6%) was noticed in sarcomatoid MM cases. MM was favoured over adenocarcinoma in 97% of patients with positive cytologic findings that have been confirmed with immunohistochemistry. In this series, 6 cases were inadequate and 5 cases were initially reported as atypical (C3) while 64 cases (41.5%) were reported as negative for malignancy. On revision of the cytology slides, only 3 cases were upgraded from benign to suspicious compared to 2 cases downgraded from suspicious to atypical but no significant improvement to the diagnosis could be made on revision. These data suggested that a cytologic diagnosis contributed useful information in patients with malignant epithelioid and biphasic pleural MM. Limitations of the cytological examination of MM should also be acknowledged.

O31

Accuracy of post-mortem imaging in diagnosing cause of death in adults: A study of 100 coronial autopsies

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In the first large validation study of post-mortem imaging in non-forensic autopsies, 100 unselected adult deaths reported to the Coroner were investigated using whole body CT and MRI, followed by full autopsy. Radiologists had access to the clinical summary, but were blinded to the autopsy findings. Following reporting, radiology and autopsy findings were reviewed and discrepancies discussed. This was performed in 6 batches, each discussed before the next group was reported.

There was a major discrepancy between radiological and autopsy cause of death in 30% of cases. There was no improvement with increasing experience of imaging-autopsy correlation. Radiologists were asked to indicate their level of confidence in the cause of death and whether autopsy would be required if this was a routine service. Confidence levels were: definite 45%, probable 27%, possible 18% and unascertained 9% of cases. In 46% of cases, the radiologists indicated that autopsy was not required. For these, the major discrepancy rate was 13%. The commonest errors on imaging were missed diagnoses of coronary disease (9) and pulmonary embolism (6).

The major error rate in cases where radiologists provided a confident cause of death is similar to that for clinical death certificates. If imaging were to replace traditional autopsy in routine practice, this error rate may be considered acceptable. However, some common causes of sudden death are frequently missed on imaging. Large systematic errors in mortality statistics will, therefore, result unless these weaknesses of post-mortem imaging are addressed.

O32

Predicting the cause of death based on the available clinical history

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New legislation may allow deaths that are currently subjected to post mortem to be certified without autopsy. This study evaluated the accuracy with which the cause of death was predicted before autopsy.

A predicted cause of death was formulated before autopsy on unselected patients. This was compared to the autopsy result Predictions were made on 122 male and 92 female patients, age 24-102 years (median 72 years). 169 died in the community and 45 had been admitted. 52% of predictions were accurate. The correct organ system was indicated in 74.5% . Consultants were less likely to make an accurate prediction than students, ST1s or ST2-5s (45.0% vs 49.5%, 51.8% and 68.6% respectively). 81 cases were predicted as IHD but this was confirmed in only 45 (51.2%). 88 patients died of IHD but 43 were not predicted. There were 23 cases of pulmonary embolism only 5 of which were diagnosed before autopsy.18 cases were predicted as pulmonary embolism but died of other causes. Two cases of intracerebral haemorrhage were correctly predicted but 3 were not.

These results indicate that an exact cause of death was predicted in only half of all deaths. We accept the need to reduce the overall number of autopsies. However we suggest that a sample of all deaths should undergo autopsy in order to provide accurate information on the causes of death and the changing patterns of disease

O33

Hsp-27 expression in prostate cancers: A predictive biomarker of aggressive disease and a potential therapeutic target

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Globally, prostate cancer is the 5th commonest malignancy and the 4th commonest to affect men. Clinically, the disease ranges from relative indolence to highly aggressive. There is an urgent requirement stratify prostate cancers at diagnosis into those that will behave aggressively from those that may be managed conservatively. This study has analysed the histopathological expression of Hsp-27 protein in TMAs constructed from a cohort of 553 men with conservatively-managed prostate cancer over more than 15 years. Immunohistochemically-detected Hsp-27 accurately predicted the aggressive prostate cancers ($p<0.001$) while negative cancers were relatively indolent. Hsp-27 expression was related to Gleason score ($p<0.001$). Poor-prognosis cancers identified by Hsp-27 expression showed a significant negative trend with ETS gene rearrangement ($\chi 2 = 31.4$, $p<0.001$) but not with ETS non-rearrangement. The study emphasizes the clinical value of assessing Hsp-27 and ETS rearrangement status as valuable biomarkers at diagnosis to identify men with aggressive prostate cancer who require immediate clinical management. Biochemical data obtained from prostate cancer cell-lines suggest that apoptotic and cell-migration pathways regulated by Hsp-27 may contain biologically-appropriate targets susceptible to novel chemotherapeutic agents likely to prove effective in managing aggressive prostate cancers.

O34

Clinical measurement of prognostic gene signatures in prostate cancer using immunohistochemistry and real-time Poly(A) PCR

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Microarray studies have identified predictive gene signatures for most cancers, including prostatic cancer, but require validation in and translation to the clinical arena. We have used both immunohistochemistry and real-time PCR to test the clinical utility of a range of novel microarray identified predictive markers in prostate cancer.

Immunohistochemistry was performed for ARMET, Jagged1, MTA1 and NM23 in 36 archival prostatic needle core biopsies and an H-score measured for each in tumour tissue (derived from % positivity and staining intensity). There was no significant correlation of H-score with Gleason grade, PSA or survival. Twenty-six fresh needle-cores were collected from patients undergoing diagnostic biopsy. RNA was successfully extracted from all samples (mean 10.9 ng/µl) and globally amplified using Poly(A) PCR. qRT-PCR was then used to measure expression of Jagged1, MTA1, NM23 and ARMET against the housekeeping gene GADPH; expression of KLK3 (PSA) and TFF2 (pancreas specific) were used as positive and negative controls. Apart from TFF2 all genes were expressed in 20/26 samples, in decreasing amount for MTA1, AMACR, ARMET, Jagged1 and PSA. Expression was compared to Gleason score and PSA at diagnosis; AMACR correlated with Gleason score ($R2=0.55$, $p=0.013$).

In this pilot study immunohistochemistry failed to validate predictive utility of these markers. However, feasibility of global expression measurement by poly(A) PCR and real-time PCR, and correlation of AMACR with Gleason score, was demonstrated, suggesting that this approach may be useful for clinical prognostic marker measurement .

Abstracts

Plenary

PL1

Mucinous and neuroendocrine carcinomas: Distinct molecular entities? A transcriptomic analysis

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Mucinous carcinoma is considered a distinct pathological entity. However, mucinous carcinomas can be divided into hypocellular (mucinous A) and hypercellular (mucinous B) subtypes, and mucinous B cancers display histological features that significantly overlap with those of neuroendocrine carcinomas. We investigated using genome-wide oligonucleotide microarrays whether mucinous and neuroendocrine carcinomas would be entities distinct from histological grade- and molecular subtype-matched invasive ductal carcinomas of no special type (IDCNSTs). Mucinous tumours were of luminal A, and neuroendocrine cancers of luminal A and luminal B molecular subtype. When analysed by hierarchical clustering in conjunction with matched IDCNSTs, mucinous and neuroendocrine cancers formed a separate cluster. Ingenuity Pathway Analysis of 1610 differentially expressed genes identified by significance analysis of microarrays (SAM) revealed that connective tissue genes were downregulated in mucinous and neuroendocrine cancers compared to grade- and molecular subtype-matched IDCNSTs. When subjected to hierarchical clustering analysis separately, mucinous A cancers formed a subgroup distinct from mucinous B and neuroendocrine cancers. SAM revealed no transcriptomic differences between mucinous B and neuroendocrine cancers, whereas mucinous A cancers displayed 26 up- and 46 downregulated genes compared to mucinous B (FDR<0.85%), and 175 up- and 76 downregulated genes compared to neuroendocrine carcinomas (FDR<0.95%). Our results provide circumstantial evidence to suggest that mucinous and neuroendocrine carcinomas are transcriptionally distinct from grade- and molecular subtype-matched IDCNSTs. These findings support the contention that mucinous B and neuroendocrine carcinomas are part of a spectrum of lesions, whereas mucinous A may constitute a discrete entity.

PL2

Mechanisms of ERβ regulation in breast cancer

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ERβ1 is downregulated in breast cancer compared to normal breast and mechanisms surrounding this are unclear. We examined how ERβ1 is silenced in breast cancer by determining methylation, loss of heterozygosity (LOH) and miR-92 regulation. Bisulfite sequencing showed extensive methylation of promoter 0N and a novel mini CpG island upstream of exon in BT20 and MDAMB453 cells. Promoter 0K was unmethylated. Cells treated with 5-aza-dC and TSA showed enhanced expression of the ERβ1 splice variant 0N-1 but not 0K-1. Methylation specific PCR of tumour-normal pairs showed ERβ1 methylation in 5/12 tumours but not normal tissue. LOH was determined using 4 polymorphic markers spanning chromosome 14q22-24 in 27 breast tumour-normal pairs. LOH was found in 21% of cases in a region adjacent to ERβ1 but not within ERβ1. There was no association between LOH and downregulation of ERβ1 by immunohistochemistry. Finally as RNAhybrid bioinformatics searching revealed a conserved target-site for miR-92 within the ERβ1 3'-UTR we investigated the role of miR-92 in ERβ1 regulation. We observed a significant negative correlation between ERβ1 and miR-92 (r=-0.511, P=0.003) in breast tumours and cell lines. Inhibiting miR-92 in MCF7 cells increased ERβ1 expression and decreased cell proliferation. Transfection with precursor miR-92 increased cell proliferation and reduced ERβ1 expression, confirming that miR-92 a negatively regulates ERβ1 expression. In summary, ERβ1 expression in breast cancer is subject to complex regulation involving DNA methylation and miRNA92.

PL3

CD24 confers a stem cell phenotype and enhances migration and invasion in colorectal cancer

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CD24 is a putative stem cell marker in different epithelia, but whether its overexpression or under expression is peculiar to cancer stem cells is to be elucidated. Moreover, the cellular mechanisms of the CD24-mediated effects are still unclear. We studied the function of CD24 in colorectal cancer (CRC) cell lines to scrutinise its cellular effects. CD24 was functionally evaluated by 1) forced expression in HCT116 using the CD24 pcDNA3.1 plasmid and 2) knockdown, by RNA interference, in HT29 CRC cell lines. The effects on proliferation, apoptosis, and colony formation in soft agar were assessed. The migratory and invasive characters of the cells were assed using the traswell migration, matrigel invasion and wounding assays. Dominant negative (DN) TCF4 expression was used to investigate the relationship of CD24 with Wnt signalling.

Forced expression of CD24 resulted in increased colony formation ($p<0.01$) compared to control. However, no effect on proliferation and apoptosis was observed as confirmed by cell cycle analysis. The migratory and invasive capacities of HCT116 cells were increased after CD24 forced expression and decreased after CD24 knockdown ($p<0.01$). Inhibition of Wnt signalling by DN-TCF4 resulted in downregulation of CD24 expression.

Conclusions: Expression of CD24 is influenced by Wnt signalling, and stimulated colony formation, thus CD24 could have a role as a marker of cancer stem cells in CRC. Moreover, its expression increased the migratory and invasive capacity of the CRC cell lines features associated with a high metastatic potential

PL4

Accelerated disc degeneration in the intervertebral discs of IL-1Ra knockout mice

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IL-1 is important in the pathogenesis of Intervertebral disc (IVD) degeneration; increasing matrix degradation enzymes and inhibiting matrix synthesis. IL-1Ra is the naturally occurring antagonist to IL-1. This study investigates the histology and features of degeneration in IL-1Ra knockout mice, to investigate whether degeneration is induced spontaneously when the control mechanism of IL-1 is lost.

Histological staining and immunohistochemistry was performed on BALB/c and BALB/c IL-1Ra knockout mice to examine degeneration and to localise and detect IL-1, MMP3, MMP7, ADAMTSs4 and 5 protein production. In addition IVD cells were isolated using collagenase and proliferation potential determined, and SAβgal staining performed to identify senescent cells.

IL-1Ra knockout mice showed increased number of immunopositive cells for IL-1, MMP3, MMP7 and ADAMTS4 compared to wildtype mice, especially within the nucleus pulposus. However ADAMTS5 was expressed by more cells in wildtype mice than IL-1Ra knockout mice. In addition, discs with high levels of IL-1 and degradation enzymes also showed histological signs of degeneration. IVD cells isolated from IL-1Ra knockout mice displayed reduced proliferation potential and increased SAβgal staining compared with cells isolated from wildtype IVDs.

This study has demonstrated that IL-1Ra knockout mice display accelerated degeneration which is associated with features seen during human disc degeneration (namely, increased matrix degrading enzymes and accelerated senescence). This suggests the natural control mechanism provided by IL-1Ra is essential for the regulation of matrix turnover and prevents degeneration in normal mouse IVD.

PL5

The role of the tumour suppressor p53 in invasion in an inducible mouse model of intestinal tumourigenesis

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BACKGROUND: Although good animal models exist for the early stages of intestinal tumourigenesis there is a need for models which recapitulate the later stages of tumour development, specifically tumour invasion and metastasis. As APC and p53 function are commonly lost in colorectal carcinomas (CRC) we have used an inducible mouse model in which tumour formation is initiated by APC loss to compare the effects of p53 loss versus mutation.
DESIGN: Mice expressing AH-Cre and APC flox were crossed to mice expressing either mutant p53 R172H (analogous to the common human R175H mutation) or p53 flox. Induction results in the loss of a single copy of APC and either loss of p53 or expression of mutant p53 R172H in the intestine and liver.
RESULTS: Median survival was 411, 315, 223 and 218 days in the $p53^{+/+}$, $p53^{flox/+}$, $p53^{flox/flox}$ and $p53^{flox/R172H}$ groups respectively.
Furthermore, a significant increase in both high-grade dysplasia (HGD) and invasive carcinomas was seen in the $p53^{flox/flox}$ and $p53^{flox/R172H}$ groups. Invasive carcinomas ranged from superficial to locally advanced. One animal, in the $p53^{flox/flox}$ group developed a lymph node metastasis.
CONCLUSION: Loss of one copy of p53 does not increase invasiveness in this model, although it appears to accelerate tumourigenesis. Homozygous loss of p53 or activation of mutant p53R172H leads to an invasive phenotype and a concomitant increase in HGD, supporting the hypothesis that p53 loss is an important event in the transition from adenoma to invasive adenocarcinoma.

PL6

RNA-i inhibition of PRKC-ζvb expression down-regulates the aggressive phenotype of human prostate cancer cells

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Protein Kinase C-zeta (PRKC-ζ) expression independently predicts poor clinical outcome in prostate cancer. Several structural variants are potentially encoded by differential splicing of the PRKC-ζ gene, although their functions remain unclear. After showing over-expression of PRKC-ζ variant "b" to be a common occurrence in human prostate cancer, we hypothesised that this variant might be responsible for enhancing cancer cell motility, invasion and metastasis. Using RNA-i directed to three different exonic sites of the PRKC-ζ_{vb} genome, we generated both transient and stable transfectants of prostate cancer cell-line PC3-M. These genetic knockdowns expressed reduced levels of PRKC-ζ_{vb} at, or below, that of benign PNT-2 prostate cells, confirmed by qPCR. PRKC-ζ_{vb} knockdown cells displayed reduced proliferation, invasion and tumorigenesis in-vitro. Diminished tumourgenicity of PRKC-ζ_{vb} knockdown cells was confirmed in-vivo. Subsequent gene-expression analysis using a 44-kilosequence Agilent oligonucleotide array has identified some of the pathways modulated following PRKC-ζ_{vb} knockdown. We now have strong evidence that enhanced expression of PRKC-ζ_{vb} is differentially involved in prostate cancer cell proliferation, invasion and tumorigenesis, thus promoting tumour metastasis. Further analysis of genes modulated following PRKC-ζ_{vb} knockdown is now identifying potential therapeutic targets for new chemotherapeutic agents to inhibit prostate cancer cell invasion and metastasis.

Abstracts

Posters

P1

Postmortem demonstration of a post-operative para-apicoaortic conduit leak

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INTRODUCTION: The medicolegal investigation of a sudden and unexpected death following a surgical procedure must address issues relating to the adequacy (or otherwise) of that procedure.
The present case illustrates the utility of the postmortem examination in the demonstration, and photographic documentation, of patho-anatomic abnormalities accompanying an unusual surgical prosthesis.
CASE REPORT: An 80 year-old man with symptomatic aortic stenosis and a previous medical history significant for remote four vessel coronary artery bypass surgery underwent an elective operation to 'bypass' the aortic valve using an 'apicoaortic conduit', a 'valved' prosthetic device anastomosed to the left ventricular apex and descending aorta.
The post-operative period was uneventful, but shortly before his intended discharge from hospital – some 10 days following the procedure – he was found collapsed, and in asystole, in a ward bathroom.
At autopsy, the significant findings were those of a left haemothorax (1600 mls) and clotted blood surrounding the apical left ventricular-conduit anastomosis, raising the possibility of prosthesis or anastomotic failure; a para-apical conduit anastomotic leak was demonstrated, and photographically documented.
Careful examination demonstrated the integrity of the prosthesis, but 'failure' of the infarcted myocardium surrounding the anastamosis.
CONCLUSION: Photographic documentation of the integrity of prostheses in post-operative deaths provides an objective and reviewable record of autopsy findings.

P2

Fatal intra-abdominal haemorrhage following percutaneous endoscopic gastrostomy

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An 83-year-old gentleman was admitted to hospital with a general decline in health, including a deterioration in his swallow. He was not managing sufficient oral intake to meet his daily nutritional requirements, so the decision was made that he should have a percutaneous endoscopic gastrostomy (PEG) tube inserted for long-term feeding. Following the procedure he became shocked, and did not respond to aggressive fluid resuscitation. He died seven hours later. Post mortem examination revealed 2.5 litres of blood and blood-stained fluid in his abdominal cavity, and a haemorrhagic pancreas. Microscopy of the pancreas showed a defect in a small-medium sized artery, probably a branch of the splenic artery. The cause of death was 1a: Intra-abdominal haemorrhage, 1b: Pancreatic trauma at PEG feeding tube insertion, 1c: Dysphagia due to cerebrovascular disease.
There is only one previous case in the literature of death due to intra-abdominal haemorrhage resulting from PEG tube insertion.1
There are similarities between the two cases. Both patients had previously had cholecystectomies, and may have had distorted anatomy due to adhesions between the stomach and liver. Perhaps as a result of this, in both cases the needle entered the stomach on the second attempt; it is postulated that the damage to the vasculature occurred during the first, unsuccessful, needle-pass.
1. Lau G, Hui Lai S. Fatal retroperitoneal haemorrhage: an unusual complication of percutaneous endoscopic gastrostomy Forensic Science International 2001 116: 69-75

P3

Post mortem in hospital in patients continue to reveal important information

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Post mortem examination has long been considered the most accurate means of determining the cause of death. Previous studies have revealed discrepancies between the ante-mortem clinical impression and post-mortem autopsy findings. New legislation may exacerbate an established decline in the autopsy rate, fuelled by clinicians' confidence in modern day ante-mortem diagnostics and intensive care. This study measures the current rate of post-mortem discrepancies in our centre with comparison to previous studies.
METHODS: Adult inpatients who died and underwent autopsy between 1st April 2008 and 31st March 2009 were identified and hospital notes were reviewed to establish ante-mortem clinical diagnoses. Major and Minor discrepancies with the final autopsy report were identified according to the Goldman classification.
RESULTS: Hospital case notes were available for 150 of 163 cases. Complete correlation between clinical and post-mortem findings was observed in 93/150 (62%). Rates of major and minor discrepancies were 25% and 13% respectively with major discrepancies occurring most frequently in patients cared for on general medical wards (36%). Major discrepancies were present in 10 (20%) of cases from intensive care units, where myocardial and mesenteric infarction, septic foci and carcinomas were the most frequently missed diagnoses. Pulmonary emboli acounted for 13.5% of major discrepencies.
CONCLUSION: These findings correlate with studies spanning 4 decades, indicating that post mortem examinations remain valuable. Any further reduction in autopsy numbers in hospital in patients could be detrimental to patient care.

P4

Signet ring cell varient of malignant melanoma mimicking adenocarcinoma

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Malignant Melanoma is well documented to metastasize to the liver and to have an extremely variable morphology. The Signet Ring Cell Variant however Is uncommon and in the case presented this could potentially have led to diagnostic and clinical errors.
A 69 year old female was admitted with right upper quadrant pain, nausea and hepatomegaly. The history obtained included hemicolectomy for diverticular disease and left eye enucleation.
Abdominal ultrasound showed multiple liver lesions; CT scan did not reveal a primary, but showed marked portal vein thrombosis. liver biopsy showed extensive tumour with signet ring cells. Initial immunohistochemistry was negative for CK7, CK20, ER, AFP, CEA, TTF-1 and LCA. S100 was focally weakly positive. Further immuno including MelanA and CD10 was requested and further radiological investigations were planned. However, before these could be completed the patient suddenly deteriorated and died.
Hospital post mortem examination revealed bilateral pulmonary emboli and multiple circumscribed tumour deposits in the liver. During the external examination a false left eye was noted. Histology from the liver lesions showed extensive tumour with signet ring cells which were positive for MelanA and focally positive For S100, Consistent with a metastatic malignant melanoma. Review of the available hospital notes revealed a single mention of choroid melanoma in an unrelated referral letter.
A mumber of learning points arise from the above; These include the importance of giving full clinical details when requesting histology and that patients may attend multiple hospitals. Definitive confirmation of clinical history should be sought.

P5

Post mortem histology and the cause of death

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INTRODUCTION: The Royal College of Pathologists (RCPath) "Guidelines on Autopsy Practice 2002" advise "as best practice, the sampling of all major organs for histology, in all autopsies". An NCEPOD report (2006) – recorded a histology rate of 19%, with recommendation for "national criteria and standards on organ and tissue retention for histopathology in coronial autopsies, in order to provide convincing evidence of the cause of death".
AIM: To evaluate our frequency of post mortem histology sampling and number of cases in which histology solely provided, or altered the final cause of death (C.O.D).
METHODS: Retrospective analysis of all adult coronial post mortem reports between 1st January and 31st December 2005.
RESULTS: 290 "non-suspicious" and 83 "suspicious" autopsies were completed. Histology was undertaken in 264 (90%), and 83 (100%) cases respectively. Of the "non-suspicious" cases, 54 were initially unascertained - 17 being subsequently provided with a C.O.D from histology alone. Alterations (significant or minor) to the C.O.D following histology were made in an additional 44 cases. Of the "Suspicious" cases, 30 were initially unascertained – 7 being subsequently provided with a C.O.D from histology alone.
CONCLUSION: The high frequency of post mortem histology sampling (93%) is in keeping with RCPath guidelines. The significant role of histology in solely providing, or altering a C.O.D in 18.2% (68/373) of cases supports the recommendation for continued histological sampling in all post mortem examinations.

P6

Post-mortem findings in a manifesting female carrier of Fabry's Disease

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Anderson-Fabry's disease is a lysosomal storage disorder with an underlying deficiency of α-galactosidase A. This disease is traditionally considered to be a disease of the male sex because of the X linked recessive pattern of inheritance, with carrier females usually presenting with mild manifestations. However, variably severe clinical manifestations of Fabry's disease in women have been reported in the literature, explained by possible Lyonisation of the X chromosome.We have recently conducted a post-mortem examination on a 38-year-old woman who was a known carrier of Fabry's disease. Electrocardiogram changes over a period of four years and echocardiographic abnormalities had prompted revaluation of her disease-carrier status as there was a clinical concern about possible change in phenotype. Post-mortem examination findings, histological features and electron microscopy supported a diagnosis of Fabry's disease. This case highlights that female carriers of Fabry's disease may develop the classical disease phenotype and Fabry's disease should not be overlooked as a cause of cardiac disease in women at post-mortem.

P7

Urorectal septum malformation: a rare cause of Potter's Sequence

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Urorectal Septum Malformation Sequence is an embryological defect occurring at 4-6 weeks gestation. It is characterised by failure of the urorectal septum to migrate caudally to fuse with the cloacal membrane dividing the cloaca. This leads to impaired development of the urogenital sinus and the rectum, culminating in an absence of perineal and anal openings and blind ending genitourinary and gastrointestinal tracts.

A 34 year old multiparous woman was diagnosed with oligohydramnios at routine ultrasound scanning. Further scanning revealed bladder outlet obstruction presumed secondary to posterior urethral valves. As the pregnancy progressed severe oligohydramnios developed with associated renal obstruction, renal dysplasia and pulmonary hypoplasia. Cytogenetics from bladder aspiration revealed a fetal karyotype of 46,XX. Cord blood level of 17 hydroxyprogesterone was mildly elevated. At 38 weeks gestation a live born infant was delivered vaginally. The baby had poor respiratory effort and died at seventeen minutes of life. A postmortem was carried out to determine the cause of death.

The infant was of appropriate size and weight with no facial dysmorphic features. There was a markedly distended abdomen with a narrowed upper chest and pulmonary hypoplasia. There were indeterminate external genitalia with a rudimentary scrotum, small phallus and a patent urethral opening. No vagina or anus were identified. Internal examination revealed a massively dilated bladder containing approximately 800mls of clear urine. There was bilateral hydroureter and hydronephrosis associated with multicystic dysplastic kidneys. A stenotic urethra was identified distal to the bladder and in continuity with the phallus. The descending colon/rectum terminated in the superior wall of the bladder. Both fallopian tubes and ovaries were identified in the abdomen however no uterus, cervix or vagina were identified. There was partial sacral agenesis.

This female infant had extensive urogenital, gastrointestinal and sacral abnormalities in association with indeterminate external genitalia despite having normal ovaries. With the exclusion of common causes of ambiguous genitalia and Potter's sequence, the features were regarded as a rare form of cloacal dysgenesis which is characterised by failure of the urorectal septum to migrate caudally to fuse with the cloacal membrane. This abnormality was initially described by Lubinsky (1980) and is a lethal condition in its complete form. Partial Urorectal Septal Malformation Sequence has been described and is compatible with life. Although the aetiology of this rare condition is unknown, possible causes include teratogen exposure and sporadic genetic defects.

P8

Anaplastic transformation in lung metastases of differentiated papillary thyroid carcinoma: an autopsy case report

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Distant metastases are unusual in papillary thyroid carcinoma and when this occurs most commonly affects lungs and bones. Anaplastic transformation in metastatic thyroid carcinoma is rare but is associated with an aggressive clinical behaviour. We present an autopsy case of an 83 year old man with a history of papillary thyroid carcinoma that had been treated with near total thyroidectomy in 1999. He presented ten years later with a 3 week history of shortness of breath, tiredness, lethargy and anaemia. Investigations showed a massive right-sided pleural effusion, initially thought to be related to an underlying pleural malignancy; however his pleural fluid cytology was negative. His condition deteriorated despite treatment, and he subsequently died. At autopsy, he was found to have extensive metastatic deposits in both lungs, which histologically and immunohistochemically were consistent with papillary thyroid carcinoma. An unusual finding was the presence of solid, pleomorphic foci within the tumour deposits, consistent with anaplastic transformation.

P9

Primary cardiac alveolar soft part sarcoma: a report of the first case described in an adult and a lesson in the utility of post mortem histology sampling

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We present a case report of an 88 year old lady with a history of cerebrovascular disease and a "stroke" 4 weeks before her death. She collapsed in her nursing home after eating and was not resuscitated. At autopsy there was an area of intracerebral haemorrhage in the left parietal lobe, a lobulated tumour in the right atrium resembling a myxoma, a tumour in the adrenal gland, food in the trachea and coronary artery disease. Cause of death was given as 1a intracerebral haemorrhage, histology to follow. Cerebrovascular disease was the presumed underlying cause. On histology however, the sections of brain contained a tumour with haemorrhage into it. Histology of the atrial and adrenal lesion showed similar appearances with morphology and immunohistochemistry supportive of a diagnosis of alveolar soft part sarcoma. This tumour usually presents in young people but may present in adults. It often goes undiagnosed until it presents with metastases, usually to the lungs or brain as in this case. Primary cardiac alveolar soft part sarcoma has been described in the literature only once previously in a child. This is the first report in an adult. It also highlights the utility of autopsy histology sampling.

P10

The functionality of epithelial-cadherin expression in lobular breast cancers

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Loss of E-cadherin (E-Cad) expression is a feature of lobular carcinoma (LC), but 15% of invasive LC show E-cad protein expression. We investigated the integrity of the E-Cad membrane complex (ECMC) to determine the cause of E-Cad protein expression loss.
METHOD: E-Cad(+) (n=34) ILC were selected from a series of 224 formalin fixed paraffin embedded ILC. These tumours were compared to control groups (E-Cad(-) ILC (n=20) and E-Cad+ ductal BC (n=12)) by immunostaining for E-Cad, α-catenin, β-catenin, γ-catenin and p120. Protein expression levels were scored for each tumour.
RESULTS: Patients were categorised into 3 discrete groups according to IHC expression patterns: Group (1) E-Cad(+) group showing a completely intact ECMC (n=18); (2) E-Cad(+) group showing absence of one or more ECMC molecules (n=9); (3) E-Cad(-) ILC group (n=18) but with defective ECMC but positive expression of p120 protein. Vascular invasion was shown to be significantly increased in Group 1 compared to Group 3 lobular BC (p=0.013).
CONCLUSION: This study suggests that approximately 66% of Cad(+) LC have an intact ECMC but a minority of cases retain E-cad expression despite an altered ECMC. Loss of E-Cad expression is associated with loss of ECMC components but all appear to retain expression of p120. In addition, the data suggest that an intact ECMC is associated with increased vascular invasiveness, possibly as a result of increased tumour cell adhesion.

P11

Computer assisted morphometric analysis as a tool for diagnosis in fibroepithelial lesions of the breast

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INTRODUCTION: Fibroadenomas and phyllodes tumours are biphasic fibroepithelial tumours of the breast, which present diagnostic difficulties for the pathologist particularly in needle core biopsies.
AIM: To develop morphometric analytical tools to assist in the differential diagnosis of fibroepithelial breast lesions.
METHODS: Three fibroepithelial breast lesions (two fibroadenomas and a benign phyllodes tumour) were digitised using an Aperio Scope, enabling computer assisted image analysis. Image J (an open source digital image analysis programme) was used to generate a grid to ensure random sampling of six fields (1 mm²) per section. Image J converted these selected coloured 1 mm² fields into binary images by thresholding and editing. Thresholding identifies stromal cells and epithelial islands, allowing an analysis of cell density and distance of individual cells to the closest epithelium. Ninety-nine random Poisson distribution of (control) points per field were analysed using the same method.
RESULTS: Preliminary analysis of the fibroadenomas showed significantly different mean cell densities (n=6 fields:P <0.07) of 1612, 2184, and the phyllodes 1139. Cell density in all three lesions is maximal within 25-50 microns of epithelium.
CONCLUSIONS: Our preliminary results highlight significant differences in stromal cell density. The position of peak stromal cell density in relation to epithelium could be a diagnostically useful measurement.

P12

Does chromosome 17 centromere copy number predict polysomy in breast cancer? A fluorescence in situ hybridisation and microarray-based CGH analysis

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Fluorescence in situ hybridisation (FISH) reveals that 8% of breast cancers display increased copy numbers of chromosome 17 centromere (CEP17, average CEP17 >3.0 per nucleus). This pattern is currently considered to represent polysomy of chromosome 17. HER2 amplified cancers harbour complex patterns of genetic aberrations in chromosome 17, in particular involving its long arm. We hypothesised that aberrant copy numbers of CEP17 in FISH assays may not necessarily represent true chromosome 17 polysomy. Eighteen randomly selected CEP17 polysomic cases and a control group of 10 CEP17 disomic cases, as defined by dual-colour FISH, were studied by microarray-based comparative genomic hybridisation (aCGH), which was performed on microdissected samples using a 32K tiling-path bacterial artificial chromosome microarray platform. Additional FISH probes were employed for SMS (17p11) and RARA (17q21) genes, as references for chromosome 17 copy number. aCGH revealed that 11 out of the 18 polysomic cases harboured gains of 17q with involvement of the centromere, one displayed 17q gain sparing the centromeric region and only one could be defined as polysomic. The remaining five cases displayed amplification of the centromeric region. Among these, one case showed 8.5 HER2 copy number mean, it was classified as not-amplified by HER2/CEP17 ratio and as amplified by HER2/SMS ratio. Our results demonstrate that CEP17 copy numbers >3.0 do not reliably identify chromosome 17 polysomy and that correction of HER2 gene status with a CEP17 probe may in some cases lead to underestimation of HER2 amplification.

P13

Mixed micropapillary-ductal carcinomas of the breast: a genomic and immunohistochemical analysis of morphologically distinct components

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Micropapillary carcinoma (MPCs) is a rare histological special type of breast cancer frequently admixed with invasive ductal carcinomas of no special type (IDC-NSTs). We have previously demonstrated that pure MPCs constitute a distinct entity at the morphological and genetic levels. In this study we compared pure and mixed MPCs and investigated whether the distinct morphological components of MPCs harboured different genetic aberrations. Using high-resolution microarray comparative genomic hybridisation (aCGH) we profiled 10 mixed MPCs and 20 IDC-NSTs matched for grade and oestrogen receptor (ER) status. We also generated tissue microarrays containing a 24 pure and 40 mixed MPCs and performed immunohistochemistry for ER, PR, Ki-67, HER2, cytokeratin (CK) 5/6, CK14, CK17, EGFR, topoisomerase-IIα, cyclin D1, caveolin-1 and E-cadherin. HER2, TOP2A, EGFR, CCND1, MYC and FGFR1 gene status was assessed by in situ hybridisation. Our results demonstrate that mixed MPCs harbour patterns of genomic aberrations and phenotype (82.5% luminal, 17.5% HER2) similar to pure MPCs. The distinct morphological components of mixed MPCs displayed strikingly similar genomic profiles. Compared to grade and ER matched IDC-NSTs, mixed MPCs more frequently harboured amplification of multiple regions on 8q (adjusted Fisher's p value <0.05) and significantly higher proliferation rates. In conclusion, mixed MPCs are more closely related to pure MPCs than to IDC-NSTs and micropapillary differentiation in breast cancer may identify a subgroup of more aggressive luminal carcinomas, even in those featuring mixed histology.

P14

A comparison of ductal carcinoma in situ size as assessed by mammography and histology

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Ductal carcinoma in situ (DCIS) presents many challenges, particularly in accurate size assessment. We have no ready access to specimen radiology and therefore resort to widely sampling specimens with a pre-operative DCIS diagnosis. We performed this review of our cases to assess correlation of histological with mammographic size.

All cases of DCIS from Breast Screening from 2004 – May 2008 were identified. The maximum dimension of DCIS was retrieved from the histology report and compared with the mammographic dimension. The slides were reviewed for cases with greater than 10mm discrepancy.

64 cases of DCIS were identified, 62 of which had radiological and histological data available. 60 (97%) underwent wide local excision, of which 7 (12%) subsequently underwent completion mastectomy and 10 (17%) re-excision. 28 (45% of the total 62) showed < 10mm difference between histological and mammographic size. In 27 (44%) the pathological size exceeded the mammographic by more than 10mm, and in 7 (11%) mammographic dimension exceeded pathological by more than 10mm. 14 (52%) of the cases in which histological size was >10mm in excess of mammographic required re-excision, compared with 2 (7%) of those showing < 10mm difference.

Our study demonstrates that there are discrepancies between histological and mammographic sizes and suggests that tumour mapping provides a more accurate assessment of maximum dimension than with specimen slice x-ray alone.

P15

Mammaglobin expression and breast cancer pathology

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Breast tumours are heterogeneous and new tumour markers are sought to improve patient diagnosis and prognosis. Mammaglobin A appears to be a suitable marker, as it is breast-specific and elevated in up to 80% of breast tumours. This study aims to examine the relationship between mammaglobin A expression in breast cancer specimens with pathological grades / markers.

Breast tumour specimens (n=100) and control benign breast conditions were analysed by immunohistochemistry for mammaglobin A expression. 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 and presence/absence of nodal metastasis were recorded.

Mammaglobin was found to be absent in benign conditions and elevated in both invasive and in situ carcinomas. There was a positive correlation between ER positive status and mammaglobin A expression (57% correlation, $p<0.05$, Chi Squared). There was also a positive correlation between lower tumour grades 1 and 2 (62 and 55% respectively) and mammaglobin A expression, whilst a negative correlation with grade 3 tumours, with mammaglobin protein expression decreasing as tumour grade increased. No correlation was found between presence/absence of nodal metastases, PR status, Her-2 status or tumour size.

Since positive ER status and lower tumour grade are associated with a better prognosis for breast cancer patients, then mammaglobin A protein expression may also be associated with better prognosis. However, long-term follow-up is required to determine this.

P16

Tubular carcinoma of the breast: further evidence to support its excellent prognosis

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Although tubular carcinoma (TC) is known to have a favourable prognosis, it is still unknown whether this subtype represents a distinct type of breast carcinoma or whether it behaves like other low-grade luminal-A type breast carcinomas. Therefore, in this study, we performed a retrospective analysis of a large well characterised series of breast cancers to assess the clinicopathological and molecular features and prognostic value of TC compared to grade 1 ductal carcinomas of the breast. RESULTS: When compared to grade 1 ductal carcinoma (207 cases), TC (113 cases) was more likely to be detected on mammographic screening, had smaller median size and less frequently showed lymphovascular invasion or nodal metastasis. Both tumour types were typically ER positive, HER2 negative and had a low proliferative fraction. TC showed less expression of PgR, P-cadherin and MUC5AC and more expression of p27.Compared to grade 1 ductal carcinoma, TC was associated with a longer disease free survival ($\chi 2 = 8.95$, $p=0.003$) and breast cancer specific survival ($\chi 2 = 8.93$, $p=0.003$). Only one patient with TC developed distant metastasis and died from the disease and this patient had an intervening recurrence as grade 2 invasive ductal carcinoma. CONCLUSION: We conclude that the biologic behaviour of TC is excellent and is more favourable than that of grade 1 ductal carcinoma. Adjuvant systemic chemotherapy may not be justified in patients with TC.

P17

Microglandular adenosis or microglandular adenoma? A molecular genetic analysis

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Microglandular adenosis (MGA) is a rare breast lesion, which has long been considered to be hyperplastic. However, atypical forms of MGA (AMGA) and invasive carcinomas arising in the background of MGA are on record. Recent studies have suggested that MGA may be a non-obligate precursor of invasive carcinomas that are negative for hormone receptors and lack HER2 overexpression (triple negative phenotype). To determine whether MGA is clonal and whether it harbours chromosomal aberrations similar to those found in matched invasive ductal carcinoma of no special type (IDCNST) we have performed a molecular genetic analysis of a case comprising MGA, AMGA and a high-grade IDCNST. The three components were separately microdissected and subjected to a high resolution microarray comparative genomic hybridisation. Identical genetic changes were detected in all components, such as gains of the whole of chromosome 7, with subsequent acquisition of additional genetic aberrations in the invasive component, suggesting that MGA was the substrate for the development of the invasive carcinoma. The presence of an extra copy of chromosome 7 in all components was further confirmed by chromogenic in situ hybridisation. Immunohistochemistry revealed concordant profiles across all components, characterised by triple negative phenotype and variable positivity for basal markers. In a way akin to colorectal adenomas and its associations with colorectal cancer, MGA is, at least in some cases, a clonal lesion and may be a non-obligate precursor of high-grade triple negative and basal-like breast carcinomas.

P18

Mutation-independent Her-2 amplification in primary breast cancer is independent of AP2 and YY1

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AIM: Success in using targeted therapy in breast cancer (BC) treatment is dependent on identifying biomarkers that will accurately predict therapeutic response in patients. Patients that overexpress Her-2 (c-erbb2) protein due to amplification of the HER2 gene are candidates for Herceptin treatment. Our aim was to investigate if overexpression of the Her2 protein could occur, in the absence of HER2 gene amplification, due to up-regulation of the transcription factors AP2 and YY1.
METHOD: AP2 and YY1 protein expression was assessed in a group (n=1,099) of well characterised patients with primary breast cancer and long term followup, using immunohistochemistry (IHC) on tissue microarrays. The HER2 status of each tumour was determined using Her2 (clone 4B5) IHC and Silver In-Situ Hybridisation to assess HER2 gene amplification on equivocal cases.
RESULT: A significant positive association was seen between nuclear expression of AP2 and YY1 (P=0.001). No significant association was found between AP2 and over-expression of HER2 gene/protein, unlike YY1 where it was shown that an inverse association with the HER2 gene (P=0.004) and protein (P=0.012) exists. Furthermore, 11 cases of Her2 overexpression in the absence of HER2 gene amplification were identified, but only 4 of these cases showed combined positive expression of YY1 and AP2.
CONCLUSION: This study suggests that Her2 protein overexpression due to non-HER2 gene amplification mechanisms can occur but our data suggests that this disease pathway is not necessarily driven by AP2 and YY1.

P19

CARM1 expression in breast cancer and luminal-like/oestrogen receptor positive subtype: clinicopathological and prognostic associations

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BACKGROUND AND AIMS: CARM1 is implicated in breast cancer proliferation due to its important role in regulation of ERα-mediated gene activation via E2F1 expression. This study investigated the biological and clinical role of CARM1 in breast cancer particularly in the ER-positive/luminal-like class.
MATERIALS AND METHODS: CARM1 protein expression was investigated in a large and well-characterised series of consecutive patients with invasive breast cancers (1130 cases) prepared as tissue microarrays (TMAs). The level of expression was assessed using the modified H-score technique and data was categorised and correlated with the clinicopathological variables, breast cancer immunophentypes and outcome.
RESULTS: Increased CARM1 nuclear expression was significantly associated with tumours of larger size, higher grade and raised mitotic counts (p=0.001), and with positive expression of markers of poor prognosis such as p53, basal cytokeratins (CK5/6/14), EGFR, HER2, P-cadherin and MIB1 (p=0.001). An inverse association between CARM1 and steroid receptor expression was found. A significant association between CARM1 expression and shorter breast cancer specific (BCSS) and disease free survival (DFS) was found in the whole series and ER-positive/luminal like cohort. Multivariate analyses showed that CARM1 expression is an independent predictor of shorter survival.
CONCLUSION: CARM1 protein expression is an independent prognostic factor of shorter BCSS and DFS in breast cancer and its elevated expression is positively associated with markers of poor prognosis. CARM1 has a potential application in assessing the clinical outcome of patients classified as ER-positive/luminal-like.

P20

Luminal breast cancer: identification of significant prognostic patho-biological indicators

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BACKGROUND: The luminal class of breast cancer (oestrogen receptor positive and HER2 negative) comprises a large percentage of breast cancer and associated with a good prognosis particularly in the lymph node (LN) negative subgroup. In this study, we investigated a LN negative luminal breast cancer cohort that had not received adjuvant therapy to identify prognostic patho-biological indicators.
MATERIALS AND METHODS: Data on clinicopathological variables and 21 biomarkers were analysed using Log Rank test to assess survival outcome. Markers showed significant survival differences were used in a multivariate Cox model to determine their independence as prognosticators.
RESULTS: The tumours were characterized by high expression of AR, PgR, CK18, Bcl2, BRCA1, FOXA1, and FHIT and low expression of CK5/6, CK14, p53, EGFR, MIB1, P-Cadherin, SMA, p63 and neuroendocrine markers. We found associations between longer breast cancer specific survival (BCSS) and lower grade (p<0.001), smaller size (p<0.001), lower mitosis (p<0.0001) and absence of vascular invasion (p=0.005). High expression of CK14 (p=0.006) and MIB1 (p=0.007) were associated with shorter BCSS while low expression of AR (p=0.011) and BRCA1 (p=0. 008) was associated with shorter BCSS. In multivariate analysis, AR, BRCA1, tumour size and grade were independent prognosticators.
CONCLUSION: Assessment of tumour grade, size, AR and BRCA1 in luminal tumours provides prognostic value and can identify tumours with a variable outcome. Our results also suggest that outcome differences within luminal tumours can be explained in part by differences in proliferation.

P21

Audit of diagnostic consistency of pre-operative core biopsies and subsequent therapeutic excision specimens of invasive breast carcinoma

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Breast core biopsy is performed routinely in the pre-operative diagnosis of breast cancer. Increasingly the information from this investigation is used to plan treatment. There are known limitations however. The purpose of this study was to compare grade and tumour type on the core and subsequent excision specimens.

We reviewed 116 needle core biopsies (NCB) and subsequent excision specimens received by our histopathology department over a six month period. Excellent correlation between histological grade on NCB and subsequent excision was demonstrated. In 96 cases, where the patients had not received neo-adjuvant therapy, histological grade comparison was consistent in 53 of 96 cases (73%, kappa=0.54). Components of the histological grade (acini formation, nuclear grade and mitotic index) agreed, respectively, in 84%, 86% and 73% (kappa index 0.67, 0.73, 0.37). Total score agreed in 55% (kappa 0.44). When scores from 20 patients who had received neo-adjuvant treatment were added, the grade, overall total score and scores for the various components remained similar. The type of invasive carcinoma remained consistent in 94% of cases.

Needle core biopsy can be used to accurately predict the histological grade and tumour type in invasive breast carcinoma. Accurate typing and grading allows stratification of patients into appropriate treatment groups and provides prognostic information. These results demonstrate that our centre compares favourably with previous published studies on this subject.

P22

VGLL1 expression in triple negative breast cancer

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The triple negative (TN) phenotype (ER, PgR, HER2 negative) have attracted attention as a poor prognostic class of breast cancer (BC). However, TN encompasses biologically and clinically heterogeneous tumours. In order to determine biomarkers characteristics of TN BC, we analysed the expression of 48000 gene transcripts in 132 invasive BC using ANN analysis and identified two novel genes (VGLL1 and SOX10) significantly associated with TN. Using a large invasive BC cohort (n=2000), prepared as TMAs, we assessed the immunohistochemical expression of these targets and investigated their association with clinicopathological variables, patients' outcome and ability to refine the classification of TN.

VGLL1 nuclear protein expression was associated with tumours showing higher grade ($p<0.001$), increased mitosis, poorer tubule formation (all $p<0.001$) and larger size ($p=0.024$). Although VGLL1 expression was associated with TN and basal-like phenotypes, univariate analysis showed association with negative expression of ER and PgR ($p<0.001$) but not HER2. VGLL1 nuclear expression showed a significant relationship with shorter breast cancer specific survival ($p=0.026$) particularly in the first 8 years after diagnosis. SOX10 nuclear expression (percentage score) showed significant associations with lower tumour stage ($p=0.004$) and grade ($p<0.001$). It was positively correlated with ER ($p<0.001$) and PR ($p=0.003$), and non-TN tumours ($p<0.001$).

We confirm that VGLL1 nuclear expression is a marker of poor prognosis and associated with hormone receptor negative breast cancer. Further studies analysing VGLL1 as a potential therapeutic target are therefore warranted.

P23

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P24

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P25

Erdheim-Chester disease of the breast

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We report the case of a 52 year-old woman who first presented with bilateral irregular hypoechoeic masses in both breasts. The masses were biopsied and reported as showing florid granulomatous inflammation. Special stains for infectious organisms were negative. The areas of abnormality persisted and were re-biopsied three months after the initial presentation. The histology from these biopsies showed a florid xanthogranulomatous reaction notable due to the presence of numerous Touton-type giant cells. This unusual morphological appearance, along with the history of persistent bilateral breast abnormalities, is consistent with the diagnosis of Erdheim-Chester disease (ECD) and the patient is currently undergoing clinical staging. ECD is a rare condition characterised by xanthomatous non-Langerhans cell histiocytosis.

It is most commonly associated with symmetrical sclerosis of both metaphysis and diaphysis of long bones. Extraskeletal manifestations may also affect the lungs, pericardium, retroperitoneum, skin and eyes (Kenn, Stabler et al. 1999).

Although manifestations in the breast have been previously reported (Andrade, Nemer et al. 2004), to the author's knowledge, this is only the second case in which a breast lump was the initial presenting feature (Barnes, Foyle et al. 2005), and certainly the first case of its type reported in the UK. Delays in diagnosis can be common in such unusual presentations, as was the experience with this case. Although rare, we would recommend that such conditions be kept in mind in the differential of such granulomatous lesions of the breast.

P26

Cerebrospinal fluid pseudocyst of the breast

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A 17 year-old female presented via her GP with a lump in the right breast. The lump had been present for 3 weeks at the time of first presentation. On examination there was a lump in the outer half of the right breast.
On ultrasound, the lump measured 17 x 13mm, and was seen to be intimately related to a ventriculoperitoneal shunt, which had been inserted previously for bilateral hydrocephalus. Ultrasound guided aspiration to dryness revealed clear fluid, which was not infected and was confirmed as cerebrospinal fluid.
Fracture of and leakage from ventriculoperitoneal shunts has been documented and the presentation depends on the site of leakage (Kalra et al. 2002). Formation of a CSF breast pseudocyst has been variously described in the literature, but usually in the context of a shunt placed many years previously, and in older women. This patient is the youngest documented case of this uncommon complication.

P27

Accessing the mammary 'forest': central ducts in human breast

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In one breast many lobes each have a central duct, peripheral branches and glandular lobules. Rational development of lobe-directed diagnosis and therapy requires understanding lobe architecture and biology. Each lobar 'tree', rooted in the nipple, is a potential portal to the mammary 'forest', motivating testing of the hypothesis of distinct duct types (A, B, C) in the human nipple. Immunophenotype data previously presented to the Society has not supported separate A and B duct populations. To this data are now added structural data. Duct perimeters were measured of 385 ducts in coronal sections of the central duct bundle in 15 mastectomy breasts, and at multiple levels for all ducts in serial HE sections of two cases. Two 3D models of ducts on the apex of the papilla were prepared from serial HE sections and one using episcopic microscopy data.

Structurally distinct A and B duct populations were not observed but spatially separated C type (peripheral) ducts were present. Ducts varied widely in size profile, with implications for their accessibility by cannulation and ductoscopy. Clustering of ducts around common openings on the nipple surface ('ostium sharing') was observed in all 3D models.

Ostium sharing and a wide range of duct calibres may largely account for the small number of ducts which can be identified externally compared with the much larger number of ducts in the central duct bundle. These relationships have implications for accessibility of different lobes for endoductal diagnosis and therapy.

P28

Predicting HER2 amplification in breast cancers with ambiguous Her2 immunohistochemistry: Can it be done? Is it useful?

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Her2 immunohistochemistry is scored negative, ambiguous or positive. Ambiguous cases are tested for HER2 amplification by FISH. The proportion of HER2-amplified ambiguous cases is uninformative about scoring boundaries. FISH of negative and positive cases does test boundary placement, but many cases need testing to determine proportions of false negatives and false positives precisely.

This study tests the conjecture that Herceptest-ambiguous breast cancers can be divided into examples likely to be HER2 amplified (2A), likely not to be amplified (2NA) and cases in which prediction is impossible (2NP). If correct, the proportion of HER2 amplified cases in each category ought to be informative about the appropriateness of scoring boundaries and could enhance quality monitoring without increased FISH costs.

Over two years, one observer scored 2009 Herceptests: 143 positive, 444 ambiguous and 1422 negative. Of the ambiguous cases, 94 were prospectively classed 2A; 125 2NP and 225, 2NA. All ambiguous cases were subsequently FISH tested (Vysis).

Of the 2A cases 90.4% were amplified; of the 2NP cases, 44.8%; and of the 2NA cases, 14.2% ($\chi 2 = 163$, $P<0.00001$). HER2 amplification was predicted correctly in 87% of the 319/444 ambiguous cases in which prediction was considered possible.

Scoring boundary placement is not obviously incorrect in this series. It is likely the proportion of incorrectly assigned negative and positive cases is substantially smaller. Prediction of HER2 amplification in ambiguous cases is possible, and may be useful for comparing Her2 IHC scoring between observers and laboratories.

P29

Genomic profiling of mitochondria-rich breast cancer

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Breast carcinomas entirely composed of cells with abundant eosinophilic cytoplasm fall into four main groups: apocrine, neuroendocrine, acinic and oncocytic carcinomas. Oncocytic carcinomas are composed of mitochondria-rich cells (mitochondria-rich breast cancer: MRBC) and their status as a discrete pathological entity remains a matter of contention. We sought to define the molecular genetic features of MRBCs and to compare them with a series of grade and oestrogen receptor (ER) status-matched invasive ductal carcinomas of no special type (IDCNSTs). Eighteen MRBCs and a series of 36 grade and ER matched IDCNSTs were microdissected and subjected to microarray comparative genomic hybridisation (aCGH) analysis using a 32K tiling path bacterial artificial chromosome array platform. MRBCs significantly differed from IDCNSTs at the genomic level. Unsupervised hierarchical clustering analysis demonstrated that they preferentially formed a distinct cluster. Gains on 3q29, 5q35, 6p21, 7q22, 8p11, 9q34, 11q13, 12q13, 16p13, 17q21, 19q13 and 20q11, and losses on 2p11, 3p12, 4p15, 5q21, 6p22, 7q31, 10q23, 11p14, 12q24, 14q13, 15q15, 18q21, 21q21 and Xq13 were more prevalent in MRBCs. Amplifications of 5q23, 6q24, 7q34, 8q23, 9q34 and 17q25 were significantly associated with MRBCs. Our results demonstrate that although MRBCs are heterogeneous at the genetic level, their distinctive histological features and molecular genetic profiles support the contention that these tumours may constitute a distinct pathological entity.

P30

Audit of the rate of recurrence in wide local breast excisions with anterior margin positivity

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The aim of this audit was to find out if wide local excisions with positive anterior margins have the same rate of recurrence as those with complete excision at all margins. During surgery the anterior margin is taken up to the level of the skin. Therefore, surgical opinion is that there should be no difference in rate of recurrence between these two groups.

We examined wide local breast excision histology reports received between 1998 and 2003 to identify all cases showing anterior margin positivity for invasive carcinoma. Cases were excluded if invasive or in-situ disease was identified at any other margin or in cavity shavings. A total of 35 cases with positive anterior margins were identified. The control group was 140 randomly selected cases of completely excised invasive carcinoma from all 5 years.

The departmental computer system was used to identify any patients with further breast pathology specimens since their original wide local excision (follow up of five to ten years). Of the 35 positive cases, one recurrence was identified, one year post-surgery (2.8%).

Of the 140 control cases, three had recurrent disease seen in mastectomy specimens, four, seven and ten years post initial surgery (2.1%).

We concluded that there was a very similar recurrence rate in both groups and anterior margin positivity for invasive malignancy did not increase the risk of recurrent disease.

P31

Identification of potential therapeutic targets in HER2 amplified breast carcinomas by integrative molecular profiling

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HER2 positive breast cancers comprise a heterogeneous group of aggressive tumours, which can be targeted with Trastuzumab and Lapatinib. Although anti-HER2 targeted therapies have been shown to increase the survival of patients with HER2 positive cancer, de novo and acquired resistance to these agents is not uncommon. Therefore, identification of additional therapeutic targets could help further refine the treatment of HER2 positive patients. There is evidence to suggest that genes whose expression correlate with copy number and are consistently overexpressed when amplified are likely to be biological drivers and may be exploited as potential therapeutic targets. To identify potential novel therapeutic targets for subgroups of HER2 positive cancers, we have integrated high resolution genome wide microarray-based comparative genomic hybridisation (aCGH) and gene expression data obtained from 58 HER2 amplified primary breast carcinomas. Recurrent amplifications mapping to 125 loci were identified. 292 genes whose expression correlates with copy number and are consistently overexpressed when amplified were identified, including HDAC2 (6q22), PPM1D (17q23), RAF1 (3p25) and AURKA (20q13), all of which are putative drug targets. Furthermore, 3650 genes were identified that significantly correlated with copy number, including 439 recurrently amplified genes. Ingenuity Pathway Analysis of these genes showed significant enrichment in various canonical pathways including oxidative phosphorylation, neuregulin signalling, IGF1 and insulin receptor signalling. Our results identified additional potential therapeutic targets for HER2 positive breast cancer and networks that may drive the biology of these cancers.

P32

Fascin expression in aggressive breast cancer

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Fascin is an actin-bundling protein involved in cell motility and has been shown to be upregulated in many malignancies and found to be associated with the tumour aggressiveness. The aim of this study was to investigate the role of fascin expression in breast cancer and evaluate its relationship with other prognostic markers.

METHOD: In this study paraffin embedded sections of 116 breast cancers were examined for fascin expression by immunohistochemistry. Her2 expression was studied by immunohistochemistry, FISH and CISH analysis.

RESULTS: Fascin was expressed in 41% (48/116) of invasive carcinomas and 27% (27/100) of the in situ components. In the tumours showing fascin expression, 38% (18/48) of the invasive tumours and 37% (10/27) of the in situ tumours also showed Her2 gene overexpression. In comparison, the tumour group which were negative for fascin, 24% of the invasive tumours and 25% of the in situ tumours had Her2 overexpression. Seventy five percent of the fascin positive and Her2 overexpressed invasive tumours were grade 3 carcinoma. In contrast 44% of the fascin negative invasive tumours were of grade 3. Fascin positive tumours had higher incidence of lymphovascular invasion (67%) compared to fascin negative group (54%). In fascin positive tumours 19% (9/48) were of higher stage (pT3 and pT4), whereas only 6% (4/68) of the fascin negative tumours were of high stage.

CONCLUSION: Fascin expression is associated with Her2 overexpression, higher tumour grade, lymphovascular invasion and higher tumour stage in breast cancer.

P33

Expression of COX-2 in invasive breast carcinomas

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COX-2 is expressed in various human malignancies, including breast cancer. However, its level of expression still remains unclear. We aimed to determine COX-2 expression in invasive breast carcinoma (IBC), and its relationship with clinopathological characteristics. COX-2 expression was analysed in 339 IBC patients by immunohistochemistry. Both intensity and extent of expression were scored. Fifty-one patients (15.0%) did not express COX-2 (score 0), whereas 69 (20.4%) expressed low levels (score 1 or 2), 138 (40.7%) expressed moderate levels (score 3 or 4), and 80 (23.6%) expressed high levels (score 5 or 6). There was a significant positive correlation between level of expression and tumour grade (Pearson's correlation coefficient, p=0.0001) and size (p=0.0037). No difference in COX-2 expression was found with regard to patient age(Pearson's correlation coefficient, p=0.565), overall survival time (p=0.526), and time from diagnosis to metastasis (p=0.212). Moreover, there was no difference with regards to patient menopausal status (chi-square test, p=0.308), ER status (p=0.227), lymphovascular invasion (p=0.227), lymph node positivity (p=0.840), and presence of associated DCIS (p=0.234). COX-2 was expressed in 85% of IBC patients, with 65% showing significant levels of expression. It was also associated with markers of aggressiveness including tumour grade and size. It may therefore play an important role in the majority of IBCs and its inhibition may have important chemopreventive and chemotherapeutic effects.

P34

PIK3CA expression in invasive breast cancer: a biomarker of poor prognosis

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Although Phosphatidylinositol 3-kinase (PIK3CA) mutations in breast carcinoma (BC) have been extensively studied, their associations with the clinicopathologic variables and patients' outcome remain controversial. Moreover, roles of its deregulation in the molecular classes of BC remain debatable. The aims of this study were to assess the prevalence and clinical significance of PIK3CA expression in a well-characterised series of BC with long term follow-up with relevance to different molecular classes.
PIK3CA protein expression was assessed in 1845 unselected primary invasive BC using TMAs and immunohistochemistry. Sections were semi-quantitatively scored using H-score.

In this study (47.6%) of cases showed PIK3CA positivity, that was directly associated with higher grade, larger size, nodal involvement, definite vascular invasion, and higher proliferative fraction (p<0.001). PIK3CA expression was significantly associated with basal-like (BLBC) and HER2+ classes and triple negative non-basal (TNnon-B) tumours (p<0.001), while the luminal class showed less frequent expression. Patients with PIK3CA positive tumours had shorter BC specific survival and disease free survival independent of other prognostic factors except grade. PIK3CA tumours were significantly more likely to metastasise to bone and liver than to lung and brain.

PIK3CA is an oncogenic biomarker associated with poor prognosis in BC patients. Although, PIK3CA overexpression was more frequent in BLBC and HER2+ tumours, its expression appeared to be a marker of higher grade/poor differentiation rather than of a particular subtype. Thus, targeting PIK3CA through specific inhibitors should include poorly differentiated tumours irrespective of their molecular subtype.

P35

MIB1 Labelling Index can classify Grade II breast cancer into two clinically distinct subgroups

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Histological grade is recognised as one of the strongest prognostic factors in operable breast cancer. Although grade I and grade III tumours are biologically and clinically distinct, grade II tumours appear to be heterogeneous and may represent a combination of both grades rather than an intermediate group between the two. Several attempts such as genomic grade index have been performed to subclassify grade II into subgroups of clinical relevance. Here we present evidence that routinely available immunohistochemical MIB1 labelling index (LI) can classify grade II into two clinically distinct subgroups.

In this study, growth fraction of 400 grade II primary operable invasive breast carcinomas were immunohistochemically assayed on full-face tissue sections using MIB1 clone of Ki-67. Growth fractions were expressed as MIB1 LI in 1000 tumour nuclei at high power magnification.

Using a 10% cut-point of MIB1LI, cases were classified into low (58%) and high (42%) proliferative subgroups. Univariate and multivariate survival analysis revealed a strong association between these subgroups and breast cancer specific survival (p=0.001), and disease free survival (p< 0.001) which was independent of other established prognostic factors (p=0.003,HR=1.7).

Our results further demonstrate that grade II breast cancer may represent combination of at least two biologically or behaviourally different entities. Assay of growth fraction in breast cancer using MIB1 IHC is a robust cost-effective tool that can subdivide grade II tumours into low and high risk populations providing additional information in planning therapies and outcome prediction.

P36

Evaluation of the first 'live' cases using OSNA for the intra-operative diagnosis of metastatic carcinoma in our hospital

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Our hospital has been evaluating the benefits of a relatively new technique in the diagnosis of metastatic carcinoma in breast cancer patients in which sentinel nodes are analysed intra-operatively for metastases using the OSNA (One Step Nucleic acid Amplification) system. In 2007, our hospital took part in a trial of the OSNA system, during which a multicentre prospective study was carried out which showed promising results. In November 2008, the technique went 'live' at our hospital, and this current study aims to evaluate the results of the first 60 patients in which the OSNA system was utilised. Presence or absence of metastases, the size of metastases (macro vs micro) and the time it took for the sample to be reported will all be assessed.

At present, of the cases collected, approximately 35% were OSNA positive (20% showed macrometastases and approximately 15% showed the presence of micrometastases) and 64.5% were negative. The time interval between sample receipt and report ranged from 40 minutes to 1 hour, depending on the number of sentinel nodes submitted.

Preliminary results show that in our hands, OSNA is an accurate, and beneficial technique for the intra-operative diagnosis of metastatic breast carcinoma in sentinel lymph nodes.

P37

Anti-apoptotic proteins Bcl-2 and Hsp27 in breast cancer development and progression

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In previous studies we have identified that normal breast from cancer-containing breasts shows reduced apoptosis and higher expression of the anti-apoptotic proteins bcl-2 and Hsp27 than age-matched breast from women without cancer. This altered apoptotic regulation could enhance tumour development. The present study compared the expression of bcl-2 and Hsp27 in normal, proliferative change, in-situ and invasive cancer in the same breast, to assess their role in progression.

67 invasive cancers with associated changes (56 with normal) and 6 DCIS with normal/benign changes were assessed for the presence of bcl-2 and Hsp27 using immunohistochemistry. Separate tissue blocks were used for each non-malignant component per case and for some DCIS. Counting was performed without knowledge of links between tissues.

Expression of bcl-2 was higher in normal than proliferative lesions ($p=0.005$), DCIS and invasive cancers (both $P<0.001$). There were no differences between proliferative and DCIS and DCIS and invasive cancer. Only 3 cancers had a higher level than their matched normal breast. Expression of Hsp27 was similar in normal, DCIS and invasive cancers but lower in proliferative lesions.

Higher levels of bcl-2 in breasts in which cancer develops could be a factor in the early stages of tumour development resulting in the failure to remove cells with DNA damage, but does not appear to have a role in progression.

P38

Altered histone modifications and their regulating enzymes in Fulvestrant resistant breast cancer cell line in vitro

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BACKGROUND: Fulvestrant is a valuable treatment in postmenopausal women with advanced breast cancer who have progressed on prior endocrine therapy. However, Fulvestrant resistance commonly emerges, where in vitro data indicate this state can have increased proliferative and invasive capacity. Thus, understanding the mechanisms responsible for Fulvestrant resistance remains a key challenge. The purpose of this study was thus to begin to examine aspects of epigenetic regulation in a Fulvestrant resistant model, profiling histone acetylation/methylation and its modifying enzymes. Such studies could reveal new therapeutic avenues to treat endocrine-resistant breast cancer.
DESIGN: Fulvestrant-resistant (FASR) breast cancer cell line was developed. Immunocytochemistry was used to compare the level of histone modifications (H3K18, H4K16, and H4K20) between the parental MCF7 and FASR. QPCR was used to compare the level of various histone modifying enzyme genes (PCAF, NCOA1, HAT1, MYST3, HDAC1, HDAC2, and EZH2) in both cell lines.
RESULTS: The level of histone acetylation (H3K18, H4K16) and methylation (H4K20) was higher in FASR cells compared to MCF-7 cells, as revealed by nuclear immunostaining. Furthermore, QPCR showed that the mRNA expression of the histone acetyl transferases HAT1 and MYST3 and the histone methyltransferase EZH2 were upregulated in FASR cells.
CONCLUSION: The study identifies differences in the level of histone modifoications between Fulvestrant-resistant and responsive breast cancer cells, accompanied by upregulation of genes that have been reported to be responsible for such modifications. Such changes may be contributory to the mechanisms underlying the gene profile of Fulvestrant resistance *in vitro*.

P39

Phosphorylated Histone 3 Mitotic Index (PMI); a step towards a more objective grading system in breast carcinoma

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BACKGROUND: Assessment of growth fraction is regarded as a powerful prognostic factor in breast cancer (BC). Several studies have examined the role of phosphorylated histone H3 (PH3), as a marker of mitotic figures and its potential as a growth fraction marker in breast cancer.
AIM OF THE STUDY: To assess the reliability of PH3 in detecting mitotic figures in BC by comparing PH3 mitotic index (PMI) with two other methods of growth fraction assessment; H&E mitotic index (MI) and MIB1 labelling index (MLI) and to identify any relationship between PMI and clinical variables or patient outcome.
METHODS: 200 consecutive cases of invasive BC were stained immunohistochemically for Anti-phospho-Histone H3 (ser10) and MIB1. PMI was calculated by counting the number of PH3 positive cells in 10 fields (x400 magnification) in the area of highest mitotic activity.
RESULTS: There was a correlation between PMI, MI, and MLI ($p<0.001$), where 89.2% and 80.6% of high PMI had high MI, and MLI respectively. High PMI was associated with high histological grade ($p<0.001$), and larger tumour size ($p<0.001$). In addition patients with low PMI showed longer overall survival ($p=0.04$). This significance is maintained in the multivariate analysis when compared with other component of Nottingham grading system.
CONCLUSION: PMI could be used as a reliable method of assessing the growth fraction in BC, which could improve objectivity of the Nottingham grading system, and potentially help selection of patients suitable for adjuvant chemotherapy.

P40

The value of nipple discharge cytology

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The value of nipple discharge cytology is uncertain. In this study patients with nipple discharge cytology from a single duct discharge from 2000 to 2005 were reviewed. 1121 specimens from 840 patients were reported during this period. The standard protocol was a mammogram in women over 35 years and investigation of any clinical or mammographic abnormality. 59 women had ipsilateral carcinoma identified at the time of nipple discharge cytology or on follow up. 28 women with a simultaneous B5 core biopsy or C5 FNA were excluded from subsequent analyses. 212 of the remaining 812 patients had further investigation. The relationship between the most atypical nipple discharge result in each patient and subsequent pathological findings was analysed. Carcinoma was identified in 16 of 665 (2.4%) with a benign nipple discharge cytology result, 13 of 134 (10%) classified as atypia of uncertain significance, 3 of 12 (25%) classified as suspicious of malignancy and in 1 of 1 classified as malignant on nipple discharge cytology. The commonest benign diagnoses were benign papilloma in 85 and duct ectasia in 29. Multidisciplinary discussion about the need for further investigation is essential after a diagnosis of atypia of uncertain significance, suspicious of malignancy or malignancy on nipple discharge cytology.

P41

Pathological follow-up of B3, papillary lesions of the breast – an audit

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National screening guidelines state that breast cores containing intraductal papillomas (IDP) should be scored as B3 and that papillomas should be excised due to their positive association with ductal carcinoma in situ (DCIS) and Invasive malignancies. Here we audit all the breast cores diagnosed as containing intraduct papillomas (IDP) over a ten year period at Aberdeen Royal infirmary, contrasting those cores taken as part of the breast screening program with those taken through other referral routes.

11% of the "screening" IDP cores were taken at the same time as an additional breast core that contained DCIS or invasive malignancy. Of the 89% of remaining IDP cores, 24% of the subsequent duct resections contained a new diagnosis of DCIS or malignancy. A quarter of the "non-screening" cores were associated with DCIS or malignancy, either in the IDP core itself or in an additional core taken at around the same time. 11% of the subsequent resections in the non-screened group show a new diagnosis of DCIS.

The differential pick-up rates for new diagnosis at core and resection reflects a "self" or "clinical" referral step undertaken by symptomatic patients, independently of formal screening. Such patients have a higher pick-up rate at initial or additional core and a subsequently lower pick-up rate at subsequent resection.

P42

Treatment surgery for breast carcinoma – where has the pre-operative information gone?

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INTRODUCTION: When sampling wide local excision/mastectomy specimens, the risk of taking inappropriate blocks and reporting delays can be minimised if appropriate pre-operative information is available. This data includes tumour location, size, histological type and grade. Information supplied on request forms submitted by specialist breast surgeons was audited and compared to data captured by the pathologist during multi-disciplinary meetings (MDM).
METHOD: 123 breast specimens were audited for: tumour location (diagram or description), tumour size and type, indication of more than one lesion and microcalcification. The presence of these data items captured by the pathologist at MDM was recorded.
RESULTS: A diagram was drawn on request forms (n=123) in 50 cases (41%), location stated in 50 (41%), size in 14 (11%) type of tumour 70 (57%) and where multiple tumours were present 6 of 8 cases (75%) and calcification 7 of 12 cases (58%). In 73 of 123 cases (59%) pathologist data capture was available from the MDM and a diagram was recorded in 72 of 73 (99%), written location in 73 of 73 (100%), size 63 (86%) and type 64 (88%). In 4 of 4 cases (100%), more than one lesion was documented and calcification was mentioned in 9 of the 11 cases (82%).
CONCLUSION: This audit shows that important preoperative information for the pathologist is often omitted on request forms. Where the pathologist captured the information at MDM, a near complete dataset was achieved. Specialist request forms, which include a diagram, should provide a fuller dataset.

P43

Biological features of oestrogen receptor negative primary invasive breast cancer in older women and correlations to different treatment regimes

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Hormone insensitive oestrogen receptor alpha negative (ERα-) breast cancer (BC) has proposed a challenge in the treatment of women above 70 years of age. This study aimed to determine the biological characteristics of ERα- tumours in elderly patients and correlate these with their outcome to different treatment regimes.

Primary invasive BC patients (≥70 years) with primary invasive breast cancer with ERα H score ≤50 presenting to Nottingham Breast Institute between 1987-2007 (n=185) were chosen. Core needle biopsy specimens were immunohistochemically stained for PgR, HER2, ERβ2 and Ki67. First-line treatment regimes were evaluated in terms of patients' outcome and breast cancer specific survival rates. Pathology was evaluated in terms of tumour grade and stage. Correlations between tumour markers and different treatment regimes were determined.

In this study, ERα- patient tumours were more likely to be grade 3 (75.7%), stage 1 (55.6%), PgR negative (97.2%), HER2 negative (75.3%), ERβ2 positive (80.2%) and Ki67 negative (58.3%). The highest breast cancer specific survival rate (78%) was noticed in surgically treated patients (74%) of patients. HER2 and ERβ2 expressions were associated with shorter local recurrence-free time ($p<0.05$).

The biological characteristics of ERα- in elderly patients were similar to those of younger patients. Surgery was the most common primary therapy used with the highest breast cancer survival rate, but carried risks of local, regional and distant recurrences. This evokes further research into surgery with the use of systemic therapy in these patients.

P44

Columnar cell lesions are the early precursors of some forms of invasive breast carcinoma: a new genetic map for the evolutionary pathway of low nuclear grade breast neoplasia (LNGBN) family

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There is evidence to suggest that a number of low nuclear grade invasive breast cancers (LNGBC) and putative precursor lesions may consist in a family of interrelated lesions. To identify the molecular genotypic profile of lesions belonging to the LNGBN family, 15 LNGBCs and matched coexisting columnar cell lesions (CLLS), ductal carcinoma in situ (DCIS) and lobular neoplasia (LN) were microdissected and subjected to high-resolution array-comparative genomic hybridization (aCGH), single nucleotide polymorphisms (SNPs) analysis, and loss of heterozygosity analysis. Results were validated using fluorescence and chromogenic in situ hybridisation and immunohistochemistry. We observed that at the genetic level, lesions from the same patient displayed remarkably similar patterns of genetic aberrations (Spearman's correlations 0.55-0.89; $p<0.00001$). All CLLs, low grade DCIS, LN and their matching invasive carcinoma harboured gain/amplification of 1q31-32 and loss of 16q12, 16q21 and 16q23. In addition to the aberrations found in CCLs, in situ and matching invasive components displayed additional genetic aberrations. Amplification of cyclin D1 was detected by CISH in ILCs and their matching LN and FEA lesions. Our results provide strong circumstantial evidence to suggest that CCLs are the earliest morphologically identifiable non-obligate precursors of more advanced lesions in the LNGBN family and that that loss of 16q and gain 1q are the earliest genetic changes in this family of lesions.

P45

Histological grading of breast cancer on needle core biopsy: does immunohistochemistry (IHC) assessment of proliferation offer improvement?

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BACKGROUND: Previous studies report discordance in grading between needle core biopsy (NCB) and surgical breast cancer (BC) excision specimen (SES). Misassignment of grade may affect clinical decisions, potentially excluding patients from neo-adjuvant therapy. A main cause of grade discordance is the underestimation of mitotic counts on NCB compared to the gold standard: H&E mitotic counts in SES. This study aims to determine a reliable method for assessment of proliferative activity on NCB.
METHOD: BC proliferation was assessed using H&E mitotic counts (using cut-off defined by the Nottingham grading system per 10 high power field) and 2 IHC proliferation biomarkers (MIB1 and PPH3) on a series of 101 NCBs and their corresponding SES.
RESULTS: H&E mitotic counts on CNB were significantly lower than in SES ($p<0.001$). No significant difference was observed between NCB and SES scores when MIB1 ($p=0.13$) and anti-PPH3 ($p=0.07$) IHC were used. Compared to the "gold standard" H&E on SES ≥22, better concordance was observed using both MIB1 (Area Under Curve (AOC)=0.91, $p=0.02$) and anti-PPH3 (AOC=0.89, $p=0.09$) when compared with H&E mitotic counts (AOC=0.81) using ROC analysis.
CONCLUSION: Although NCB undersampling of heterogeneous breast tumour or trauma are commonly cited reasons, this pilot study suggest that underestimation of mitotic count may result from an inability to detect mitotic figures on H&E stained NCB. Future studies for improving the method of assessment of H&E mitotic counts on NCB are needed.

P46

Estrogen receptor β2 location defines outcome in breast cancer

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Hormone therapy has been a cornerstone for treating ERα-positive breast cancer. The identification of estrogen receptor (ERβ) suggested it may have additional prognostic/predictive values in breast cancer management. We elucidated the prognostic significance of ERβ1 and -2 by immunohistochemistry using well-validated antibodies in 757 breast tumours with comprehensive follow-up. ERβ2 was the most important isoform in terms of breast cancer survival with nuclear expression associated with better OS and DFS and predicted response to endocrine therapy. Conversely, cytoplasmic ERβ2, with or without nuclear staining, was associated with poor outcome; expression of only cytoplasmic ERβ2 predicted significantly worse outcome. Next we studied ERβ2 expression/function in cell lines. As observed in breast tumours, both nuclear and cytoplasmic ERβ2 expression was seen. Using Mitotracker, ERβ2 colocalised in mitochondria and was coexpressed with Ki67. Additionally ERβ2 showed a punctate nuclear expression pattern with several large nuclear speckles observed. These did not colocalise with the nuclear proteins nucleolin, nuclear speckle antibody or coilin. Treatment of cells with the transcriptional inhibitor actinomycin D showed a significant reduction in speckle size and number over time. This was not observed with the protein synthesis inhibitor cyclohexamide. In summary nuclear and cytoplasmic ERβ2 expression differentially affects breast cancer outcome. In vitro studies suggest cytoplasmic expression is associated with metabolically active proliferating cells while nuclear ERβ2 is associated with transcription. Measuring ERβ2 expression and location in clinical breast cancer could provide a more comprehensive picture of patient outcome, complementing ERα.

P47

STAC2 expression predicts worse outcome in basal-like breast cancer

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Basal-like cancers (BP) have attracted attention as a poor prognostic class of breast cancer. However, BP appear to encompass biologically and clinically heterogeneous tumours. In order to refine BP definition, we analysed 48,000 gene transcripts in 132 invasive breast carcinomas using ANN analysis and identified three novel genes (SUPT5H, STAC2, PRL3) significantly associated with BP (cytokeratin(CK)5/6 and/or CK14 positive). Using a large invasive breast carcinoma cohort (n=2000), prepared as TMAs, we assessed these targets immunohistochemically and investigated associations with clinicopathological variables, patients' outcome and ability to refine BP classification.

Cytoplasmic STAC2 protein expression was associated with lower tumour grade ($p<0.001$) but not with stage, VI, or size. STAC2 was associated with CK14 ($p=0.025$), but not CK5/6 or BP, and a shorter breast cancer specific survival (BCSS;$p=0.042$). STAC2 positive BP tumours had a significantly shorter BCSS and disease-free survival (DFS) compared with STAC2 negative BP tumours, independent of grade, size and stage ($p<0.01$). Nuclear SUPT5H protein expression was associated with BP ($p<0.001$) but not other clinicopathological variables or patient outcome. PRL3 protein expression was not associated with BP or patient outcome.

This study confirms the biological and clinical heterogeneity of the BP and the difficulties in translating global gene expression data into routine practice using IHC. We have identified a novel subgroup of BP showing STAC2 expression that have significantly worse clinical outcome. Further studies analysing the role of STAC2 are therefore warranted.

P48

Clinical and pathological correlation of the diagnosis of asbestosis

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INTRODUCTION: Asbestos exposure leads to number of pathological conditions, including asbestosis. According to 1997 Helsinki Criteria, pathological definition requires histological evidence of diffuse interstitial fibrosis (DIF), and either 2 or more Asbestos Bodies (AB)/cm^2, or count of uncoated asbestos fibres, in range recorded for asbestosis by same laboratory.
AIMS: Determine concordance of clinical and pathological diagnosis of asbestosis.
METHODS: All autopsy reports produced at a South Wales DGH, between 1997-2007, were identified and examined. Initial reports selected for review included cases with, either history of asbestos exposure or history of interstitial fibrosis.
RESULTS: 5000 autopsies performed. 46 cases selected, as had evidence of clinical/radiological "asbestosis". 28 (61%) had histological evidence of DIF. 6 (21%) had sufficient AB's on light microscopy (LM), pathologically asbestosis. 6 (21%) had scanty AB's, only 1 called asbestosis after fibre analysis. 16 (58%) cases had no AB's; after fibre analysis, resulted in 1 Asbestosis. Overall only 8/28 (29%) cases with DIF were histologically asbestosis, majority of rest labelled UIP. 18 cases did not have histological DIF, AB's on LM or sufficient fibres for asbestosis. Most cases had subpleural fibrosis and diffuse pleural plaques, possibly source of clinical error.
CONCLUSIONS: Asbestosis rare at autopsy, clinical definition representing <1% of all autopsies performed over 10 years. Only 8 of 46 cases (17%) was pathological confirmation made. Either clinical criteria are poor or pathological criteria are too stringent. It raises issue of validity of United Kingdom Compensation Scheme.

P49

An audit of thoracic frozen sections

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INTRODUCTION: Thoracic Frozen Sections in a South Wales Trust occurs between two hospital sites; they are performed at tertiary centre but reported via Telepathology, at local DGH
AIMS: Quantify workload, notice provided, timeliness and accuracy.
METHODS: Prospective audit; all frozens over ten week period in 2007 recorded and followed up.
RESULTS: 19 cases identified; 18 booked in advanced, 4 were cancelled (22%), 14 occurred (78%), 1 not booked; 15 frozens occurred.

Notice Given Beforehand for Booked Frozens	Number of Frozen Section Cases
0 hours	1
1 hour	6
2-3 hours	1
4-7 hours	3
8-23 hours	6
24+ hours	2

Only 1 of 4 cancellations were 1+ hour before booked time, rest cancelled at booked time or after laboratory enquiries. Of 14 booked cases, 8 (57%) on time, 5 were 2 hours late (36%) and 1 (7%) re-scheduled new time after original time elapsed 14 of 15 (93%) actual frozens had "Frozen Sections" on request form, 1 did not (7%). Mean reporting time 30 minutes, range 15-60 minutes. 14 of 15 cases (93%) had diagnosis confirmed on paraffin sections. One false-negative (7%) case identified; no false-positives. Minimum 40 hours consultant time saved using Telepathology for diagnosis.
CONCLUSIONS: Telepathology for thoracic frozen sections highly accurate, saving significiant amount of Consultant time. Most not given adequate warning, have high cancellation rate and "frozen section" not always written on form. Telepathology has risk of prolonging time between theatre arrival and reporting to surgeon.

P50

Role of transbronchial fine needle aspiration in diagnosis and staging of lung cancer

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INTRODUCTION: Transbronchial Fine Needle Aspirations (TBFNAs) are performed at a hospital in South Wales, for diagnosing and staging patients with pulmonary malignancies.
METHODS: All TB-FNA's received in between 01/01/2003 and 31/12/2006 were identified, database of cases produced, generating retrospective audit.
RESULTS: 112 specimens received from 84 patients. 53 patients (63%) had positive diagnosis, only 37 (70%) were picked up by bronchial brushings/washings/biopsy alone; a further 16 cases identified by positive TBFNAs - 43% increase in yield of diagnosing lung cancers, not achieved without TBFNAs. All TBFNA cases could accurately discriminate "small cell versus non-small cell cancer", but easier to subcategorise "non-small cell" category in washings and brushings than TBFNAs.
In terms of nodal staging, 16 cases identified of node TBFNAs, where there was positive bronchial brushings or washings. 10 were from 'N1' region – 6 showed "non-small cell carcinoma", 80% deceased by the audit date (4 months – 2 years survival) and 4 "negative for malignancy", 50% were deceased by audit date (9-15 months survival).
6 cases were from 'N2' region – 3 showed "small cell carcinoma", 100% were deceased within 6 months, and 3 showed "non-small cell carcinoma", 100% were deceased within 13 months.
CONCLUSIONS: TBFNAs useful in diagnosis of lung cancers and are useful in staging patients for nodal spread at same visit as diagnostic bronchoscopy. Staging information will provide information regarding patients' prognosis, allowing decisions as to which patients would benefit from resections.

P51

Mitral valve prolapse. Is there a cardiomyopathy linked to floppy mitral valve?

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BACKGROUND: The risk of sudden death in mitral valve prolapse is very rare, however, it is still twice as in the general population which is a source of concern because of the very high prevalence of this valvular abnormality in the industrialised world.
DESIGN: We investigated cardiac changes in 25 cases who died suddenly with a prolapsed mitral valve.
RESULTS: Sex (13F: 12M) and age (average age =40, range 21-79) was equally distributed in the cohort. Fibrosis alone was present in 56% cases (n=14) and predominated in females (64%, n=9). Left ventricle hypertrophy (LVH) alone was present in 8% (n=2) only in the male population. Fibrosis and left ventricle hypertrophy was present in 28% (n=7) and the sex and age was equally distributed. The myocardium was normal in 8% (n=2). Whole hearts were received for 15 cases and the average heart weight was 412g.
CONCLUSIONS: Abnormalities of the myocardium, of which fibrosis was the most common, were present in 92% of cases with mitral valve prolapsed which suggests a possible cardiomyopathy linked to floppy mitral valve. It is also possible that the floppy valve is secondary to the cardiomyopathy.

P52

Elucidating a marker panel useful in subcategorising non-small cell lung carcinoma

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One third of small biopsy samples from non-small cell carcinomas show insufficient features to allow confident subtyping and this may hamper treatment selection. Does immunohistochemistry aid subtyping in such undifferentiated cases?

50 bronchial biopsy cases diagnosed as 'Non-small cell carcinoma, not otherwise specified' which had definitive subtyping on resection were reviewed. These were stained for AB/PAS, TTF1, S100A7, p63, cytokeratin 5/6 and HMWCKs. Any combination of intracytoplasmic AB and PAS positivity was regarded as a positive mucin stain. Immuno-scoring was semi-quantitative, assessing distribution (0, 1-10% +, 11-50% ++, 51-100% +++) and intensity (light +, moderate ++, strong +++). The score distribution for each antibody allowed overall grading into low and high level staining. Positive (PPV) and Negative (NPV) Predictive Values, Sensitivity and Specificity were calculated for individual markers and combinations of markers to predict tumour histotype.

44 cases had sufficient pre-operative biopsy material for study. Of these, the surgical resection diagnosis was as follows: 23 squamous; 10 adenocarcinomas; 8 large cell; 2 adenosquamous and one combined large cell neuroendocrine-adenocarcinoma. TTF1 and mucin positivity predicted adenocarcinoma with 69%sensitivity, 97% specificity, 90% PPV & 88% NPV. P63 alone was the best positive predictive marker of squamous histology, whilst the combination of p63 with AB/PAS score offered the best sensitivity (78%) and specificity (92%) for a 'non-squamous' histotype.

In conclusion, the combination of AB/PAS, p63 and TTF1, scored at the appropriate level, allows accurate prediction of the resected tumour histotype in 82% of cases.

P53

Dendriform pulmonary ossification associated with lymphocytic thyroiditis in a young black African woman

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A 45yr old Nigerian woman had been managed for gunshot injury sustained to the left forearm and was nearing discharge when she suddenly developed respiratory distress and died. The injury had been extensive and necessitated reverse saphenous vein-ulnar artery graft and external fixation of communited/segmental left elbow fracture/dislocation, awaiting flap surgical graft skin repair.

At autopsy we observed extensive bilateral pulmonary subpleural and parenchymal calcific lesions, especially involving the lower and middle lobes. These tiny worm-like calcific lesions dropped out of tiny spaces as the fingers rubbed the cut surfaces of the lungs. Clots in the pulmonary vessels were not completely accepted to represent emboli. Other organs showed no significant abnormalities. Histology surprisingly revealed lymphocytic thyroiditis additional to confirming dendriform pulmonary ossification-DPO and background focal interstitial pulmonary fibrosis.

Post mortem radiography of both lungs showed extensive reticular opacities. On review, the chest radiograph at entry had shown reticular shadows, which could neither be explained by the attending clinicians nor the radiologists and had persisted despite antibiotic therapy. Serum calcium levels were normal.

DPO has not been previously reported from this environment and its association with lymphocytic thyroiditis has also not been reported in the English literature. The occurrence of DPO in a relatively young female with asymptomatic thyroiditis should be noted. DPO should be considered as a differential diagnosis when reticular shadows on chest Xray cannot be easily resolved as to specific aetiology and are persisting after drug therapy for possible infections have been completed.

P54

Cardiac amyloidosis associated with ventricular rupture: a case report and literature review

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Ventricular rupture is a well recognised complication of myocardial infarction and a cause of sudden cardiac death. Senile systemic amyloidosis (SSA) affects 25% of people over the age of 80. It tends to diffusely affect the heart and may manifest itself as conduction defects, restrictive cardiomyopathy and progressive heart failure. It preferentially involves the myocardial interstitium and tends to spare the vascular compartment. This contrasts with primary amyloidosis (AL) which typically affects the vessels and is associated with a worse prognosis.

We present two unusual cases of female nonagenarians who died of ventricular rupture associated with acute myocardial infarction and significant vascular and interstitial amyloid deposition. In the first case, significant coronary artery narrowing by atheroma may explain the development of myocardial infarction. In the second case, however, there was no evidence of coronary or epicardial vessel obstruction; amyloid was largely confined to the intramural coronary arteries. Such a regional distribution of myocardial infarction with patent epicardial vessels has not previously been described in the setting of amyloidosis. It is presumed that coronary artery spasm, to which these cases are prone, is a possible explanation for the acute myocardial infarction.

In summary, we propose that the combination of infarction and significant amyloid deposition made both cases more prone to ventricular rupture.

P55

Pleural angiosarcomas: pitfalls for the pathologist

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Pleural angiosarcomas are rare tumours which may clinically, radiologically, morphologically and immunophenotypically mimic malignant mesothelioma. Pleural angiosarcomas represent a pitfall to the unwary pathologist. There exist medicolegal implications with respect to personal injury asbestos claims.
We present three cases of pleural epithelioid haemangioendothelioma which clinically presented as mesothelioma. All three subjects were male aged 48, 55 and 73.

Clinically, each case presented with non-specific respiratory symptoms and imaging revealed a diffuse pleural tumour. Contrary to clinical expectation the pathology revealed an epithelioid tumour with neovascular lumina and hyaline stroma. Immunohistochemistry revealed positivity for vascular markers CD31 and CD34 confirming the endothelial nature of the neoplasm.

Diagnostic pitfalls exist as the unwary pathologist may not appreciate that pleural angiosarcomas may be epithelioid, biphasic or sarcomatoid, closely mimicking mesothelioma. Moreover, as seen in one of three cases the tumour may express cytokeratin. Additionally, the “typical” mesothelial markers D2 40, thrombomodulin and WT1 were positive. An awareness that all three mesothelial markers may be expressed in endothelium should prevent misdiagnosis.

Pleural epithelioid vascular sarcomas are an important pitfall to the unwary pathologist. A pleural epithelioid tumour lacking calretinin and CK5/6 expression, or lacking broad spectrum cytokeratin expression should prompt use of a panel of vascular markers. An awareness that some mesothelial markers are excellent endothelial markers also prevents misdiagnosis.

P56

Is there potential to reduce pulmonary embolism mortality through optimising use of caval filters?

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BACKGROUND: Pulmonary embolism (PE) is said to cause 10% of deaths of hospital patients. Caval filters are believed to be effective in preventing fatal PE yet indications for use are limited. We sought to address this inconsistency: are we missing the opportunity to use caval filters to prevent death from PE?
METHOD: All death notification and autopsy reports at this hospital for 2007 were reviewed to identify deaths associated with PE. Case notes were then examined for risk factors including indications for caval filter placement. Autopsy records for community deaths were also reviewed.
RESULTS: There were 95732 inpatient admissions and 1309 (1•4%) inpatient deaths during 2007. Of these 342 underwent autopsy. PE contributed to death in 9 of 342 (2.6%) autopsy proven cases. PE was given as a cause of death on the certificate of a further 6 patients who did not undergo autopsy. Thus PE was documented as a cause of 15/1309 (1•1%) deaths representing 0•02% of all inpatient episodes. PE was documented as the direct cause of death for 13 inpatients. PE was documented as a contributory cause of death for 2 inpatients.
CONCLUSIONS: Our data suggest that the death rate from PE is substantially lower than the widely accepted figure, a figure that informs NICE policy. Very few deaths could be prevented by use of caval filters according to accepted indications. A more liberal policy of filter use based on risk factors might have limited benefit at a substantial cost.

P57

An audit on diagnostic value of cytology in malignant mesothelioma

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BACKGROUND: The cytological diagnosis of malignant mesothelioma (MM) is considered to be of limited value in some of the literature, with sensitivity varying from 0 to 90%. Therefore, we assessed the accuracy of cytology in the diagnosis of MM, in our hospital, by comparing it with the corresponding histology.
METHODS: Cytology and histology positive cases of MM were retrieved retrospectively from 2001 to 2008. Cytology-histology mismatch cases were identified, with histology being the gold standard. Mismatch cases were reviewed to ascertain the reason for mismatch. In cytology cases of MM without corresponding histology, radiological and clinical follow up data were considered as gold standard.
RESULTS: There were 15 cases with cytology diagnosis of MM, out of these 9 cases were histology positive for MM (9/15). There were two cases with cytology diagnosis of MM which were negative on initial histology specimen but were positive on subsequent biopsy. There were 12 cases of cytology-histology mismatch, out of which 4 cases showed features of MM on review. There were 2 mismatch cases of sarcomatoid/desmoplastic MM which do not exfoliate readily and are therefore difficult to diagnose on cytology. The overall sensitivity of cytology in diagnosis of MM was 45% and the positive predictive value was 90%. The maximum attainable sensitivity by reviewing the cases was 72% and positive predictive value was 100%.
CONCLUSION: Cytology along with ancillary tests appears to play an important role in the diagnosis of MM. Clinical, radiological and histological correlation aids the diagnosis.

P58

Two contrasting cases of 'idiopathic giant cell aortitis'

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We present two contrasting cases of idiopathic giant cell aortitis. One case concerns an otherwise fit and healthy 22 year old girl, and the other is of a fit healthy 68 year old lady.

Both patients presented clinically with symptoms suggestive of cardiac failure. Investigations confirmed the presence of aortic root and aortic arch dilatation, with both patients subsequently undergoing aortic valve and arch replacement.

Histological examination of the aortic valves and ascending aorta in both cases showed evidence of regurgitation and "Giant cell aortitis" respectively. Further investigations have failed in both cases to determine the presence of a unifying diagnosis.
In particular, neither case has evidence to suggest a systemic vasculitis. With this in mind, both cases have subsequently been classified as " Giant cell aortitis" of idiopathic type

This classification is reasonably uncommon. "Giant cell aortitis" within these two age categories present us with different differential diagnoses to consider prior to the assumption that the disease is idiopathic.
We will discuss all the major unifying diagnoses in detail such asTakayasu's arteritis, Rheumatoid artheritis, temporal arteritis and syphilitic aortitis, with particular reference to their clinical presentations and investigations to aid with determing a unifying diagnosis.

P59

Diagnosing lymph node metastasis - how easy is it?

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Neuroendocrine tumours of the lung amount to 20% of all lung cancers. They can be broadly divided in 4 subgroups: typical carcinoid tumour, atypical carcinoid tumour, large-cell neuroendocrine carcinoma and small-cell lung carcinoma. The small-cell lung cancer is the most common, whilst the large-cell variant is rare. However, both these tumour progress rapidly and are often metastatic by the time of presentation.

We discuss the case of a 74-year-old male, who presented with a mass in the left groin. Macroscopically, this was a lymph-node. Microscopy showed that part of this node that had been completely replaced by tumour with the morphological appearances of a carcinoma. The tumour was immunopositive for the neuroendocrine markers Chromogranin, Synaptophysin, CD68 and TTF-1, but was immunonegative for Cytokeratin and Thyroglobulin. These features strongly suggested a tumour of neuroendocrine origin.

Subsequent, PET scan analysis revealed a focal lesion in the lung with very low uptake. Furthermore, there was no mediastinal, thoracic or abdominal foci. The radiological appearances of this lung lesion were characteristic for a neuroendocrine-type of carcinoma, thereby supporting our diagnosis.

Large cell neuroendocrine carcinomas well known to behave in a odd pattern of metastasis and thus should never be ruled out, especially when-as in this case, presenting at sites anatomically distant from the primary.

P60

Primary cardiac low grade sarcomas mimicking myxomas. Pitfall in diagnosis

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We present two cases of primary cardiac sarcomas which were referred with the diagnosis of myxoma. The first case was an aortic tumour in a 47 year old male and the second case was from a left atrial mass in a 62 year old female. The tumours had a gelatinous appearance and on histology showed large areas of bland spindle/stellate cells in a myxoid stroma, looking superficially like myxoma. However, more cellular foci showing nuclear pleomorphism and scattered atypical mitotic figures were present indicating these were sarcomas. Extensive sampling is needed to detect these tumours and focal cellular areas need careful scrutiny in order not to miss this important diagnosis.

Cardiac tumours are uncommon and cardiac sarcomas rarer still. Their macroscopic appearances can mimic myxoma. It is important to identify these tumours as their prognosis is extremely poor.

P61

Evaluation of touch preparation cytology during frozen-section diagnosis of pulmonary lesions

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Intraoperative frozen section (FS) examination in thoracic surgery is a rather reliable method for diagnosis and staging of pulmonary lesions and provides a valuable guide in directing the extent of the ongoing surgical procedure. However, the contribution of touch preparation cytology (TPC) to FS diagnosis is still unclear. Aim: to assess the utility of routinely performed TPC during FS diagnoses of pulmonary lesions. Method: In this study, FS and TPC of all patients who underwent FS diagnoses of pulmonary lesions in a 5-year period were reviewed by two pathologists. Results: A total of 149 consecutive patients underwent intraoperative FS procedure; of those 104 cases had TPC available for review. TPC was diagnostic or contributory to FS diagnosis in 94 (90%) cases, and non-contributory in 10 cases. Of the non-contributory TPC, 9 cases were inadequate due to low cellularity while 1 case (mucinous bronchoalveolar carcinoma) was non-diagnostic on TPC. There was no false positive result. In all cases with granulomata with or without necrosis (10 cases), TPC was diagnostic. In 3 cases, TPC was the only diagnostic tool since FS was not completed. In conclusion, TPC showed high sensitivity and specificity rates and was contributory to FS diagnosis of pulmonary lesions. TPC provides a fast less expensive method of diagnosis, utilize minimal amount of tissue and can save processing of fresh frozen tissues in certain situations such as tuberculous lesions.

P62

Is epithelial to mesenchymal transition occuring in buds of microinvasion from vulval intraepithelial neoplasia?

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PURPOSE: Several mechanisms have been implicated in mediating initial local invasion in invasive carcinoma. One of the proposed mechanisms is via a constellation of changes referred to as epithelial to mesenchymal transition (EMT), but this has rarely been definitively demonstrated in real clinical samples. We conducted a pilot study to establish whether EMT occurs at the multiple buds of microinvasion which are seen to develop from high grade vulval intraepithelial neoplasia (HG-VIN), which are unlikely to be explained by clonal evolution alone.
PATIENTS AND METHODS: Four cases of HG-VIN with multiple foci of microinvasion and one case of invasive squamous cell carcinoma of the vulva were examined by quantitative fluorescence microscopy using the HistoRx AQUA image analysis system. Sections were stained for a panel of EMT markers (E-cadherin, CD24, TWIST, SNAIL, Ep-CAM, and Claudin 7). Each image was reviewed for differences in expression between the normal tissue, HG-VIN, areas of microinvasion, and frankly invasive carcinoma. The quantitative intensity of immunofluorescence staining per unit area of invasion was also analysed using AQUA-Analysis software.
RESULTS: No significant differences between the areas suspicious for EMT and background epithelium were demonstrated either visually or on AQUA scoring.
CONCLUSION: These results suggest that EMT does not occur in microinvasive foci in the setting of HG-VIN and local invasion is mediated by other mechanisms.

P63

The expression of P85-alpha phosphoinositide-3-kinase (PI3K) in cervical neoplasia

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INTRODUCTION: PI3K has been implicated in cervical carcinoma and some reports suggest a relationship with HPV. Mutations described in its 2 subunits can lead to constitutive activation of PI3K, which drives cell proliferation, survival, protein synthesis and cell motility.
AIM: To explore the expression pattern of PI3K in cervical neoplasia, its role in pathogenesis and determine its utility as a diagnostic marker.
MATERIALS AND METHODS: A total of 104 cases were selected to represent normal cervix (17), CIN1 (14), CIN2 (17), CIN3 (20), squamous cell carcinoma (16), CGIN (10) and adenocarcinoma (10). Immunohistochemistry was performed using a monoclonal antibody against the p85α subunit of PI3K. Staining intensity was assessed using a visual scoring scale (0= undetectable, 1+= weak, 2+= moderate, 3+= strong and 4+= very strong). Percentage area of immunoreactivity was quantified in squamous lesions using image analysis software.
RESULTS: Cytoplasmic expression of p85α in normal squamous epithelium was minimal (1+) and confined to the basal layer. The intensity of staining and area of epithelium stained increased with worsening histological grade of squamous neoplasia with SCCs showing the highest p85α staining ($p<0.0001$). Normal endocervical cells showed moderate staining (2+) however adenocarcinomas stained more intensely (score 3-4+) than both CGIN and benign endocervical cells.
CONCLUSIONS: Increased expression of p85α occurs in all grades of cervical squamous and glandular neoplasia and may play a role in the pathogenesis of these lesions. PI3K (p85α) is a potential diagnostic marker that may help in the diagnosis of high grade CIN and CGIN.

P64

Mapping the functional domains of anillin responsible for sub-cellular localisation

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The localisation of anillin alters through the cell cycle being nuclear in interphase and redistributing to the cleavage furrow after the dissolution of the nuclear membrane at the onset of mitosis. We have set out to discern the nuclear functions of anillin and ask how and why cells choose to have such a large pool of anillin. We have engineered a range of N and C terminal deletion mutants of human anillin and created by site directed mutagenesis mutants of all of the putative nuclear localisation sequences (NLS). We find that the first 120 amino acids at the N terminus of anillin is the minimum region essential for its nuclear localisation. This region contains two of anillin's five putative NLS. Following individual mutagenesis of all five NLS we have determined that the only NLS essential for nuclear localisation is located between amino acids 64 to 72. Deletion of the C-terminal 143 amino acids (including the predicted septin-binding domain) alters the distribution of cytoplasmic anillin causing the formation of filament-like structures. Conversely, when the C-terminal half of anillin which contains the septin binding domain (amino acids 452-1125) is expressed as a truncated form, septin 9 localisation is severely disrupted with loss of septin filament structures. We have thus demonstrated that the individual domains of anillin are essential for its sub-cellular localisation and have identified its only functional NLS.

P65

Chromogenic dual ISH – a novel method for HER-2 assessment

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Chromogenic Dual ISH – a novel method for HER-2 Assessment?
In the last decade, bright field in situ hybridisation (ISH) tests have been successfully applied in clinical practice for the assessment of HER2 status in breast cancer cases. One limitation of this method is the need for separate chromosome 17 (CHR17) correction in a subset of cases where the increased number of HER2 copies may be the result of CHR17 polysomy. The recent development of automated chromogenic dual ISH, allows detection of HER2 and CHR17 on the same slide. Our aim was to compare chromogenic dual ISH with the separate silver-ISH (SISH) and CHR17-correction methods currently used in our lab.
Approximately 50 cases of SISH-evaluated breast carcinoma in which CHR17 correction had been performed were evaluated by chromogenic dual ISH. These included unselected consecutive cases and selected cases of highly-amplified and non-amplified HER2.
All non-amplified (negative) and highly-amplified (positive) cases were correctly identified by chromogenic dual ISH. Interpretation of equivocal cases and those with very low level of amplification was also facilitated.
The results of our study indicate a high consensus between CHR17-corrected SISH and chromogenic dual ISH.
In clinical practice HER2 status can conveniently be assessed in the context of the histology using a fully automated bright field ISH method. Our data suggests that, for equivocal cases, using chromogenic dual ISH to evaluate HER2 and CHR17 on the same slide makes such assessment easier and quicker for the pathologist.

P66

Immunohistochemistry markers in drug development - manual versus automated scoring

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A suite of exploratory IHC biomarkers has been developed to aid decision-making in early oncology drug development. The biomarkers are related to the hallmark areas of cancer e.g. apoptosis, proliferation, vascular modulation and invasion. The biomarkers are utilised in clinical trials to assist evaluating biologically effective doses, give insight to proof of mechanism and proof of principle. Also these biomarkers are being deployed across drug projects to understand the strengths and weaknesses of the suite. Antibodies for IHC have undergone a stringent validation process. Formalin-fixed, paraffin embedded sections were incubated with primary antibody and detected with an HRP-conjugated secondary antibody, visualised with DAB, and counterstained with haematoxylin. The slides were first scored by eye by a histopathologist according to standard templates and then by a scientist using semi-automated image analysis (Chromavision ACIS II system). Analysis of the histopathologist-scored slides demonstrated associations between markers in similar biological effect areas. Comparisons of manual and automated scores for certain nuclear markers showed acceptable profiles using Bland-Altman plots with no overall bias (E.g. Spearman's Rank Correlation Coefficient for Ki67=0.75). However, there were large differences between some scores, particularly vascular markers for micro-vessel density. This is likely due to the ability of the histopathologist to independently determine vessel formation. In conclusion semi automated image analysis techniques offer the opportunity to increase the throughput and decrease the inter-user variability of IHC scoring, however, at present the technique is only suitable for certain selected biomarkers.

P67

Digital quantification of immunohistochemical staining for p53 and the spindle assembly checkpoint protein, BUBR1

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The Spindle Assembly Checkpoint (SAC) is the regulatory mechanism through which, the chemotherapeutic agent, Paclitaxel, exerts its cytotoxic effects, modulated in part by the SAC protein BUBR1 (Greene LM et al, 2008). BUBR1 transcription is largely controlled by p53 (Oikawa et al. 2005). Interestingly, Paclitaxel confers a survival advantage in patients whose tumours show p53 accumulation (Kupryjanczyk J. et al 2008).

The purpose of this study was to investigate the IHC expression of p53, a nuclear stain and BUBR1, predominantly a cytoplasmic stain, in a cohort of 80 epithelial ovarian cancers, using a tissue microarray platform. Staining was quantified manually and digitally, the latter using an Aperio image analysis platform.
RESULTS: p53 and BUBR1 IHC staining patterns were assigned manual scores from 0-6/6, with scores of 1, 2 and 3, assigned for intensity and distribution of staining. Automated scores were generated using trained nuclear and colour deconvolution algorithms. Automated and manual IHC scores for both antibodies showed significant correlation ($p<0.0001$). Two patterns of BUBR1 staining were observed: diffuse cytoplasmic staining and punctuate nuclear staining, which may reflect the presence of soluble BUBR1 and insoluble, kinetochore bound BUBR1. Nuclear BUBR1 positivity was generally seen in tumours without cytoplasmic staining. P53 accumulation did not correlate with either cytoplasmic ($p=0.4836$) or nuclear ($p=0.8362$) BUBR1 staining.
DISCUSSION: Digital image analysis provides accurate and reproducible IHC quantification of both nuclear and cytoplasmic staining. No correlation was identified between the IHC expression of BUBR1 and its transcription factor p53.

P68

Osteoclast formation and osteolysis in pigmented villonodular synovitis

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Pigmented villonodular synovitis (PVNS) is a diffuse villous or nodular tumour-like synovial lesion that affects joints and can result in periarticular osteolysis with formation of multiple cysts in bone in about one third of cases. To determine the pathogenesis of PVNS, we analysed expression of macrophage and osteoclast markers and mechanisms of osteoclast formation and resorption in 10 cases of PVNS. All giant cells and a few scattered mononuclear cells in these lesions expressed osteoclast-related markers including vitronectin receptor. CD14 and HLA-DR were not expressed by giant cells but there were numerous CD14+/CD68+/HLA-DR+ mononuclear cells. Giant cells isolated directly from PVNS were capable of lacunar resorption. Mononuclear cells differentiated into osteoclasts in the presence of receptor activator for nuclear factor κ B ligand (RANKL) and macrophage-colony stimulating factor (M-CSF) as well as RANKL alone. CD14+ mononuclear cells differentiated into tartrate resistant acid phosphatase (TRAP) positive osteoclastic giant cells under these conditions. Our results indicate that giant cells in PVNS are osteoclast-like and that the PVNS associated macrophages, in the presence of RANKL, are capable of osteoclast formation and lacunar resorption. We are currently investigating the effects of osteoclast inhibitors, such as bisphosphonates, on giant cells and CD14+ve cells isolated directly from PVNS tumours.

P69

Skull mass as the first manifestation of recurrent multiple myeloma in a renal transplant patient. A case report

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Case report: Although there have been a few reports of recurrence of Multiple Myeloma(MM) in the transplanted kidney, recurrence of MM presenting as an isolated lesion in the brain has been rarely reported. Here we present a 60 year-old female who underwent a kidney transplantation following a rise in BUN and creatinine having shown advanced Tubulo-interstitial nephritis in her native kidney microscopic biopsy examination. Two years following her renal transplantation, she presented with a brain mass which was regarded as a possible Meningioma.

A biopsy of her transplanted kidney was performed due to her constantly raised BUN/ Cr which revealed, Myeloma cast nephropathy.
We describe an unusual presentation of recurrent Multiple Myeloma, simultaneously as a brain lesion mimicking meningioma and also in the transplanted kidney.
Key words: Multiple Myeloma, Brain Mass, Renal Transplantation.

P70

Is there still a need for marker amplification?

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Techniques that amplify immunohistochemically deposited marker have largely been replaced by antigen retrieval and reporter amplification since these are more easily incorporated into high throughput, automated procedures. There remain a number of instances where marker amplification is still beneficial e.g. where positivity is doubtful, where the power of all available amplification procedures is still inadequate to reveal exceptionally low quantities of target molecules, or for ease of observation.
The amplification of immunohistochemically deposited metal-complexed polyDAB with physical developers was systematically investigated and refined in a model system and applied to histopathological control tissue, namely Stage 4 Hodgkin's lymphoma, tonsil, and brain from Alzheimer's disease. These were immunostained for (a) the Epstein -Barr virus protein, LMP-1 (low concentration antigen), (b) the cytotoxic T-cell enzyme, granzyme B (low concentration antigen), and (c) α-synuclein (rare event) respectively.
LMP-1 and granzyme B were barely visible despite antigen retrieval and reporter amplification, but were clearly seen following additional marker amplification as were additional sites that were below the visible detection limit of the conventional system. In brain tissue, α-synuclein positive cells were visible before marker amplification, but marker amplification made these positive sites much more easily visible and facilitated rapid evaluation of large areas of tissue at low magnification.
In the absence of amplification, some low concentration sites could be easily overlooked in a busy diagnostic setting. Furthermore, the detection of additional positive sites might have implications for both diagnosis and subsequent treatment.

P71

Developing a cellular pathology service for a hospital ship in Africa – lessons learned

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Much surgery is performed in developing countries without the support of cellular pathology. A major problem is provision of cytopathologists and histopathologists for laboratories in these areas. The cost of equipment in histopathology and cytology is low in comparison to other costs of equipment required for a hospital, but consumables are frequently expensive to transport to remote regions.

I have gained experience in developing histopathology and cytopathology services for a hospital ship run by the non-governmental organisation Mercy Ships. This provides healthcare to countries particularly along the West Africa coast. There is a laboratory on board and if appropriately trained staff are available histopathological slides are prepared on board and an internet-based telepathology system used for diagnosis. When technical staff in cellular pathology are not available, fixed tissue may be sent back for processing to a country where a diagnostic service is available. I provide an on-site diagnostic "one-stop" cytology service when required at the medical screenings that occur when the ship first visits a port.

From my experience in this unique situation I have learned valuable lessons that can be shared on how cellular pathology services may be initiated and supported in a developing country. In particular, when developing a cellular pathology service in such an environment, cytopathology can provide a low-cost and reliable diagnostic method that requires the minimum of reagents and can be of invaluable help to the management of patients presenting with a variety of neoplastic or non-neoplastic conditions.

P72

A novel nuclear detection algorithm for the automatic analysis of immunohistochemistry staining

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Computer based analysis of digital histopathology images can potentially improve the accuracy and efficiency of interpreting immunohistochemistry (IHC) staining by eliminating subjectivity and intra-observer variability. We developed a novel method that uses edge and gradient information from the image to detect the nuclei locations. A nuclear mask was created and applied to the image to compute nuclear staining. An inverse nuclear mask was applied to compute cytoplasmic staining. Our method was compared to four nuclear detection algorithms: GraphCuts, Connected Components, Watershed, and Aperio. Two datasets were used: MIB-1 expression in neuroendocrine carcinoma of the gastrointestinal tract, and ERβ expression in breast cancer. Nuclear location/staining detected by the algorithms were compared with human scores. As shown in the Table our in-house nuclear detection method was the most superior at locating the nuclei in both ERβ and MIB-1 stained images.

	ERβ		MIB1	
Algorithm	Sensitivity	Accuracy	Sensitivity	Accuracy
In house	0.72	0.39	0.85	0.67
Aperio	0.70	0.40	0.80	0.64
GraphCuts	0.66	0.30	0.66	0.48
Watershed	0.45	0.24	0.45	0.35
CC	0.45	0.24	0.45	0.35

CC = connected components

Preliminary results show that our method is as least as good as Aperio when correlated with the scores generated by humans. Further modifications are ongoing to improve this and to better distinguish normal and tumour cells and stroma.

P73

Towards a national historical archive of pathology

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Currently pathology archives and collections are unavailable for review. We are digitising historical collections of previous Professors of Pathology and reference collections inaccessible to the profession and public. Our aim is to make these freely available electronically. The website will be launched at this meeting. Selected material from personal collections of Professors Mathew Stewart, 1918 – 1951, R Willis, 1950 – 1955 and Soft Tissue Sarcoma collections will be represented also accompanying historical information. These collections are the basis of several reference books including "Pathology of Tumours" by Professor Willis, first published 1948.

The majority of these collections are based on case referrals and slides with accompanying data including case histories and original diagnosis. Some cases have been reclassified but original classifications are included where available.

Parts of the collection have less data but will be included due to their rarity and educational/historic value. The project includes images of related historical documents, watercolour illustrations of specimens and background information on the main contributors including personal diaries. We are creating a library of between five to ten thousand digitised images of slides and matched data.

The library is a valuable reference collection of rare and disappearing conditions, a source of valuable historic data and a unique insight into pathology from the first half of the 20th century. We hope with collaborations to include other famous pathologists and their work. This project applies modern technology to a precious resource, increases accessibility of the material and makes it available for future generations.

P74

Aeroplanes and doughnuts: a model approach to small group and practical skills teaching

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Doctors starting specialist training are required to teach their peers and participate in undergraduate teaching. These generic skills are not emphasised in undergraduate curriculae. This session addresses this by providing an approach to small group and practical skills teaching. This new session was delivered to 18 year one Speciality Trainee doctors in Histopathology. The session was two hours long with an hours interactive demonstration of small group teaching methods and an hour on practical skills teaching.

We aimed to demonstrate a variety of small group techniques which can be used to promote interaction and effective teaching.The practical skills teaching used novel examples, including doughnuts cut up as wide local excisions, illustrating a structured and cognitivley cogent method of teaching practical skills using the Advanced Trauma Life Support model.

We evaluated the session to ameliorate future teaching. Fifteen out of eighteen doctors responded. Reassuringly, 86% of participants felt that the session would help with their future teaching. For the small group teaching, 60% thought that the teaching was good and 40% excellent. For the practical skills teaching 80% rated it as good, 13%, excellent and 7% average. 33% stated the best aspect was the practical skills teaching,13% the learning special techniques, and 13% small group methods. The worst aspects were, adult learning methods 13%, length of the session 13% and practical skills 33%.

Tranee pathologists need to be competent teachers. Establishing a basic understanding of small group and practical skills methods gives the confidence to teach well.

P75

A training feedback questionnaire - democracy in action? or the lunatics are taking over the asylum?!

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THE IDEA: Medical education and training adults is no longer a one way street where "teacher knows best". Trainees are often encouraged to participate in training delivery. In the Wales Deanery there are 17 histopathology training posts with rotation to 5 hospitals across three NHS Trusts and specialist training in paediatric pathology, neuropathology and forensic pathology.

In 2007 a "user satisfaction survey" was developed to identify and address any problem areas of the training scheme and provide positive feedback to trainers about well received aspects of training. The questionnaire was anonymous and covered surgical, cyto- and autopsy pathology. Questions covered areas such as "the number of cases you report", "one to one teaching", "constructive and appropriate feedback" and "how involved you feel in the department".

THE RESULTS: Trainees were surveyed in April 2007 and April 2008. There were improved scores in 2008 especially in paediatric pathology. Examples of how the questionnaire had an impact include a change in practice for cytology teaching in a DGH which led to improved scores for cytology teaching and the number of cases reported. In DGHs improved MDT participation also improved the score for "how involved you feel".

The questionnaire allowed trainees to participate in the delivery of training and provided positive feedback for trainers. The results were presented to the department and the Wales Deanery. We intend to repeat the questionnaire annually, to identify what changes are being made to improve training and to encourage trainee participation in shaping their training.

P76

Audit on monitoring of BCR-ABL positive CML patients receiving imatinib

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BACKGROUND: Balanced reciprocal translocation between chromosome 9 and 22 resulting in BCR-ABL thyrosine kinase, has a central role in the pathogenesis of CML. This protein is inhibited by imatinib and assessing response is crucial in the treatment of CML. This study aims to audit the methods and frequency of this assessment in a DGH Haematological department and compare it to the current practice recommended by British Committee for Standards in Haematology

METHOD: Data was collected using a performa on all newly diagnosed CML patients (2 year period) attending the haematology clinic.

RESULTS: All patients were monitored for haematological, cytogenetic and molecular response. This was assessed using haematological parameters, philadelphia chromosome positivity in bonemarrow aspirate/ trephine biopsy and BCR-ABL transcript levels in peripheral blood respectively. Complete haematological response was achieved in 28 days(mean) and assessed during every clinic visit. Complete cytogenetic response was achieved in 8 months(mean) and assessed every 6 months(mode). Major molecular response was achieved in 1 patient and took 10 months. The frequency of monitoring was 3 monthly in most cases.

CONCLUSIONS: BCSH recommendations were followed with respect to methods of monitoring and molecular response monitoring. However cytogenetic response monitoring was done less frequently than recommended. It was felt that a chart detailing the various assessments with the time-line and space for results be include in the patients notes to achieve the best follow-up. A re-audit after two years will be done to assess the impact of this exercise.

P77

Audit of indications for performing gastro-intestinal biopsies

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BACKGROUND: Endoscopic gastro-intestinal (GI) biopsies comprise a large proportion of the workload in most diagnostic histopathology departments in the U.K. and represent a significant cost to the National Health Service (N.H.S.).
AIM: To investigate the adherence to guidelines for performing GI biopsies, and assess variation according to the specialty/ grade of the endoscopist.
METHODS: A list of indications and non-indications for performing GI biopsies by site was drawn up, using the RCPath publication 'Histopathology and cytopathology of limited or no clinical value (2nd edition)', in consultation with a Trust consultant gastro-intestinal physician. The indications for performing each GI biopsy received by a central London teaching hospital during June 2008 were retrospectively analysed against these standards.
RESULTS: 403 biopsy procedures were performed in 281 patients (129 M, 152 F; range 18 - 92 yrs). 26% (105/403) of GI biopsies taken in total were deemed to have been non-indicated.

ENDOSCOPIST	% BIOPISES TAKEN DEEMED TO BE NON-INDICATED
Junior doctor	28.1
Consultant physician	26.7
Consultant surgeon	15.8

CONCLUSION: A quarter of GI biopsies taken for histopathology were non-indicated, representing a siginificant unwarranted cost burden on the N.H.S.

P78

A comparative analysis of the personality types of histopathologists versus midwives in Wales

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INTRODUCTION: Myers-Briggs Type Indicator questionnaires are used in workplaces, to assess people's 'personality type'. Sixteen types are identified in the general population, but it is hypothesised that people are 'drawn' to occupations due to their personality types.
AIMS AND OBJECTIVES: Do histopathology trainees in Wales disproportionately belong to certain personality types? Midwives were also recruited into study, as envisaged that this profession is diametrically opposite in the nature of its work.
METHODS: Histopathology trainees in Wales and midwives within the same NHS trust filled in questionnaire taken from a Meyers-Briggs website.
RESULTS: 16 replies received from histopathology trainees and 15 from qualified midwives:

Personality Type	Histo pathologists	Midwives
INTJ	7	2
INTP	0	0
INFJ	2	1
INFP	0	0
ISTJ	1	1
ISTP	0	0
ISFJ	1	0
ISFP	0	0

Personality Type	Histo pathologists	Midwives
ESTJ	2	2
ESTP	0	2
ESFJ	1	1
ESFP	0	0
ENTJ	1	3
ENTP	0	2
ENFJ	1	1
ENFP	1	0

Nine 'types' were identified in histopathologists, 44% belonging into one type, INTJ, the 'Rational Masterplanner', the highly scientific type - important qualities in histopathologists. Nine 'types' were also noted in midwives, but there was no dominant type. 65% of histopathologists were in 'introverted' groups, compared to 27% of midwives (Chi-Squared Test, p=0.03).
CONCLUSIONS: Despite limited sample number, exercise appears to support notion that histopathologists are more 'introverted' than midwives, and disproportionately made up of INTJ personality type, a type only found in 1% of general population.

P79

Adequacy of lymph node sampling in resection specimens for colorectal cancer – audit against the Royal College of Pathologists recommendations

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Following the publication of evidence that Dukes B colorectal carcinomas were being understaged due to inadequate lymph node sampling, the Royal College of Pathologists (RCP) recommended that a mean of 12 lymph nodes should be examined (second edition of the dataset).
The aim of this audit was to address whether reporting of colorectal carcinoma complies with the RCP Guidelines (2007).
METHOD: 50 consecutive colorectal resection specimen reports were audited recording: length and site of resection, accuracy of recording lymph node blocking, the number of lymph nodes examined and identification and reporting of the apical node.
RESULTS: the mean number of nodes examined was 15 (median 14; range 1-39). The length of the specimen was stated in 68% of cases. The number of nodes was related to the length of the specimen (r=0.21). Greater numbers of nodes were found in more proximal resection specimens. The mean number of lymph node blocks was 7.8 (range 1-19) and the number of nodes per block was recorded in 86% of cases. The apical node was blocked separately in 58% and reported in 84% of cases.
CONCLUSION: the mean number of nodes retrieved was in line with RCP recommendations but in 17 of 50 cases less than 12 lymph nodes were examined. There was no apical node comment in 16% of cases.

P80

Audit of reporting time of urgent gynae cytology samples

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Requesting gynae-cytology as urgent indicates a high clinical need and a necessity to monitor turn-around time. National standards do not exist but historically a 5 day turnaround has been considered acceptable. This baseline audit evaluated the turn-around time (TAT) for such samples and identified causes of delay in reporting.

Data was prospectively collected over one month. All urgent cases were tracked with a form recording times of receipt, booking, processing, primary screening, re-screening, checking, consultant referral, and authorising; as deemed appropriate for the case. Data was collated and analysed in Excel. Of 5587 samples received, 276 (4.9%) were requested as urgent. Overall, 31 cases were reported in over 5 days (11.23%). This included 14 negatives, 6 borderlines, 9 mild, 1 moderate and 2 severe dyskaryosis. Taking weekends into consideration, 4 cases were reported in over 5 days (1.4%). Of these, 1 was affected by reprocessing; 1 delayed at transit to checker; and 2 were with consultants for over 4 days.

We conclude that 5 days appear to be reasonable TAT for urgent samples in gynae-cytology and currently, ~89% of samples are meeting this standard (~98% allowing for weekends). Delays occur due to weekends, reprocessing, and consultant input. From 2010 a target of 14 day TAT from collection to patient result will, in practice, require all samples to achieve this 5 day standard and thus attention must be paid to these areas of delay.

P81

Classification of lung cancer in diagnostic biopsies: an audit

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It is accepted practice to use the term "non small cell lung carcinoma" (NSCLC) when a specific tumour type cannot be determined. This is particularly useful where there is limited tissue available for examination. However, the specific cell typing of lung carcinoma is increasingly important as newer chemotherapeutic regimens are developed.
This study assessed observer specificity and interobserver variability between three consultants. Analysis was undertaken on small diagnostic biopsies in order to assess variance of classification and the influence of sampling technique.
514 cases were included. Consultant A was most specific, reporting 20.6% as "NSCLC not otherwise specified" compared with 46.2% and 40.3% by Consultants B and C respectively. The difference was highly significant ($Chi2 = 30.4818$, $df = 4$, $p < 0.001$).
For each level of specificity (high, medium, low), there was no marked difference in the reporting of CT guided (CTx) and bronchoscopic biopsies (BBx). However, BBx provided more small cell (28.3%) and squamous (22.7%) diagnoses than CTx which provided only 8.6% and 17.1% respectively. Conversely, CTx had more cases diagnosed as Adenocarcinoma (30.3%) than BBx which had only 11.2%. These differences may be due to anatomical distribution of tumour type.
This study provides evidence for introducing measures to increase reporting specificity and compares favourably with literature reports of pre-operative diagnostic accuracy.

P82

Modelling the dynamics of tuberculosis infection – an educational simulation

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The dynamics of tuberculosis infection in Africa was explored using systems thinking techniques. Information gathered from Cochrane reviews and other definitive literature sources were collated using a cognitive mapping process. This produced 29 linked concepts. A central tendency analysis showed that the 2 factors 'getting infected' and 'immunocompromised' were most linked to the other concepts with 18 links each. A domain analysis showed that 'getting infected' had the most immediate linkage. From the cognitive map a number of causal loop diagrams were extracted. Qualitative analysis of these indicated that the number of infected individuals in the population was the key driver of the disease, a not entirely unexpected finding. These diagrams also showed that compliance with treatment was one of the key factors in reducing the number of infected individuals in the population and thus the spread of infection. From these diagrams a quantitative system dynamics model was produced using standard system dynamics software. System behaviour over time was simulated looking at the outputs of infected and non-infected individuals over a period of 20 years. Sensitivity testing was used to evaluate the effect of different levels of treatment compliance on the infection rates over this period. The simulation produced a qualitatively deeper understanding of the dynamics of infection that was better than static graphical displays.

P83

Urgent histopathology specimens

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Anecdotally there has been a large increase in the number of urgent cases over the last few years, thought due to time targets for diagnosis and MDTs.
We studied the case workload over the last 10 years looking at the proportion of cases sent as urgent, which specialities contribute most to urgent cases, the turnaround time for urgent cases and the legitimacy of an urgent label.
We collected data for the month of September for each of the last 10 years.
The proportion of urgent cases increased by 897% (1.09% in 1998, 9.78% in 2008) over the study period.

Gynaecology and gastro intestinal (GI) were the main contributors to urgent cases both in number of cases and number of blocks, with urgent gynae cases representing 15% and urgent GI cases representing 60% of all urgent cases in September 2008. Most urgent cases were either related to 2 week wait referrals or required for an MDT meeting. Many of the GI 2 week wait urgent cases were biopsies taken during an otherwise negative endoscopy.

Overall, the data shows a steep increase in the proportion of urgent cases with two week wait referrals and MDTs being the apparent cause of this increase. Many of these cases may be spuriously urgent as a negative endoscopy will trigger some other investigations (e.g. barium enema) and the biopsies generated for it should not be labelled as urgent.

P84

Histopathology training schools – the right work-training balance?

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Anecdotally it has been suggested that the Histopathology Training Schools have led to too much formal training and less apprentice-based training while carrying out service work. The Royal College of Pathologists (RCPath) suggests the following workload as a guide for histopathology trainees:

Surgical pathology:	500 cases per annum
Post mortem:	20 per annum
Cytopathology:	300 cases per annum

The aim of this study was to measure the performance of ST1 histopathology trainees against these standards and at the same time discover how much additional formal training they had received. A questionnaire was sent to all ST1 trainees relating to the period August 2007 until August 2008.

30% of questionnaires were returned. The target of 500 surgical cases was easily achieved by all trainees (mean 800, highest 1500). Not all trainees had reported sufficient cytology cases: mean reported gynaecological cytology specimens was 122 and non-gynaecological cytology was 158. The number of post mortems ranged from 14-59 (mean of 31). Trainees attended at least three full weeks of block teaching and had at least one formal teaching session at ST1 level each month. Many also attended local FRCPath courses.

Four trainees had not carried out enough post mortems, partly due to poor availability in some centres. Most trainees who had reported insufficient cytology had a deficit in gynae cases. However, most trainees achieve a balance of regular formal teaching at an appropriate level and also comfortably achieve the RCPath workload targets.

P85

Where are they now? A survey of histopathology trainees, 2001–2008

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Histopathology training schools were introduced in 2001 to address a manpower problem. The 3 initial schools have now expanded to 12, with a total of 313 trainees being enrolled up until the 2008 intake.
A questionnaire was sent to all trainees recruited through the schools. It asked about demographics, career aspirations, and, for those who had left training before completion, life after histopathology.

A 58% return rate was recorded and all data were anonymised. Since the introduction of run-through training in 2005 trainees tended to be younger, female and to have come straight from Foundation Training. Prior to this date a higher proportion of trainees were recruited from medicine, surgery and overseas pathology posts. Where stated, aspirations of trainees varied between general histopathology (49%), specialisation (31%) and research (7%), with 13% undecided.

The average annual attrition rate is 7%, and 15 "leavers" responded to the survey. Of these, 5 had entered histopathology following Foundation Training. Reasons for leaving training included job dissatisfaction, a desire for career change, failure to adapt to histopathology and some local issues.

Our results show that the attrition rate in histopathology is low, and suggest that the majority of trainees remain satisfied with their career choice. We have insufficient data to suggest that those leaving may serially change careers. The first year of training is particularly intensive: we believe that more Foundation rotations and taster weeks in histopathology may further reduce the rate of those leaving the specialty.

P86

Trends in phone call enquiries in a pathology department: an audit study

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Phone call enquiries over a period of 8 weeks were audited to determine their frequency, causes and relative distribution among various sub-specialities and various staff members. There were obvious discrepancies in their frequencies among various sub-specialities and individual staff members reflecting varied trends in the attitudes of both pathologists and clinicians in communicating pathology results. Enquiries due to delay in the issuing of reports constitute a minor component. On the other hand, the need for an urgent result for various unexpectedly arising reasons constituted a significant percentage. Unreasonable expectation on part of the service users within one sub-speciality was suggested by the data. Addressing the issues highlighted by the audit study can be helpful in reducing time wasted due to unnecessary enquiries and in increasing awareness of service users of acceptable turn round times within the histopathology speciality as opposed to other laboratory disciplines. This simple and basic continuous audit work can also be a useful tool in early detection and identifying of requirements or issues within the service that need to be addressed or resolved.

P87

An impending crisis in the provision of histopathology expertise for mouse functional genomics

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The generation of new mouse models of human disease is accelerating rapidly, due to the completion of whole-genome sequencing efforts and technological advances in the manipulation of the mouse genome. We sought to investigate manpower issues in the provision of histopathology expertise for mouse functional genomics and compared this to the perceived demand from principal investigators (PIs). Through the European Commission (EC)-funded PRIME pathology training initiative, two questionnaires were devised to collect information from pathologists and EC-funded PIs on the current provision of mouse histopathology expertise in Europe and the demands for this service. We find that pathological analysis is being performed almost exclusively by professionally qualified pathologists, generally employed in clinical diagnostic posts, where the work is undertaken as collaboration outside of their contractual commitments but without previous training in veterinary or comparative pathology. The results indicate that there is a lack of both trainees and provision of specialist training in this field. Unsurprisingly, the availability of diagnostic expertise and advice falls far short of the number of genetically engineered mice (GEM) being generated for analysis. We analyse these results with reference to previous studies and discuss solutions for the future recruitment, training and funding for pathologists in mouse functional genomics in Europe.

P88

Audit of testicular tumours post publication of the minimum data sets (2000-2009) – experience of a large teaching hospital

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INTRODUCTION: Consistent , highly standardised testicular tumour classification and reporting are crucial for tumour staging, clinical management and follow up. The Royal College of Pathologists have published minimum datasets (MDS) for reporting testicular cancers since April 2000.
AIMS AND OBJECTIVES: To analyse compliance in reporting of testicular cancer cases at Royal Free Hospital (RFH) compared to the core data items detailed in MDS between 2000-2009.
MATERIALS AND METHODS: This audit had three components:
1. Cases from 2000-2008 were electronically retrieved. Printed reports were reviewed to document the presence/absence of core data items including size, histological type, vascular invasion, ITGCN in addition to the turn-around time.
2. Histology slides were reviewed from 2004-2008 to investigate for the entry of correct data and errors /omissions made.
3. After presentation of the audit findings, a re-audit assessing whether there is improvement in the reporting has been achieved in 2008-2009.
RESULTS: A total of 226 cases were retrieved, 91 of which were available for review. 90% complied fully with macroscopic data items, where as vascular, tunica invasion, ITGCN were not mentioned in 10-17 % of reports. Review of the histology slides showed no major discrepancies. The data from the final phase of the audit are currently being analysed.
CONCLUSION: The overall standard of reporting testicular cancer cases and compliance to the MDS were found to be good at RFH, but a more focused approach was needed. Careful macroscopic description and inclusion of the relevant microscopic findings were highlighted.

P89

The effect of regulation and governance on research led by pathologists or involving pathology in the UK

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There have been recent reports that the regulatory and governance environment in the UK relating to: the involvement of NHS patients in research; the use of human biological samples in research; the use of personal and health information in research; and, the need to gain NHS Research & Development Office and Research Ethics Committee approvals are affecting the willingness and ability of pathologists to lead research or contribute to research. The survey reported here gauged the diversity, utility and availability of guidance to assist researchers navigate the regulatory and governance environment. It also assessed the overall opinion of pathologists and other cancer researchers on the regulatory and governance environment.

A total of 242 individuals participated in the survey. Of these, 73% were active in research using human tissue and 61% were involved with pathology as consultants, clinical scientists, biomedical scientists or in-training. Most identified several regulators as concurrently applicable to their work. The overall environment was perceived as strict and complex and particularly problematic for pathologists and those actively working in human tissue based research. Willingness to do research is impaired as many find it difficult and some do not do research as a result. Available guidance was seen as confusing, unhelpful and time wasting. Most respondents sought guidance from multiple sources.

This survey suggests that guidance should be consolidated into an authoritative multi-regulator endorsed resource and made available via a restricted number of sources, principally via NHS Research and Development Offices and applicable regulators.

P90

A template for development of a policy for access to data and/or biological samples

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There is growing awareness that without the sharing of data and samples, medical research will become increasingly inefficient. At the same time, it is recognised that there must always be safeguards around the movement of samples and data to protect the interests of the donors or data subjects. Protection is provided by a regulatory and ethical framework which sets the boundaries for access. However, we believe that the lack of practical resources in this area is leading to duplication of effort as researchers and funders repeat the same background work each time a policy is needed for a new study or collection.

We present a template for access policy development that can be considered by a variety of funding and research organisations for adaptation to their purposes. This is not intended to impose policy and practice but rather to provide a practical instrument which (i) reflects established good practice, (ii) can be tailored to circumstances, and (iii) helps avoid unnecessary duplication of effort. It differs from existing guidelines which simply (though usefully) state principles by providing example text that can be used directly in a policy or MTA.

The template has been informed by a consultation, which received responses from research funders, regulatory bodies and biobanks, as well as individual researchers, healthcare professionals and patient representatives. The consultation responses strongly supported our aims and indicate a surprising degree of agreement on the general principles whilst highlighting the need to allow flexibility and minimise bureaucracy.

P91

Galectin-3 immunostaining in cytological and histopathological diagnosis of thyroid lesions

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Galectin-3 is a human lectin linked to malignant transformation in thyroid gland. We aimed to evaluate the diagnostic role of galectin-3 in differentiating benign from malignant thyroid lesions in cytological and histological samples. We included 19 multinodular goiter (MNG), 19 follicular adenoma (FA), 13 follicular carcinoma (FC), and 28 papillary carcinoma (PC). Galectin-3 immunostaining was applied on histological sections and for the available preoperative FNAC (28 cases)

The positivity percentage of galectin -3 in histological materials was 10.5%, 92.3%, 93% for non-malignant, FC and PC respectively. According to H score, glaectin-3 immunostaining was significantly lowered in FA)1±2.8(as compared to papillary (158.5 ± 88.6) and follicular carcinomas (150 ± 83.9) (P>0.0001). However, there was no statistically significant difference between FC and PC (P= 0.56) or between classic and follicular variants of PC (P= 0.51). Sensitivity, specificity, positive and negative predictive values for galectin-3 staining were 93%, 89.5%, 90.5% and 92% respectively. Combination of standard cytological evaluation with galectin-3 immunostaining markedly improved sensitivity (71% versus 85%), specificity (75% versus 94%), positive predictive value (83% versus 92%) negative predictive value (60% versus 87.5%), and diagnostic accuracy (72% versus 90%).

We suggest Galectin-3 as a supplementary immunostaining in histological and cytological diagnosis of difficult thyroid lesions.

P92

Computerized nuclear morphometry in diagnosis of thyroid lesions with predominant follicular pattern

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Background:Differential diagnosis of thyroid lesions with predominantly follicular pattern is one of the most common problems in thyroid pathology. Development of more objective and reproducible tools for diagnosis is needed. This work aimed at studying the role of nuclear morphometry in differential diagnosis of different thyroid lesions having predominant follicular pattern. Material and methods: Semiautomatic image analysis system was used to measure a total of 8 nuclear parameters in 48 thyroid lesions including seven nodular goiter (NG), 14 follicular adenoma (FA), 14 follicular carcinoma (FC) and 13 follicular variant papillary carcinoma (FVPC). Results: The parameters related to nuclear size (area, perimeter, maximal nuclear diameter, nuclear size) and nuclear shape (L/S ratio, Form_AR) were significantly higher in malignant (FVPC & FC) than non-malignant lesions (NG &FA). The mean area and size (AUC 71%) were the most reliable, followed by perimeter (70%), MaxD (70%), form-AR (68%), and LS ratio (67%) P<0.05. The MinD (61%), NACV (56%) were not reliable for diagnosing malignancy (P>0.05). Nuclear area and size (AUC 77%) were the most reliable parameters for differentiation between FVPC and FA. The best cut off value for mean nuclear area and size were ≥39.9 and ≥27.7 respectively However, there was no quantitative difference between FVPC and FC or between FC and FA. Conclusion: Nuclear morphometric parameters may help in the differentiation between FVPC and FA but they are not useful in the differentiation between FVPC and FC or between FC and FA.

P93

Adequacy, accuracy and reliability of fine needle aspiration cytology in thyroid diseases: an audit study

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The aim of this study is to assess: 1) The adequacy (including content and quality) of the submitted thyroid FNA samples, 2) The accuracy of the diagnosis compared with the final diagnosis and 3) The reliability of the FNA method as a diagnostic technique for thyroid disease. This is measured as a percentage of definitive correct diagnoses to total number of FNA with the same diagnoses. All FNA reports issued during a two years period (2006 - 2007) are examined. Those that followed by resection specimens are correlated to the final histological diagnoses.
A total of 174 FNA samples from 148 patients were received. The results are further subdivided into the following categories: 1) Cases with no histological follow up, 2) Insufficient or unsatisfactory FNA material 3) Accurate or correct diagnosis 4) Discrepancy. The discrepancy is further subdivided into: 1) Discrepancy not related to the FNA sample. 2) Discrepancy of no clinical significance. 3) Discrepancy of clinical significance.
A significant 67% of cases, with one or more than one FNA performed, had no histological resection follow-up. However, cases with histological follow-up showed no discrepancy of clinical significance. Discrepancy not related to the FNA sample occurred mainly in relation to incidental papillary carcinoma as this diagnosis was made in 16% of the cases where there was no suspicion in the FNA material.

P94

Is an EVG necessary for the diagnosis of giant cell arteritis?

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BACKGROUND: Elastic van Gieson (EVG) stain is used routinely to identify the internal elastic lamina in biopsy specimens from clinically suspected cases of giant cell arteritis (GCA). It is well recognised, however, that disruption of the internal elastic lamina is not specific for GCA and current American College of Rheumatology guidelines omit structural changes to the vessel wall from recommended diagnostic criteria.
AIM: To assess whether use of EVG stain contributes to the recognition of histological features of GCA, compared with examination of haematoxylin and eosin(H&E)-stained sections alone.
MATERIALS AND METHODS: A retrospective series of 40 temporal artery biopsies positive for GCA were identified from the APEX computer system of a large university hospital trust, using standard SNOMED codes. H&E-stained sections were reviewed against published diagnostic criteria and classified as positive, negative, or equivocal, for GCA. The integrity of the internal elastic lamina on both H&E- and EVG- stained sections was recorded for each case.
RESULTS: Histological review of H&E-stained sections demonstrated diagnostic features of GCA in 38 of 40 (95%) of cases. Disruption of the internal elastic lamina was apparent in 85% of H&E-stained sections and 100% of the EVG-stained sections.
CONCLUSIONS: Histological review of 40 cases of biopsy-proven GCA indicates that features demonstrated by EVG make no contribution to diagnosis in a majority of cases. It is therefore recommended that EVG be reserved for use as a supplementary investigation in cases with equivocal findings on H&E-stained preparations.

P95

Audit of head and neck fine needle aspiration cytology: a two year cytology/histology correlation

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We present a two-year audit on head and neck cytology assessing parameters to improve cytology service and diagnostic accuracy.
All head and neck FNAC specimens reported in 2006/2007 at UHBNHSF Trust were retrieved and compared with histology. Cases without correlation were reviewed.

The number of cases received in 2006/2007 was 610/568. Number of cases with histology follow-up in 2006/2007 was 144/139. Mean turnaround time in 2006/2007 was 5/6 days. Total unsatisfactory cases in 2006/2007 were 211/123 (33/21.6%). There were 12 false negatives and no false positives. Specificity for both years was 100% and the sensitivity in 2006/2007 was 92.7/79.5%.

12 cases interpreted as false negatives based on histology were reviewed by 2 Consultant Pathologists. 9/12 specimens were lymph nodes and were reported as a lymphoma on subsequent histology- 6 Hodgkin lymphoma, 2 diffuse large B-cell lymphomas, one Grade 3 follicular lymphoma. On review, occasional bi-nucleate cells were identified in 3 cases and few “blastic” cells were noted in 4 cases- none diagnostic of lymphoma. Remaining 3 cases were adenoid cystic carcinoma, metastatic squamous cell carcinoma and Warthin’s tumour – on review, all these 3 cases lacked representative cytology material. False negatives in our audit largely included lymphomas; this could be reduced by performing immunohistochemistry and clonality tests, for which, in addition to routine smear preparations – needle washings should be obtained.

P96

Cytological features of metastatic salivary duct carcinoma of the parotid gland to pleural fluid

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Salivary duct carcinoma (SDC) is an uncommon aggressive malignancy of the parotid gland. This is the first cytological description of a case of a 44 year-old man with metastatic SDC to pleural fluid. He presented with shortness of breath due to unilateral pleural effusion 14 months after poorly differentiated salivary duct carcinoma had been diagnosed histologically by radical parotidectomy. The effusion was cellular with numerous large cohesive groups of epithelial cells on a background of reactive macrophages. The cells had an oncocytic appearance with marked pleomorphism and central nucleoli.
A cell block preparation showed multiple small cohesive groups of epithelial cells with a scalloped outline and suggestion of cribriform glandular morphology.
Immunocytochemical stains supported a diagnosis of SDC with positivity for CK7, androgen receptor and GCDFP-15. CK20 and TTF-1 were negative. Detailed cytological description of this rare malignancy in pleural fluid may aid cytologists in raising the possibility of a first diagnosis of metastatic SDC in effusion fluids.

P97

Are parotid metastases from cutaneous head and neck squamous cell carcinomas associated with metastases to the neck nodes?

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Are Parotid Metastases from Cutaneous Head and Neck Squamous Cell Carcinomas Associated with Metastases to the Neck Nodes?
BACKGROUND: Cutaneous squamous cell carcinomas of Head&Neck tend to metastasize to the parotid gland. Parotidectomy and neck dissection is the standard mode of treatment in such cases. However the incidence of simultaneous involvement of neck nodes is not well understood.
AIM: To assess the frequency of neck node involvement in the presence of metastases to the parotid gland.
METHOD: 17 cases of metastatic squamous cell carcinoma to the parotid gland were reviewed and divided into 2 groups.
Tumour present in the Parotid gland only (including intraparotid lymph nodes.)
Tumour present in the parotid gland and in the lymph nodes of the neck dissection specimen.
RESULTS: The presence of metastatic squamous cell carcinoma to the parotid gland was confirmed in all 17 cases (in 7 there was histological evidence of intraparotid lymph node involvement). In 2/17 cases metastases was also seen in level 2a and 2b of ipsilateral neck dissection. In both cases the tumour was also present in the surrounding soft and bone tissue.
CONCLUSION: Our data shows that parotid metastases from cutaneous Head&Neck squamous cell carcinomas tend to be restricted to the parotid gland. Neck nodes are involved in very advanced disease where soft tissue and bone is also infiltrated. We speculate that patients may not need neck dissection if pre-operative assessment does not show soft tissue involvement.

P98

A cytological perspective on two uncommon salivary gland spindle cell lesions

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Spindle cell lesions of salivary glands are uncommon and can be diagnostically challenging both on surgical specimens and pre operative fine needle aspiration cytology (FNA). We describe two such lesions. A 34 year old man presented with a rapidly enlarging mass in the submandibular gland. An ultrasound scan suggested a hyperplastic lymph node and a guided FNA was performed. The hypercellular aspirate comprised loose aggregates of small spindle cells embedded in stromal fragments with branching capillaries and myxoid substance. Immunohistochemistry with SMA was positive. A diagnosis of a spindle cell lesion consistent with nodular fasciitis was favoured. This was confirmed on histological sections. The second case involved a 68 year old man who presented with a hard mass in place of the submandibular gland. FNA revealed pleomorphic spindle cells with nuclear hyperchromasia which occurred in fascicles and storiform patterns. There was expression of both vimentin and cytokeratin. Our diagnosis of a spindle cell variant of squamous cell carcinoma was confirmed on histology. The cytological features in each of these spindle cell lesions which aided in categorising these as benign or malignant are emphasised. We highlight the differential diagnoses that one should consider and the potential pitfalls that may occur if such tumours are encountered in clinical practice.

P99

A two-year audit of ultrasound guided fine needle aspiration of cervical lymph nodes

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Ultrasound (USS) assisted/ guided fine needle aspiration has the advantages of allowing accurate localisation of small and deep- seated lesions, with a plausible resultant increase in adequacy rates. 250 USS guided neck node fine needle aspirations (FNA) (from 212 patients) were conducted between 1/1/07 and 31/12/08 at our centre by radiologists. Data for this audit was collected from USS reports and subsequent cytology reports.

On USS, 34% of cases were diagnosed as benign and 61.6% were identified as malignant. In 4.4%, the radiologist was uncertain of the diagnosis. On subsequent cytological examination, 9.6% were considered inadequate, 50.4% diagnosed as benign and 40% diagnosed as malignant. In 70.3% of cases, the radiological and cytological diagnoses were in agreement. The positive predictive value for a malignant diagnosis by radiology was 67% with a negative predictive value of 98% resulting in 99% sensitivity and 59% specificity.

This audit has helped us assess the current standards of the fine needle aspiration service for neck nodes provided by the radiology department at our centre and we aim to re-audit these aspects of the service regularly in the future.

P100

Abnormalities of 7q in splenic marginal zone lymphoma

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BACKGROUND: Splenic marginal zone lymphoma (SMZL) is a poorly characterised low grade B-cell lymphoma. Risk stratification and histological diagnosis of SMZL remain challenges, due to a lack of specific phenotypic and genetic markers.
METHODS: Copy number changes were assessed with 1Mb resolution aCGH. Changes on chromosome 7 were further studied by tile-path aCGH and FISH. Somatic hypermutation in the rearranged IGH genes was examined by PCR and sequencing. 14 cases underwent expression array analysis. Expression of miRNAs in the minimally deleted region on 7q were analysed using qRT-PCR.
RESULTS: 1Mb array CGH revealed recurrent gain of 3q (15%), 8q (19%), 9q33 (19%),12q (12%),18 (7%), and recurrent loss of 7q (38%) and 8p (12%). Tile-path aCGH analysis of the cases with 7q deletion showed an 5.72Mb region spanning 124.274- 129.95 Mb at 7q31.32-32.3 as the minimal common deleted region. A cluster of miRNAs are present in this region, and these showed non-significant overexpression in 7q deleted cases. Bioinformatically predicted miRNA target genes also appeared to be overexpressed in such cases. Somatic hypermutation of the rearranged IGH gene was seen in 66%.
CONCLUSION: Deletion of a 5.72Mb region at 7q31.32-32.3, is a frequent event in SMZL (32.6%), and appears relatively specific to SMZL. A cluster of miRNAs in the region appear to be underexpressed in 7q deleted cases and predicted miRNA target genes also appear overexpressed.

P101

Analysis of lymphoreticular neoplasms in PTEN+/- transgenic mice

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Transgenic mice heterozygous for an inactivating mutation in the PTEN tumour suppressor gene develop multiple types of tumours. This is influenced by other genetic alterations such that mice hypomorphic for the PDK1 kinase are relatively protected from the tumour susceptibility conferred by the PTEN mutation, those harbouring mutations in the LKB1 gene have an increased frequency of tumour formation. Most common amongst these tumours are lymphoreticular neoplasms. We have performed a detailed analysis of 40 enlarged lymph nodes from Pten mutant mice, three nodes were subsequently excluded because of incomplete data. Morphological and immunocytochemical analysis were performed, although in mice light chain restriction is uninformative and CD5, CD10 and bcl6 expression patterns differ in mouse compared to human. The cases were classified according to the Bethesda classification of murine lymphomas. Almost all cases had major involvement of the superficial cervical and intra-parotid lymph nodes, involvement of thoracic nodes, spleen and extranodal sites were seen in some cases. We found that 36/37 lymph nodes were replaced by a lymphoma with a follicular architecture while 1/37 was diffuse. Immunocytochemistry confirmed that 36/37 lymph nodes were follicle centre cell lymphomas. The majority (28/36) of the follicular lymphomas was bcl2 negative. The one remaining lymphoma (from a PTEN+/-LKB1+/-PDK1+/fl animal) was a diffuse large B cell lymphoma. We conclude that mutations in the PTEN tumour suppressor gene predispose to the development of follicular lymphoma in transgenic mice and that the pathogenesis may be modified by other mutations.

P102

Modulation of lymph node sinus endothelial expression of LSECtin, DC-SIGN, DC-SIGNR, Lyve-1 and CD31 with local environment

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LSECtin is a recently identified C-type lectin encoded in a gene cluster with DC-SIGN, DC-SIGNR and CD23 on chromosome 19p13.3. Antibody or ligand-mediated engagement triggers rapid LSECtin internalisation, suggesting it acts as an antigen uptake receptor that may recognize host or pathogen-derived proteins.

We demonstrated that LSECtin expression is restricted to liver, lymph node and bone marrow sinus endothelial cells. We investigated whether LSECtin, DC-SIGN and DC-SIGNR, the functionally related protein Lyve-1, and PECAM-1 (CD31) demonstrated modulation of their expression levels on lymph node sinus endothelium in relation to local microenvironment.

Reactive LSE demonstrated strong expression of LSECtin, DC-SIGN and DC-SIGNR, but patchy low level expression of Lyve-1 and CD31. In granulomatous conditions, there was some loss of LSECtin, DC-SIGN and DC-SIGNR and little change in Lyve-1 or CD31 expression. In conditions with necrosis (Kikuchi's lymphadenitis and caseating granulomatous inflammation), there was marked LSECtin and more moderate DC-SIGN and DC-SIGNR, with Lyve-1 and CD31 upregulation. When metastatic melanoma or squamous cell carcinoma was present in the lymph node strong expression of LSECtin, DC-SIGN and DC-SIGNR was seen, but Lyve-1 and CD31 expression was less prominent. In Castleman's disease, only CD31 expression was seen on any foci of hyaline vascular proliferation.

LSECtin, DC-SIGN, DC-SIGNR, Lyve-1 and CD31 show modulation of expression by lymph node sinus endothelial cells in response to the environment within the lymph node. Further studies are needed to determine whether this modulation of expression may be used as a diagnostic or prognostic feature.

P103

Increased YY1 level and colocalisation with Bcl-2 predicts favourable outcome in follicular lymphoma

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Follicular lymphoma (FL) has a wide range of behaviour, some patients having an indolent course and others developing aggressive disease. There are presently no reliable means to distinguish between these groups. The transcription factor Yin-Yang 1 (YY1) may be prognostic in FL, at both mRNA and protein levels, though this requires validation and correlation with tumour biology.

Ki67 percentage, grade, YY1 protein levels and T-cell and macrophage markers were used in a multivariate analysis for survival in 26 cases of FL. YY1 protein level was the strongest predictor of outcome (P=0.018), none of the rest of the markers being significantly associated with outcome. Dual quantum dot based immunofluoresence was performed for YY1 and BCL2, and for YY1 and CD20 in 26 cases of FL. Spectral imaging was used to measure the percentage colocalisation of YY1 and BCL2, and of YY1 and CD20, including the expression intensity in the areas of colocalised signals. Kaplan-Meier survival analysis demonstrated association of higher percentage co-localisation of YY1 with BCL2 with longer survival (P=0.014) together with longer survival in cases with a higher level of YY1 expression within areas colocalised with BCL2 (P=0.017). Colocalisation of YY1 and CD20 was not associated with survival.

These results support the previous findings of survival prediction by YY1 in FL, indicating possible use as a clinical biomarker. They also suggest that YY1 may be negatively regulating BCL2 in FL, suggesting that YY1 could be a potential novel therapeutic target.

P104

Adequacy in sampling and histopathological reporting of bone marrow trephine biopsies

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Bone marrow trephine biopsy is important in the diagnosis of various haematological and non-haematological diseases. There is no agreed standard for the criteria that define adequacy of the biopsy. There are, however, various recommendations within the literature, which include a minimum length of 15mm or the presence of 5 well preserved intertrabecular marrow spaces. In this retrospective study, we reviewed 100 consecutive trephines with respect to their pre-processed length, the grade of haematologist performing the procedure, the patients' BMI and the final diagnosis in an attempt to determine useful criteria for sample adequacy.

79 cases were less than 15mm in length, although only 19 were reported as inadequate. There were 61 cases less than 15mm which were called adequate, of which 19 were called normal. Senior haematologists tended to take longer biopsies than juniors, with a greater consistency in length. However, there was no significant difference between these groups in the percentage reported as inadequate ($p>0.05$). Obese patients (BMI>30) yielded significantly shorter trephine biopsies than non-obese patients ($p<0.05$). Finally, we show that to obtain a 95% probability of adequacy, a minimum pre-processed trephine length of 15.7mm is required ($p<0.05$). This value corresponds to the lower limit of previously suggested lengths.

It is proposed that, in cases less than 15mm, a comment should be made about the small size of the biopsy and that it is not entirely possible to exclude a focal lesion.

P105

Extra-levator abdominoperineal excision for low rectal cancer: clinical results of a European multicentre study

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Abdominoperineal excision (APE) is associated with worse outcomes compared with anterior resection for rectal cancer. We have previously shown that extra-levator APE removes more tissue around the tumour, reducing CRM involvement and intraoperative perforations (IOPs) compared to standard APE surgery. The optimum operative position, perineal reconstruction method and patient morbidity remain unknown.

We received clinical data, pathological reports and specimen photographs for 176 extra-levator APE specimens from 11 European specialist colorectal surgeons and compared them to 124 standard specimens from 8 surgeons. Pathological dissection was performed using standard methods.

Blood loss, time to patient discharge and sexual/urinary complications were similar. However, extra-levator surgery was associated with an increase in perineal wound complications (38% vs. 20%, p=0•02), which was partially reduced by using myocutaneous flaps or Permacol™ during perineal reconstruction. Extra-levator perineal dissection in the prone position removed significantly more tissue per slice in the distal rectum compared to lithotomy (2333mm^2 vs. 1964mm^2, p=0•0008) resulting in a lower IOP rate (6% vs. 21%, p=0•03).

Extra-levator APE appears safe and although perineal complications are increased compared to standard surgery, enhanced reconstruction may reduce this risk. Additionally, extra-levator perineal dissection in the prone position removes more tissue and reduces intraoperative perforations compared to lithotomy. We estimate that the widespread adoption of this operation would improve survival rates by 10% leading to the saving of around 200 lives per year in the United Kingdom alone and many more if translated around the world.

P106

Specimen length, pathologist experience and type of operation are the only factors that affect lymph node yield in rectal cancers

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INTRODUCTION: The number of lymph nodes harvested (LNH) following colorectal cancer resection is considered to be a marker of "surgical quality". The aims of this study were to study factors influencing LNH and lymph node size in a single pathologist series.
METHODS: 127 consecutive rectal resections reported by a single pathologist were identified from a prospectively collected database. All harvested nodes had area and diameter measured using image analysis software. Factors that may have influenced LNH were studied by univariate analysis and if significant were subjected to multivariate analysis.
RESULTS: Overall median LNH was 35 nodes/patient (IQR 24-43). On univariate analysis increased specimen length, later position in the series, operation type (AR vs. APER), operating surgeon, higher TME score, position in relation to peritoneal reflection were associated with an increased LNH. Of note, T stage, N stage and neoadjuvant therapy did not statistically influence LNH but were associated with a reduced LN area. On multi-variate analysis LNH was predicted by increased specimen length, operation type and later position in the series.
CONCLUSIONS: In this series LNH was higher than generally previously reported and only longer specimen length, operation type and later reporting in the personal series were independently associated with increased LNH. This suggests there is a learning curve associated with LNH in rectal cancers. In this series less pathologically advanced tumours and prior use of radiotherapy were not associated with reduced LNH, as has been previously reported, but was associated with a reduction in LN size.

P107

The surgeon and a male pelvis – key determinants in TME quality?

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INTRODUCTION: Total mesorectal excision (TME) surgery for rectal cancer is associated with lower rates of circumferential resection margin involvement and improved locoregional control. The aims of this study were to identify factors associated with a good TME score and to determine if formal feedback improved subsequent TME score.
METHODS: Factors that may influence the TME score of 82 consecutive anterior resection specimens, reported by a single pathologist, were compared between specimens graded as poor/ moderate against those graded as good. In this study, 'high volume' surgeons were defined as those who operated on 9 patients or more over the study period. Mid way through the study period surgeons were presented with their TME results.
RESULTS: TME scores were poor, moderate and good in 15%, 30% and 55% respectively. Patient's male gender (66% vs. 35%; p=0.008) and operating surgeon (p=0.023) were statistically linked to good TME scores. There was no association between TME grade and: age, pre-operative radiotherapy, LN harvest and distance to nearest circumferential margin. Higher volume surgeons were more likely to produce good TME than lower volume surgeons. Good TME scores improved after feedback of performance from 51% (20/39) to 58% (25/43), p=0.270.
CONCLUSIONS: In this study, the operating surgeon and patient's male gender are significantly associated with good TME scores. Higher volume surgeons appear more likely to achieve good TME scores than lower volume surgeons. Formal feedback of TME scores shows a trend to improvement in surgical performance.

P108

Extremely well differentiated Barrett's adenocarcinoma: a diagnostic challenge

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Barrett's oesophagus is the major risk factor for oesophageal adenocarcinoma. The purpose of Barrett's surveillance is to detect progression of neoplasia at an early, treatable stage. We report progression in a 60 year old male of an exceptionally well differentiated oesophageal adenocarcinoma to pT3 pN1 despite surveillance. Extremely well differentiated Barrett's adenocarcinoma has some similarity with adenoma malignum of the uterine cervix. Lack of glandular maturation with loss of mucosal polarisation, and glands in unusual loci are clues to the diagnosis in a background of Barrett's dysplasia. This case also demonstrates the difficulty which can arise in diagnosing Barrett's dysplasia, which is important for risk assessment in Barrett's oseophagus. The role of surveillance endoscopy for Barrett's oesophagus remains controversial, but this case emphasizes the need for high quality histopathology and clinical correlation when Barrett's surveillance is undertaken.

P109

HER2 overexpression in gastric cancer: rare, heterogeneous and of no prognostic value - conclusions from 924 cases of two independent series

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BACKGROUND: Patients with gastric cancer (GC) have a poor survival and biologicals such as Trastuzumab have not been used routinely in these patients. Studies in breast cancer indicate that response to Trastuzumab depends on membranous HER2 overexpression or HER2 amplification. Existing data on HER2 expression and its clinical relevance in GC are still limited and controversial.
METHODS: HER2 expression was investigated by immunohistochemistry using full sections from 418 GC from Germany and tissue microarrays constructed from 506 GC from England. The 'DAKO score' and a continuous percentage scale were used in parallel for scoring. Results were compared to clinicopathological parameters and patient survival.
RESULTS: HER2 expression showed prominent intratumoural heterogeneity. 6% of all GC showed HER2 expression in more than 5% of tumour cells and 91% of these were intestinal type GC. In both series, no relationship was found between HER2 expression, patient survival or TNM stage.
CONCLUSIONS: This is the largest study to date confirming in two independent GC series that HER2 expression is not related to patient prognosis. Based on HER2 expression status, our results indicate that only a very small subgroup of intestinal type GC may potentially respond to Trastuzumab. In contrast to breast cancer, prominent heterogeneity of HER2 expression in GC was observed which will make pre-treatment HER2 testing in endoscopic biopsies challenging. Further studies are warranted to investigate whether serum levels of HER2 or HER2 radionuclide imaging may be more suitable to predict response to neoadjuvant HER2 therapy in GC patients.

P110

Expression of delta-like ligand 4 (Dll4) and markers of hypoxia in colon cancer

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PURPOSE: Dll4 is a ligand for Notch-1 and 4, selectively expressed in endothelium. It is upregulated by hypoxia and vascular endothelial growth factor-A (VEGF) and has been reported to play a role in establishing a functional blood supply in experimental tumours. Evidence from xenograft studies suggests that inhibiting Dll4 expression may overcome resistance to anti-VEGF therapy. The aim of this study was to characterize the expression of Dll4 in colon cancer and assess whether it is associated with markers of hypoxia and prognosis.
EXPERIMENTAL DESIGN: One-hundred and seventy-seven colon cancers (John Radcliffe Hospital, Oxford, UK) were represented in tissue microarrays. Immunohistochemistry was performed using validated antibodies against Dll4, VEGF, hypoxia inducible factor (HIF)-1α, HIF-2α, prolyl hydroxylase (PHD)1, PHD2, PHD3 and carbonic anhydrase 9.
RESULTS: Dll4 expression was observed in the endothelium of 71% (125/175) of colon cancers, but not in the endothelium of blood vessels adjacent normal colonic mucosa (0/107, $p<0.0001$). VEGF expression was significantly associated with HIF-2α ($p<0.0001$) and Dll4 ($p=0.010$). Dll4 was not significantly associated with survival ($p=0.94$). Only HIF-2α had a significant prognostic effect ($p=0.027$), with borderline significance in multivariate analyses (hazard ratio 1.61, 95% confidence intervals 1.01 to 2.57, $p=0.044$).
CONCLUSION: Endothelial expression of Dll4 is not a prognostic factor, but is significantly associated with VEGF. Assessing which patients express Dll4 may be critical in predicting response to new therapies that target Notch or VEGF signaling. The co-expression of Dll4/VEGF may define a phenotype similar to pre-clinical models associated with resistance to anti-VEGF therapy.

P111

Gastric parietal cell vacuolation mimicking gastric signet ring cell carcinoma

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Histological recognition of subtle gastric mucosal infiltration by diffuse-type adenocarcinoma is a well-recognised area of diagnostic difficulty. We present two examples of marked cytoplasmic vacuolation of parietal cells mimicking signet ring cell carcinoma.

Patient A, a 70 year-old male with a benign oesophageal stricture treated with long-term lansoprazole, a proton-pump inhibitor (PPI), underwent endoscopy. The stomach was difficult to distend, linitis plastica was suspected, and the gastric corpus was biopsied. Patient B, a 67 year-old male, underwent endoscopy for dyspepsia, resistant to lansoprazole therapy; inflamed proximal duodenum was biopsied.

Initial examination of both sets of biopsies showed markedly vacuolated cells within the mucosa, considered suspicious of signet ring cell carcinoma. At the periphery of the vacuoles were compressed nuclei and slender wisps of eosinophilic cytoplasm. Focally these cells appeared to 'infiltrate' the lamina propria; elsewhere they seemed to be contained within native glandular structures. Special stains failed to show mucus in the vacuoles, and immunostaining with anti-H+/K+ATPase antibodies showed strong cytoplasmic positivity, confirming that the affected cells were parietal cells. In patient A these were native parietal cells within oxyntic glands while in patient B they were parietal cells within gastric heterotopia of the duodenum.

Marked parietal cell vacuolation appears to be a hitherto undescribed pitfall in the diagnosis of signet ring cell carcinoma. The cause of the vacuolation is not established, but may be related to disruption to the intracellular canalicular system of parietal cells by long-term PPI use.

P112

Case Report – Mortality due to vesico-colic fistula in a case of Well Differentiated Papillary Mesothelioma (WDPM) with amyloid stroma

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WDPM is a mesothelial tumour of uncertain/low grade malignant potential. We report a case of an 88-year-old female admitted with collapse, distended abdomen and lower abdominal mass. Abdominal ultrasound some 4 years previous revealed a soft tissue pelvic mass. At that time, invasive diagnostic procedures were refused. During the final hospital stay, the patient was noted to have faeculent urine, and a diagnosis of vesico-colic fistula was made. The patient died a week later.
Post mortem examination revealed a 16cm firm pelvic mass, with multiple small, peritoneal nodules. Microscopy showed a well-differentiated papillary neoplasm with florid hyaline stromal cores. The tumour invaded the pelvic peritoneal serosa, the bladder and bowel, forming a vesico-colic fistula.
The tumour immunophenotype was AE1/3 +, D2-40 +, mesothelin +, calretinin +, CEA -, CD15 -, Ber-EP4 -, MOC-31 - and TTF-1 -. Overall the appearances were of a WDPM. Hyaline stroma showed congophilia with apple green birefringence indicating amyloid deposition.
There are two points of interest – firstly, no case of WDPM has previously highlighted fatality from vesico-colic fistula. It is speculative whether earlier diagnosis would have impacted upon management; at present due to paucity of cases, there appears little consistency in determining optimal treatment. Second (of academic interest) no WDPM has been associated with amyloid stroma.

P113

Mapping the spread of stem cell clones in human intestinal crypts

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We aimed to demonstrate how individual stem cell clones spread through the normal human intestinal crypt, in order to determine patterns of stem cell progeny migration and to obtain further evidence as to the location of the stem cell niche within the human intestinal crypt.

Serial transverse sections were cut through frozen human colonic epithelium and a histochemical stain performed to highlight silent clonal mutations in the mitochondrial encoded enzyme cytochrome c oxidase. Partially-mutated crypts were identified and clonal cell populations mapped using image processing software. The crypt map allows the path taken by the mutated clone to be fully visualised from crypt base to crypt luminal surface.

Our mapping in the small bowel supports the location of the stem cell niche as being above the Paneth cells in the human small intestine. In the human colon we have shown that cells capable of forming large clones are located in cell positions 1-3 in the crypt, supporting this as the site of the stem cell niche. However, in the colon more complex patterns are also seen: migration of clones is far from a simple straight line from the crypt base to the luminal surface, and clones are seen arising from almost half way up the crypt – this could represent a mutated stem cell clone that has been lost from the niche, or a mutation in a committed progenitor cell. Combining these techniques with lineage analysis will allow further insights into the biology of this important system.

P114

Prognostic factors in colorectal carcinoma – an audit on reporting quality

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INTRODUCTION: Guidelines published by the Royal College emphasize the importance of prognostic factors such as lymphnode numbers, serosal involvement and extramural vascular invasion (EMVI). The latter two parameters are particular important in Dukes B cancers as patients will qualify for adjuvant therapy.
AIMS: To audit the standard of reporting against college guidelines with additional emphasis on Dukes B tumours.
METHODS: 258 cases from 2007/2008 were audited for number of retrieved lymph nodes and incidence of serosal involvement and extramural vascular invasion.
RESULTS: Cases fell into the following groups: Dukes A 17%, Dukes B 43% and Dukes C 40%. The mean and medium number of lymph nodes was 20.1 and 18 respectively: (17% < 12 nodes, 40% 12-19 nodes, 43% > 20 nodes). The mean number of lymph nodes retrieved from colectomies was 21.9 and from anterior resections with and without preoperative treatment 16.5 and 19.5 respectively. In 43% of cases EMVI was identified and 34% showed serosal involvement. In the Dukes B group in 54% of cases adverse prognostic features were reported: 27% showed serosal involvement (38% of colonic tumours and 9% of rectal tumours) and 35% showed EMVI.
CONCLUSION: Our overall results compare well with current guidelines. Furthermore, in over 50% of Dukes B tumours adverse prognostic parameters were identified.

P115

The involvement of the circumferential margin in rectal specimens

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Our aim was to assess the percentage of rectal specimens excised at The University Hospital of South Manchester, with a positive circumferential resection margin (CRM) in the period 2004-2008, and the reasons behind this.

In rectal cancers, a positive CRM is defined as the presence of tumour within 1 mm of the circumferential margin. The CRM has a significant prognostic impact on the rates of local recurrence, distant metastasis and survival.

A total of 95 rectal cancers (arising at or below the peritoneal reflection), were excised. Data retrieved included operation type, site and size of tumour, TNM stage, margin and blood vessel involvement, plane of surgical resection and use of radiotherapy. Follow-up data collected included use of chemotherapy, recurrence rate and patient status. Cases were assessed to see whether the CRM was involved due to direct tumour spread or lymph node/blood vessel involvement.

Seventeen cases were CRM positive (18%). If only elective cases were considered the CRM positive rate fell to 12%. A positive CRM was due to direct tumour spread in 75% and lymph node involvement in 25% of cases. Nine positive CRM cases received pre-operative radiotherapy (5 long course and four short course). There were no cases of local recurrence. There was a positive correlation between positive CRM and emergency operation type, increasing stage, increasing tumour size and the presence of venous invasion. Our CRM positive rate was found to be competitive compared to published data.

P116

Xanthogranulomatous cholecystitis with gall bladder adenocarcinoma

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AIM: An interesting case of gall bladder adenocarcinoma with xanthogranulomatous cholecystitis.
CASE REPORT: A 62 year lady with painless jaundice. The CT scan showed biliary stricture with possible multifocal biliary malignancy including gall bladder. Biliary biopsy confirmed cholangiocarcinoma but a discussion at MDT meeting including a review of CT scan failed to differentiate between inflammation & neoplastic process. On surgical exploration the gall bladder was thickened and full of pus with a hard nodule at the fundus. Also a hard mass at porta hepatis with enlarged lymph nodes, invasion into portal vein, and the liver hilum. Considering this to be an extensively invading malignancy a radical procedure was carried out.
PATHOLOGY REPORT: The gall bladder showed an irregular bright yellow lesion involving full thickness of the wall at one end. On histology a well differentiated adenocarcinoma associated with florid xanthogranulomatous cholecystitis. The adenocarcinoma was primary with epithelial dysplasia. The yellowish tissue including the tissue around surgical ties comprised xanthogranulomatous inflammation only.
CONCLUSION: The co-existence of xanthogranulomatous cholecystitis and gall bladder carcinoma has been described in only 6 more cases before this to the best of our knowledge. But in all these association was confirmed only on review of gall bladder cases. However, clinical suspicion occurs more frequently necessitating extended surgical resection due to poor prognosis of gall bladder carcinoma.

P117

Audit of reporting colonic polyps in bowel cancer screening programme

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INTRODUCTION: The NHS Bowel Cancer Screening Programme (NHS BCSP) will, in due course, become the largest programme for bowel cancer screening in the world. It offers a unique opportunity to improve survival in this condition as well as clarifying the importance of current diagnostic criteria and identifying the biological potential of precursors of colorectal cancer.
AIM: To audit the reporting of colonic polyps against the key features in NHS bowel cancer screening programme and to assess the quality of specimen handling and reporting.
METHODS: A retrospective audit of colonic polyps received over three months in 2008 at Royal Oldham Hospital. Reviewed all histology reports, original cards and NHS bowel screening Proforma .
RESULTS: Of 50 cases analysed in 4 cases (8%) the site was not mentioned, 6 (18%) cases type of adenoma was not mentioned, 20 (50%) cases the dysplasia was mentioned as mild, moderate and severe, in 1 (2.5%) case grade of dysplasia was not mentioned, in 6 cases (15%) comment on excision was not made and none of the proforma was completely filled
CONCLUSION: There was lack of consistency in reporting colonic polyps in our department. We proposed following recommendations:
Pathologist to adhere to guidelines of NHSBCSP.
To fill NHSBCSP proforma in complete
To encourage clinician to provide site of the lesion

P118

Expression of COX-2, NF-kappa-B-p65, NF-kappa-B-p50 and IKK-alpha in malignant and adjacent normal human colorectal tissue

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COX-2 is selectively over-expressed in colorectal tumours. The mechanism of COX-2 induction in these tumours is not fully understood, although evidence suggests a possible link between NFkappaB and COX-2. We hypothesized an association between COX-2 expression and NFkappaB-p65, NFkappaB-p50 and IKKalpha in both epithelial and stromal cells in human colorectal cancer. Using immunohistochemistry, we measured COX-2, NFkappaB-p65, NFkappaB-p65 NLS (active form), NFkappaB-p50, NFkappaB-p50 NLS (active form) and IKKalpha expression in matched colorectal biopsy samples comprising tumour and adjacent normal tissue from 32 patients. We have shown that all proteins were up-regulated in malignant colorectal epithelial cells. Moreover, stromal cells of malignant and surrounding normal colorectal tissue were found to express COX-2. In all cell types of malignant tissue, as well as in VECs of neighboring normal tissue, COX-2 expression was strongly associated with NFkappaB-p65 expression (Pearson correlation, p=0.019 for macrophages, p=0.001 for VECs, p=0.002 for fibroblasts (malignant tissue), and p=0.011 for VECs (non-malignant tissue)) but not NFkappaB-p50 or IKKalpha, suggesting that in these cells, COX-2 induction may be mediated via activation of the canonical NFkappaB pathway. Finally, the lack of association between COX-2, NFkappaB-p65 or IKKalpha with the clinical severity of colorectal cancer as determined by Duke's stage, suggests that COX-2, NFkappaB-p65 and IKKalpha expression are possibly early post-initiation events, which could be involved in tumour progression.

P119

Colonic biopsies – A tour of duty

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There is a subjective impression that the histological examination of colonic biopsies is of limited value, when those biopsies are taken from patients presenting with weaker clinical signs and no endoscopic abnormalities. In addition there are increasing financial and time pressures on departments to deal efficiently with increasing sample numbers. Could we justify not looking at these small biopsies in this sub-group of patients?

354 consecutive colonic biopsy cases were audited: 251 of these yielded pathological diagnoses; 103 yielded no diagnostic abnormality. Each case comprised between 1 to 6 colonic biopsies (total biopsy number 720). The commonest indication for colonoscopy was change in bowel habit (115 patients), of which most were for diarrhoea. 52 request forms offered no clinical indication for the investigation.

80 sets of biopsies were from macroscopically normal large bowels. 61 of these revealed no diagnostic abnormality, 8 showed (usually mild) melanosis coli, 9 inflammatory changes, 1 non-specific changes and 1 microscopic colitis. Of 37 macroscopically normal cases investigated for diarrhoea alone, 30 provided no pathological diagnosis, 4 showed melanosis coli, 1 inflammatory changes, 1 non-specific changes and 1 microscopic colitis.

Overall, 19/80 (23%) of macroscopically normal large bowels and 7/37 (19%) of macroscopically normal bowels investigated for diarrhoea alone revealed a diagnostic abnormality including melanosis coli. Given these findings, a policy not to examine macroscopically normal endoscopy specimens in this cohort would miss a substantial number of diagnoses, adversely effecting patient management. We conclude that examination of these biopsies is justified.

P120

Gastric heterotopia: a case series and review of the literature

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Heterotopia is a term derived from the Greek for "other place" and refers to the presence of normal mature tissue at foreign sites. Gastric heterotopia is diagnosed when fundic glands with parietal and chief cells as well as pyloric glands are found in any anatomical region other than the stomach. It is reported to have occurred throughout the gastrointestinal tract, however there are only 42 cases of gastric heterotopia of the rectum appearing in the literature since the first case was reported by Ewell and Jackson in 1939. It is thought that heterotopic tissue may occur as a consequence of abnormal regeneration of mucosal cells following trauma, secondary to displacement of normal cells during the fourth week of gestation when the oesophagus and stomach develop or due to irregular differentiation of pluripotential endodermal stem cells. This tissue can exhibit any pathology which occurs in the stomach including colonization with Helicobacter pylori and may be asymptomatic, or can present with intestinal obstruction, ulceration, bleeding, perforation, intussusception, and pain. No cases of malignancy have yet been reported.

We present a review of the literature and a series of cases of gastric heterotopia including the case of gastric heterotopia in the rectum of a 43 year old male who presented with bilateral illiac fossa pain, bloating and diarrhoea. Digital examination and routine blood tests were normal and a barium enema examination showed a constant filling defect. The diagnosis was made on histological analysis of a surgically excised rectal “polyp”.

P121

Quality improvement in reporting colorectal cancer resection specimens

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Good evidence exists that the introduction of the Royal College of Pathologists (RCPath) minimum datasets has improved the information content of reports for colorectal cancer (CRC). The 2nd edition of the RCPath dataset (2007) also addresses the quality of reporting with the provision of minimum standards for key adverse prognostic features.
AIM: The purpose of this study was to assess any improvement in the quality of CRC reporting by comparison with the new minimum dataset.
METHOD: A series of 50 consecutive CRC specimens were selected from the end of 2008 and reviewed retrospectively. These data were then compared with a series of 100 cases from 1999-2000. The specific standards recommended in the RCPath minimum dataset are: Mean number of lymph nodes (12), frequency of serosal involvement (20% colon, 10% rectum) and frequency of extramural vascular invasion (>25%).
RESULTS: The 2008 cases met the required standards: Mean lymph nodes 12.3, serosal involvement 19% overall and extramural vascular invasion 28.5%. The 2000 series however fell below the required rate for lymph node count and extramural vascular invasion. The rate of serosal involvement was higher than expected with one third of cases being positive.
CONCLUSION: It seems unlikely that the number of lymph nodes per resection has increased and therefore the increased node yield, together with the increased rate of extramural vascular invasion, represents a substantial quality improvement.

P122

The novel oncogene CTEN and its role in cancer metastasis

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C-Terminal Tensin like (CTEN), a member of the Tensin gene family, appears to modulate integrin function to control cell motility. This study was designed to clarify the role of CTEN in cancer metastasis. Using quantitative RT–PCR and immunohistochemistry, CTEN is up-regulated in 62% of cell lines and 69% of tumours compared with normal mucosa respectively. Forced expression of Cten in HCT116 and SW480 colorectal cancer cell lines did not affect cell numbers, although it did confer resistance to staurosporine-induced apoptosis ($p<0.005$). Furthermore, Cten induced epithelial–mesenchymal transition in tumour cells accompanied by repression of E-cadherin as well as significant increase in both cell migration (transwell migration and cell wounding assays, $p<0.001$ and $p<0.05$, respectively) and cell invasion (invasion through Matrigel, $p<0.001$). On the other hand, Knockdown of Cten in SW620 colorectal cancer cell line showed a significant reduction in both cell migration ($p<0.001$) and cell invasion ($p<0.001$) in SW620 Cten knocked-down cells compared with transfected scramble control. Western blotting analysis showed that ectopic expression of Cten and its knocked-down were associated with up-regulation and down-regulation of CD24, ILK and E-cadherin respectively. In this study, we have demonstrated, for the first time the link between CTEN and CD24, ILK and E-cadherin indicating that CTEN is an oncogene in colorectal cancer which stimulates EMT, cell migration and invasion and may therefore have a role in tumour progression.

P123

Losses of chromosome 5q and 14q mark a subset of gastric cancers with good clinical outcome

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To improve clinical outcome of gastric cancer patients, most emphasis is on improving therapeutic regimens, including more extensive surgery as well as (neo)adjuvant chemotherapy. The present study set out to identify, based on genome wide DNA copy number profiling, subgroups of patients, who are not likely to benefit from intensified therapy. DNA of 206 gastric cancer patients was isolated and analyzed by genome wide array comparative genomic hybridization. DNA copy number profiles were evaluated and correlated to lymph node status and survival. Frequent (>20%) DNA copy number gains were observed on chromosomes 1p, 6p, 7p, 7q, 8q, 11q, 12q, 13q, 16p, 16q, 17q, 19p, 19q, 20p, 20q, 21q and 22q, and losses on chromosomes 4p, 4q, 6p, 6q, 9p, 13q and 21q. Lymph node negative gastric cancers showed significantly more losses on chromosomes 5q11.2-q35.1, 10q11.23-q21.3 and 14q32.11-q32.33. In addition, losses on 5q11.2-q31.3 and 14q32.11-q32.33 were highly correlated to good clinical outcome, in both lymph node negative and positive gastric cancer patients.
CONCLUSION: By genome wide DNA copy number profiling we have identified a subgroup of gastric cancers, marked by losses on chromosomes 5q11.2-q31.3 and 14q32.11-q32.33 that have an excellent clinical outcome after surgery alone, and patients with these tumours are unlikely to benefit from additional intensified therapies. Possible biological mechanisms might involve loss of heat shock proteins located at these chromosomal regions.

P124

A preliminary audit of the clinical utility of pancreatic fine needle aspirates and bile duct brushings

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BACKGROUND: Since 2005, our hospital has experienced a 78% increase in the number of pancreatic fine needle aspirates (PFNA) and bile duct brushings (BDB) requested. Although the specificity of these tests has never been questioned, their sensitivity varies in different centers.
RESULTS: These are the results of an audit of all the PFNA and BDB carried out between Jan 2007 to March 2009. A total of 150 samples were identified. 23% of PFNA were diagnosed as insufficient, 41% as benign/reactive and 36% as highly suspicious/malignant. 5% of BDB were diagnosed insufficient, 70% as benign/reactive and 25% as highly suspicious/malignant. Cystic lesions of the pancreas accounted for 50 % of the inadequate diagnoses. Only 2 out of the 11 samples obtained from cysts were reported as benign. Upon correlation with histology, the specificity of these tests was 100% - all cytologies reported as malignant were neoplastic on histology. There were 5 false negative PFNAs and 14 false negative BDBs, most likely due to sampling error.
RECOMMENDATIONS: To assess the true sensitivity and specificity of these tests, a multi-disciplinary audit involving input from the radiologists and clinicians needs to be conducted to evaluate the outcome of patients that have not had surgery. The low cellular yield of the content of pancreatic cysts should also be acknowledged.

P125

Neutrophil-to-lymphocyte ratio predicts overall survival and disease recurrence in colorectal cancer

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BACKGROUND AND AIM: The systemic inflammatory response has been shown to predict survival in colorectal cancer (CRC). Neutrophil-to-lymphocyte ratio (NLR) provides a crude measure of the acute inflammatory response. We sought to determine if NLR along with other histopathological factors had a prognostic role in CRC.
METHOD: 401 patients who underwent resection of their CRC between September, 2000 and January, 2004 were identified retrospectively. 43 with perforation/evidence of sepsis were excluded. NLR was calculated from pre-operative full blood count. An NLR >5 was deemed elevated. Other histopathological parameters were collected. Overall and disease-free survival were calculated.
RESULTS: 358 patients with 5 years follow-up were analysed. NLR predicted overall survival and disease recurrence. Other factors that predicted overall survival were age, CRP >10, lymphocytopaenia (lymphocytes <1), Duke's/T-stage, number of positive LNs, and vascular invasion. Factors that predicted recurrence included lymphocytopaenia, Duke's/T-stage, number of positive LNs and vascular invasion.
CONCLUSIONS: Systemic inflammatory response (measured via NLR) seems to predict prognosis. Whether this is due to host or tumour factors has yet to be elucidated. T-lymphocytes in tumour infiltrate have been shown to correspond with good prognosis in CRC. Our results suggest that lymphocytopaenia predicts overall and disease-free survival. Whether this is a reflection of local tumour immune response or the systemic response warrants further investigation. In summary NLR appears to be a simple test that can be used to help indicate prognosis pre-operatively in CRC patients.

P126

Physiological hepatic nuclear vacuolation – how long does it persist?

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Nuclear vacuolation is a distinctive histological feature of non-alcoholic fatty liver disease. It can help distinguish it from alcohol induced liver disease. There are, however, other associations of nuclear vacuolation of which the commonest is childhood. How long this physiological change persists is not known.

To address this question liver biopsies from 872 patients with chronic hepatitis B (a condition known not to be associated with nuclear vacuolation) were studied to assess the frequency of nuclear vacuolation at different ages. All the patients studied had a BMI of less than 25 kg/m2 and an alcohol intake of less than 15 units per week, as well as no other risk factors for liver disease.

The frequency of nuclear vacuolation, in the absence of fatty change, fell from 13% at age 20-24, to 4% in the early 30s and to 0% at age 60-64.

In conclusion, physiological hepatic nuclear vacuolation is common in the 20s and persists into the 30s. This knowledge can help in the assessment of liver biopsies in which nuclear vacuolation is a feature.

P127

Endometrioid adenocarcinoma arising in a background of peri-hepatic and hepatic endometriosis

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Malignant transformation of extra-ovarian endometriotic foci is rare but it has been documented in visceral organs, pleura and umbilicus. Furthermore, hepatic endometriosis is very rare with only 17 cases reported in the literature to date. Endometrioid histological type is the most frequent although endometrial stromal sarcoma arising on a background of liver endometriosis has been reported

We report a 46-year old lady who presented with jaundice and mildly elevated liver function tests. She had a long history of endometriosis and had undergone a hysterectomy with bilateral salpingo-oophorectomy more than 12 years ago. Histology at that time showed adenomyosis and endometriosis but no evidence of malignancy. A CT scan revealed a large exophytic tumour involving the gallbladder and extending to involve segment III of the liver. An initial liver biopsy showed hepatic endometriosis and a biopsy of a gallbladder lymph node showed an endometriod adenocarcinoma.

A right hepatectomy was performed. Histology showed an endometrioid adenocarcinoma confirmed by immunohistochemistry. It involved both the liver and peri-hepatic tissue indicating an origin from either liver and/or peri-hepatic endometriotic foci.

P128

EBV-associated smooth muscle tumour in the liver and synchronous renal oncocytoma in a renal transplant patient

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We describe the unusual synchronous occurrence of an Epstein-Barr virus-associated smooth muscle tumour in the liver and a renal oncocytoma in a 55 year old gentleman post renal transplant. The patient had previously undergone a right nephrectomy for renal cell carcinoma. He developed IgA nephropathy with end stage renal failure and received a renal transplant. On follow-up a mass lesion was detected in his native left kidney and a nodule in segment V of the liver, presumed to be renal cell carcinoma with liver metastasis.

A left nephrectomy and segment V liver resection were performed. The lower pole of the kidney contained a circumscribed, 13mm haemorrhagic tumour. The cut section of the liver revealed a 22mm, well circumscribed, homogenous, grey-white lesion.

Histology from the kidney showed an oncocytoma, simple cysts, multiple papillary adenomata and end-stage renal disease. The liver lesion comprised a moderately cellular spindle cell tumour with strong expression for Smooth muscle actin and H-caldesmon and strong nuclear positivity for Epstein Barr virus by in-situ hybridisation.

Epstein Barr virus associated smooth muscle tumours in the liver are very rare. There is no consistent relationship between their histological features and clinical outcome. They constitute part of the differential diagnosis of spindle cell lesions in the liver in immuno-compromised patients and need to be distinguished from metastatic leiomyosarcoma.

P129

Re-audit of prostatic TRUS biopsies – 'closing the loop'

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INTRODUCTION: Prostatic transrectal ultrasound (TRUS) guided biopsy service at a small district general hopsital, first audited in 2007. Re-audit performed in 2009, in order to "close the loop" of the audit cycle. Between audits, several protocol changes to specimen handling have occurred, including submitting cores into two blocks, colour coded, in-house Racemase and using Racemase and 34BE-12 as cocktail on same slide.
METHODS: All specimens coded as TRUS biopsies, between 01/01/2008 and 30/09/2008, were identified by Telepath computer system.
RESULTS: 178 cases identified in re-audit, up from 161, representing 11% increase in cases. Mean reporting turnaround fell from 6.2 working days (wd) to 5.1 wd; % of cases requiring ICC increased from 9.3% to 19.7%; proportion of ICC cases using Racemase increased from 60% to 86%; Mean turnaround for ICC cases decreased 13.4 to 8.0wd.
In 2007, main omission was not stating length of longest involved core (stated 84% of cancer cases); all other items >95% of cases. By 2009, stating lengths was 99%, but fall in perineural infiltration (99% to 95%), extraprostatic spread (96% to 94%) and PIN (99% to 91%).
CONCLUSIONS: Turnaround has improved despite more ICC and higher workload. All important microscopic items are mentioned in most cases, improvement seen in stating length of longest involved core. Counteracting is small decrease in commenting on perineural/extraprostatic involvement and PIN. Improved turnaround must not be at expense of quality of issued reports.

P130

A case of type III collagen nephropathy

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We present a case report of a 45 year old man with a history of type I diabetes mellitus who presented with intermittent haematuria and heavy proteinuria. The clinical differential diagnosis was IgA nephropathy or diabetic nephropathy. Renal biopsy was performed. Histology showed enlarged glomeruli with thickening of the mesangium and glomerular basement membrane (GBM) with eosinophilic material which was negative for congo red and stained red on EVG. Electron microscopy showed GBM and mesangial deposits of fibres with a periodicity typical of type III collagen. Type III collagen nephropathy is seen in nail patella syndrome but has also been described without skeletal abnormalities. The patient has normal nails and patellae, and pelvic X-ray and ophthalmic screening for other abnormalities seen in nail patella syndrome are normal. There is no family history of nail patella syndrome. He is undergoing further genetic testing but the described mutations in LMX1B shows poor genotype-phenotype correlation.

P131

Penile cancer reporting: the Swansea experience and a study of Royal College of Pathologists dataset reporting

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Resections for penile cancer are an uncommon specimen within most laboratories. Following recommendations from NICE - "Improving Outcomes in Urological Cancers" - specialist penile cancer MDTs were established and the RCPath dataset for reporting penile cancer was published in November 2006. We report on the experience in Swansea, the penile cancer centre for South and Mid Wales, comparing histology reports before and after the dataset was introduced to assess reporting of core data items. 80 penile cancer specimens were reported from 2003-2008 including 53 large penile resections, with increasing frequency. There were 17 cases of CIS and 63 cases of squamous carcinoma. Since the dataset was introduced penile resections are reported almost exclusively by urological pathologists, and reporting of core data items has improved. Macroscopic core items include tumour size, location and distance to margins, the latter being the only item recorded less frequently since the dataset introduction. Microscopic core items include tumour subtype, grade, pT stage, vascular invasion, margin status, lymph node status including extracapsular spread and presence of CIS. Reporting of all microscopic features has improved since the introduction of the dataset, for example the pT stage reporting has improved from 50% cases to 83% cases, and reporting of vascular invasion has improved from 58% cases to 83% cases. Even reporting of non core items such as associated skin lesion eg.BXO has also improved from 63% cases to 81% cases. Anecdotally the urological surgeons prefer reports in a dataset type layout for ease of identifying prognostic indicators.

P132

Outcome for patients whose prostate biopsy was non-diagnostic

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The aim is to establish what was the outcome for patients whose prostate specimen was histologically suspicious of, but not diagnostic of, adenocarcinoma. There are no existing standards on how to manage such cases. It poses a risk of clinical error. We are not aware of the subject being audited before in any UK Pathology Department.

Follow up pathology of 135 patients were analysed. It encompasses a period of 7 years. The diagnosis of malignancy was generally not made as the atypical focus was too small. 71% of patients had the specimen repeated, 41% of them within 3 months and 8% more than 12 months later. 29% did not have any histological follow up. 36% of the repeats had cancer. We looked into the number of repeat samples before final diagnosis was made, the amount of tissue occupied by cancer, perineural and perivascular invasion, grade of adenocarcinoma, radical treatment and usage of LP34. PSA level was rarely measured in these patients.

Historically diagnosis of malignant change within prostate gland was very important as patients were managed whenever possible with radical treatment. With the new NICE guidelines "Prostate Cancer, February 2008", low risk patients with adenocarcinoma are offered active surveillance. Similarly, patients with non-diagnostic specimen should have no more than PSA velocity monitored with possible repeat of the biopsy. Detection of clinically insignificant prostate cancer is an adverse effect of biopsy.

P133

Immunohistochemical expression of cyclin A in testicular biopsies of fertile and infertile men: correlation with the morphometry of seminiferous tubules

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Cyclin A is a member of the cyclin family of proteins, which are required for both the mitotic and meiotic divisions that characterize spermatogenesis in human and other mammalian species. The data about cyclin A expression in various human spermatogenic disorders and its relationship to the morphology of seminiferous tubules is not well clarified. This study aimed to evaluate the immunohistochemical expression of cyclin A in testicular biopsies of different spermatogenic disorders correlating with the morphology of seminiferous tubules using morphometry tools. Immunohistochemical evaluation of cyclin A was carried out on testicular biopsies obtained from 48 infertile males (non obstructive azospermia) and 15 normal subjects together with using semiautomatic morphometric analysis for evaluation of seminiferous tubules. Cyclin A is expressed in 100% of normal and hypospermatogenesis groups and in 80% of maturation arrest group, with complete absence in Sertoli cell only group. In positive cases, cyclin A stained the nuclei of spermatogonia and primary spermatocytes with higher intensity of expression in normal cases compared to infertile group. Cyclin A expression was significantly associated with the different examined morphometric parameters. Cyclin A is involved in both mitosis and meiosis of human spermatogenesis and may have a role in testicular development. Morphometry of human testis is intimately correlated with the testicular histopathology.

P134

An audit of the use of intraoperative frozen sections of ureteric margins during radical cystectomy

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Frozen sections of ureters are routinely performed during radical cystectomy in our hospital.
We reviewed the frozen and paraffin sections of distal ureteric margins from 112 consecutive radical cystectomies performed during 2003-2008. We also reviewed the pre-operative bladder biopsies to identify possible features associated with margin positivity in this group.
229 frozen sections on 217 ureters from 112 patients were reviewed. 38(16.6%) sections from 29 ureters in 23 patients showed abnormalities at the distal margin ranging from low grade dysplasia to invasive carcinoma, including 6(2.6%) from 4 patients with carcinoma in-situ. Sequential resection with frozen section did not result in negative margins in 24(11.1%) ureters. Of these, 6 had carcinoma in-situ at the proximal margin in the final specimen. False-positive and false-negative rates for frozen section compared with subsequent paraffin section were 0.4% and 1.3%. Sensitivity and specificity were 92.5% and 99.5%. In 33 patients, pre-operative bladder biopsy showed carcinoma in-situ; only 6(18.2%) of these had abnormal frozen sections. Pre-operative biopsies from 8 patients showed lymphovascular invasion, but only 1(12.15%) of these had an abnormal frozen section.
In our hands, the sensitivity and specificity of ureteric frozen sections are high. However, given the low incidence of margin positivity, the routine use of frozen section in this context remains controversial. We did not identify any consistent predictive features in the pre-operative biopsies to allow accurate patient stratification.

P135

The weight of the prostate gland is an excellent surrogate for gland volume

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BACKGROUND: It has been suggested that the volume of the prostate gland at radical prostatectomy can be calculated from its three dimensions as the volume of an ellipse using the formula: prostate gland volume = width x height x length x 0.532.
AIM: To evaluate the relationship of prostate gland weight and volume.
MATERIAL AND METHODS: 20 consecutive radical prostatectomy specimens were assessed. After inking the right and left side of the specimen to permit later orientation, the seminal vesicles were transected at the base of the gland. The prostate gland was weighed using an electronic scale and the weight recorded in gms. The gland was then completely immersed in a measuring jar filled with water and the volume of displaced water measured in cc.
RESULTS: A linear regression of prostatic weight (gms) against volume (cc) produced a regression coefficient of $\beta = 0.9151$ indicating that the weight of the prostate gland in gms closely corresponds to the volume of the gland in cc.
CONCLUSION: The weight of the prostate gland is an excellent surrogate for its volume. The specific gravity of the prostate gland is about 1.

P136

Malakoplakia of the prostate gland; a clinical, radiological and histological mimic of prostate cancer. A report of two cases in prostate needle biopsy

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Malakoplakia is relatively more common in the urinary bladder and is rarely encountered in prostate biopsies. We describe 2 cases of malakoplakia in prostate needle biopsies in which the clinical and radiological findings were highly suspicious for locally advanced prostate cancer.

An 86-year-old man with a raised serum PSA of 9.3 ng/ml, malignant feeling prostate on DRE examination and discrete hypoechogenic areas in both prostatic lobes on transrectal ultrasound scanning (TRUS) underwent prostate needle biopsies. The biopsies showed chronic inflammation with sheets of histiocytes and Michaelis-Gutmann bodies. There was no evidence of malignancy. A diagnosis of malakoplakia was made. Subsequently serum PSA fell to 0.5ng/ml and there was no evidence of prostate cancer on clinical follow-up.

A 75-year-old man with a raised serum PSA of 149 ng/ml, clinical stage T3 prostate cancer on DRE examination and bilateral hypoechoic areas on TRUS underwent prostate needle biopsies. The biopsies showed features similar to that in the first case and a diagnosis of malakoplakia was made. Subsequently serum PSA fell to 7ng/ml and there was no evidence of prostate cancer on clinical follow-up.

Prostate cancer can closely resemble histiocytes hence awareness of the possibility of malakoplakia is essential to avoid a catastrophic erroneous diagnosis of high-grade prostate cancer.

P137

Extraprostatic pelvic tumour: a potential pitfall in prostatic needle biopsies

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Most lesions identified on prostate needle biopsies are either of prostatic origin or tumours involving the prostate from adjacent organs such as the urinary bladder or rectum. Rarely extraprostatic tumours may be sampled by prostatic needle biopsy. We present an extraprostatic pelvic leiomyosarcoma that masqueraded as an enlarged prostate gland on digital rectal examination and transrectal ultrasound (TRUS) examination resulting in needle biopsies that were purported to be from the prostate gland.

A 68-year-old gentleman underwent TRUS guided prostatic biopsies to investigate a serum PSA of 7.7ng/ml. On rectal examination he had an extremely large, benign feeling prostate. TRUS showed a markedly enlarged prostate with a homogenous appearance consistent with benign prostatic hyperplasia. All eight biopsies showed paucicellular stroma with scattered enlarged spindle cell nuclei. No prostatic glandular element was present in any of the biopsies. On immunostaining, the spindle cells were positive for smooth muscle markers and c-KIT negative. The differential diagnosis included atypical stromal hyperplasia and a symplastic leiomyoma. Further investigations were recommended.

An MRI scan showed a large mass extending low down into the pelvis, below the prostate and encircling the urethra. An anterior pelvic exenteration was performed and revealed a cellular spindle cell lesion external to the prostate gland with the histological and immunohistochemical features of a low-grade leiomyosarcoma. The prostate gland showed high grade PIN but no invasive malignancy.

This case illustrates the importance of considering the unusual possibility of an extraprostatic lesion when examining prostate needle biopsies.

P138

Intraganglionic benign prostate glands: a potential pitfall in the diagnosis of prostate cancer

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Perineural invasion is an important criterion for the diagnosis of prostatic adenocarcinoma and this phenomenon is believed to represent tumour spread along the path of least resistance. While benign glands may abut and indent nerves, circumferential perineural, intra-neural and intra-ganglionic extension of prostate glands are considered diagnostic of invasive adenocarcinoma. A solitary case of intra-neural benign prostate glands has been reported in the literature. To our knowledge, presence of benign prostate glands within ganglia has not been described. We present a case of a 63-year-old gentleman who underwent radical prostatectomy for prostatic adenocarcinoma diagnosed on trans-rectal ultrasound guided biopsies. The prostatectomy specimen showed an invasive Gleason sum score 4+3=7 prostatic adenocarcinoma. However, in a single section, 3mm from the main tumour, morphologically benign prostatic glands with inconspicuous nucleoli and distinct basal cell layer were identified within an intra-prostatic ganglion. Intraganglionic extension of prostatic glands is not absolutely pathognomonic of prostate cancer. Awareness of this potential pitfall, careful morphological evaluation of glands within ganglia, and judicious use of basal cell marker immunohistochemistry in morphologically difficult cases would prevent a misdiagnosis of malignancy in this uncommon situation.

P139

Vascular invasion as a prognostic determinant in renal tumours: a prospective follow - up of 285 cases of renal cell carcinoma with complete histological examination of the tumour renal sinus interface

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The TNM classification for renal tumours (2002) includes vascular invasion within the T3b category as 'gross tumour extension into the renal vein (including its segmental muscle-containing branches) or inferior vena cava (IVC) or its wall below the diaphragm'. Previous studies from our centre and others have alluded to the prognostic importance of more proximal vascular invasion (microvascular invasion: MVI) in the renal sinus. This category is currently not identified separately within the TNM classification.

We have examined the prognostic significance of MVI in a prospective study. The tumours were dissected using the 'Cardiff protocol' whereby the entire tumour-renal sinus interface is blocked; we have previously reported a consistent increase in identification of vascular invasion using this method. Pathological data was collected prospectively and of 285 cases 63 had MVI, 27 renal vein invasion and 24 IVC invasion. Follow up of up to 8 years gives approximate five year disease specific survival of 90% for cases with no vascular invasion, 80% in cases with MVI only, 65% in cases with renal vein invasion and 45% in cases with IVC invasion using Kaplan-Meier survival analysis plots. Thus, as might be expected, the risk of tumour related death increases with increasing extent of vascular invasion.

We conclude that determining the extent of vascular invasion gives useful prognostic information and this justifies a methodological approach to dissection of the nephrectomy specimen in order to identify all vascular invasion.

P140

Correlation of tumour volume in prostate biopsies with Radical Prostatectomy (RP) specimens: a search for the most accurate morphometric variable

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INTRODUCTION: Histopathological data documented in core biopsies of prostate cancer are critical for further management. They include Gleason score and an assessment of tumour volume. There is no golden rule in reporting the latter, although providing either the linear length of cancer in mm or a percentage estimate of involvement are widely accepted.
AIMS AND OBJECTIVES: This study aims to analyse the various morphometric measurements of tumour volume in core biopsies and to identify which variable is most predictive of the tumour volume in radical prostatectomy (RP) specimens.
METHODS AND MATERIALS: RP specimens from 2003-2008, and their preoperative core biopsies were included. Gleason scores, laterality, and margin involvement were assessed. Different morphometric criteria of core biopsy involvement including the number of cores involved, total percentage of the tumour length (TPTL), mean cancer length (MCL) and greatest percentage, greatest length of cancer were correlated with the total tumour volume at RP.
RESULTS: A total of 40 cases were retrieved, reviewed and morphometric variables determined in each case. Gleason scores correlated in 55% of cases. Out of the numerous variables used, TPTL was the most reliable indicator of tumour volume if involvement was > 5% and the tumour volume was between 1-3 ml. Conclusion: Standardised reporting of core biopsies is required. Although estimation of the TPTL provided a more accurate estimation of the tumour volume in the RP specimens than percentage or length of tumour, other clinical parameters such as serum PSA and Gleason grade remain more reliable.

P141

Pure intertubular pattern classical seminoma: a report of 5 cases

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Intertubular growth pattern of classical seminoma at the periphery of a solid tumour mass presents little diagnostic difficulty. However, when growth pattern is exclusively intertubular, tumour cells can be easily overlooked on macroscopy and histology. Pure intertubular seminomas are rare and only 15 such cases have been reported. We describe the clinicopathological features of 5 cases of exclusively intertubular seminoma.

The patients were aged 29-53 years (mean 34.6). A history of undescended testis was available in 2 cases. One patient presented with testicular swelling and in another the tumour was an incidental finding on ultrasound scanning performed during investigation for infertility. In 3 cases tumour was not suspected pre-operatively.

On macroscopy, the testis was of normal size in 3 cases and atrophic in 2. A 10mm tumour nodule was present in one case; no tumour mass was seen in other cases.

On histology, the tumours were composed of dispersed seminoma cells infiltrating between preserved seminiferous tubules. All 5 cases were associated with intratubular germ cell neoplasia. The background testis was generally atrophic with Leydig cell nodules and in 1 case Sertoli cell nodules. Leydig cell hyperplasia and lymphocytic infiltration tended to obscure the tumour cells.

Meticulous search for intertubular seminoma is particularly warranted in atrophic testis with intratubular germ cell neoplasia associated with interstitial scarring, oedema and chronic inflammation. In difficult cases, immunohistochemistry for PLAP, c-KIT and OCT4 would highlight the tumour cells.

P142

Functional and expression analysis of suppressing ribosomal protein L19 in prostate cancer

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RPL19 mRNA is differentially expressed in benign and malignant prostatic cell lines and tissues. *In-situ* hybridization confirmed it to be a powerful biomarker of prostatic malignancy and as accurate as Gleason score in predicting patient outcome. As part of the ribosomal protein complex, RPL19 modulates the synthesis of cellular proteins, hence contributing to the malignant phenotype. RNAi silencing directed against exon 11 of RPL19 variant "c" inhibited expression of the gene in PC3M prostatic cancer cells. Stable RPL19-silenced transfectants were constructed and cloned. Quantitative PCR of the transfectants confirmed a 70% reduction in expression in the malignant cells to levels at, or below, those of benign prostatic PNT2 cells. Transfected RPL19 cells were less adhesive and invasive than their parental cells. *In-vivo* experiments confirmed that silencing RPL19 reduced tumourgenecity. Transfectant RNA expression was analysed by two-colour Human Genome DNA Expression Microarray (Agilent Technologies) against malignant PC3M cells. GO term enrichment analysis performed separately produced lists of significantly up- and down-regulated genes to identify significant functional terms and potential pathways involved, indicating possible mechanisms of prostate cancer dissemination and metastasis modulated by RPL19.

P143

Basaloid carcinoma of the penis – pathognomic geographic pattern of cytokeratins distinguish this tumour from high grade usual type squamous cell carcinoma

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INTRODUCTION: Basaloid Carcinoma (BC) of the Penis often pursues an aggressive course. It may be difficult distinguish this tumour from high grade Usual Type Squamous Cell Carcinoma (UT) histologically. We describe a unique histopathological profile, which characterises Basaloid Carcinoma.
PATIENTS AND METHODS: Eleven cases of BC were compared with 10 control cases of UT. Follow up data was available for 10 of the BC and all of the UT.
RESULTS: Cytokeratin Immunohistochemistry was helpful in distinguishing the subtypes. In BC there is central staining pattern of the tumour nests with CK14 and peripheral pattern of staining with AE1/AE3, in contrast to the diffuse positivity seen in UT with both cytokeratins. BC has a higher proliferation index (with Ki67) compared with UT.
BC presented with smaller tumour sizes and at a higher tumour stage than UT. There was similar regional nodal involvement and overall tumour associated mortality with 3 deaths in each group. Two of the BC group and one UT case had lung metastases without nodal involvement.
CONCLUSIONS: There was no difference in outcome in BC compared to high grade UT SCC of the penis. However geographic staining patterns with CK14 and AE1/AE3 are useful in diagnosis of BC.

P144

Combined processing of prostate biopsy cores is not an adequate substitute for separate processing

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The diagnosis of prostate cancer is usually based on histological examination of multiple needle biopsies. To avoid missing small cancers it is necessary to ensure that each core is represented throughout its length in a histological section. It is thought that embedding and cutting each core separately obtains the best results. Separate embedding is time-consuming and as a consequence many laboratories embed multiple cores in the same wax block; however it has never been demonstrated that this is an adequate substitute for individual embedding.

We carried out a pilot study in 18 cases by embedding multiple cores (5) in single block after inking to ensure individuals core identification. Great care was taken to ensure flat embedding and 3 levels were cut from each block. The total length of core available for histological examination on the final slide was determined by image analysis. The total length calculated was compared with the length calculated in control cases in which cores had been embedded individually.

The mean length of core examined in the cases with multiple cores embedded was 11.0 mm compared with 14.1 mm in control cases with separate embedding. The difference is highly significant ($p < 0.001$: students t-test). Implying a loss of 22% of the tissue in the combined embedded cores.

We conclude that multiple embedding although saving some technical time is not an adequate substitute for separate embedding of the cores.

P145

Is routine immunohisochemistry for BK Virus justified

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BK virus nephropathy (BKVN) of renal allografts is an important cause of allograft loss. Early recognition of BK virus infection and appropriate management might improve the outcome. Identification of the infection is usually by renal biopsy following an episode of secondary graft dysfunction. Diagnosis is usually on the identification of viral cytopathic effects by conventional light microscopy and confirmation by immunohistochemistry (IHC). Routine IHC for BKV in allograft biopsies taken for secondary dysfunction can identify cases in which cytopathic change on conventional microscopy is not present (morphology negative cases). However it is not clear how common this is and whether it has any clinical significance.

To determine the incidence of morphology negative BKV and it clinical significance we retrospectively carried out IHC for BKV on 137 allograft biopsies taken more than three months post transplant for secondary dysfunction.

Of the 137 biopsies patients 6 were BKV in at least some tubular nuclei; 3 were known BKVN having viral inclusion. The other 3 were classified as morphology negative.

The patients with known BKVN progressed with deterioration of RF despite management of their BKV; the morphology negative BKV cases were originally diagnosed as rejection and/or CAN and showed stable renal function having been managed without knowledge of BKV involvement. None had a subsequent biopsy with BKVN.

Morphology negative BKV has a significant incidence; however it is not clear if knowledge of BKV status in these patients would have improved outcome.

P146

Renal biopsy adequacy

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Renal Biopsies are vital to definitive diagnosis in various settings of renal dysfunction. Guidelines for biopsy adequacy are available: the Banff criteria for allograft biopsies, and European guidelines for native biopsies. We aimed to evaluate and compare renal biopsy adequacy between 2004-8. All biopsies were done by radiologists, using an 18G needle for native kidney, and a 16G needle for allografts.

50 consecutive renal biopsy reports from 2004, 2006 and 2008 were reviewed. Information was gathered regarding light(LM), immunofluoresence(IF) and electron microscopy(EM) samples, including biopsy length, number of glomeruli and arteries on IF and LM samples.

84% of allograft biopsies but only 14% of native biopsies were adequate for both glomeruli and arteries by respective guidelines. Only 17% of native biopsies had adequate glomerular counts alone.

The average number of glomeruli in native vs allograft biopsies was 12 vs. 14. The average length of LM biopsies was 14mm, but sample length correlated poorly with number of glomeruli. 54% IF biopsies contained adequate (>4) glomeruli for assessment, but 17 % contained no glomeruli. 37% of EM biopsies contained no glomeruli.

The adequacy criteria are less stringent for allografts than native biopsies: >6 glomeruli versus 20, respectively. Nevertheless adequacy for native biopsies was poor, suggesting a need to change practice or impracticality of guidelines. Wider gauge needle biopsy (16 vs 18) is an option, although the low correlation between biopsy length and number of glomeruli suggest that failure to fully target cortex may be more important.

P147

Peritoneal stromal endometriosis: a detailed morphological analysis of a large series of cases of a common and under-recognised form of endometriosis

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It is generally considered that a histological diagnosis of endometriosis requires the presence of both endometrioid-type glands and stroma. However, we have noticed in repeated peritoneal biopsies performed for suspected endometriosis, small nodules or plaques of endometrioid-type stroma without glands. These are often, but not always, accompanied by typical endometriosis with glands. This form of endometriosis has been previously referred to as stromal or micronodular stromal endometriosis. In this study, we reviewed a large series (n=274) of peritoneal biopsies with a diagnosis of endometriosis with a view to ascertaining the frequency of stromal endometriosis. We identified stromal endometriosis, characterised histologically by small microscopic nodules or plaques of endometrioid-type stroma, in 44.9% of these biopsies. In 6.6% of biopsies, stromal endometriosis occurred without typical endometriosis. The foci of stromal endometriosis usually had a superficial location just beneath the mesothelial surface. Associated histological features present in some cases included reactive mesothelial proliferation, inflammation, giant cell or granuloma formation, haemosiderin pigment deposition, microcalcification and decidualisation and myxoid change. Stromal endometriosis, usually in the form of superficial nodules or plaques, is a relatively common form of endometriosis which typically occurs in association with typical endometriosis but occasionally on its own. Pathologists should be aware of the existence of this form of endometriosis, the morphological features of which may be subtle. The typical location, intimately associated with surface mesothelium, may suggest that stromal endometriosis derives from mesothelial or submesothelial cells via a metaplastic process.

P148

Breast cancer metastasis in a uterine leiomyoma: case report and review of the literature

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We report the case of a 59 year old female who presented with post-menopausal bleeding. An MRI of the pelvis showed that the uterus contained a 9cm "fibroid" which had a heterogenous appearance with some areas of necrosis. Due to the atypical appearance, a hysterectomy was performed. Macroscopically, there was an intramural "fibroid" which measured 11cm and which had a variegated cut surface with a large cystic area containing necrosis in the centre. Microscopically, the presence of an intramural leiomyoma was confirmed. In addition, within the centre of the leiomyoma was a deposit of poorly differentiated carcinoma with extensive areas of necrosis. Further enquiries revealed that the patient had been treated for carcinoma of the right breast eight years previously and for carcinoma of the left breast two years previously. The histology from these resections was reviewed and immunohistochemistry was performed. It was found that the deposit of carcinoma within the leiomyoma had a similar morphological appearance and immunophenotype to the original right breast carcinoma. The final diagnosis was therefore considered to be metastatic breast carcinoma within an intramural leiomyoma of the uterus. With the exception of metastases to the ovaries, secondary tumours involving the female genital tract are relatively rare. The literature will be reviewed with regards to tumours metastasising to the uterus, specifically within leiomyomata.

P149

Reporting practices of vulval pathology

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BACKGROUND: Vulval specimens are sent to histopathologists from non-surgical and surgical specialties. This audit sets out to demonstrate the range of diagnoses, distribution of specimens to gynaecological pathologists and dermatopathologists, and the origin of specimens.
METHOD: Vulval specimen reports that were reported by gynaecological pathologists and dermatopathologists were collected from 2006, 2007 and 2008. Results show that gynaecological pathologists reported 151 cases, with 17 requiring a dermatopathology second opinion, and dermatopathologists reported 44 cases, with 2 specimens requiring gynaecological pathologist opinion. Most common diagnoses for gynaecological pathologists were epithelial hyperplasia (14%), inflammation (14%) and lichen sclerosus (14%). The most common diagnoses for dermatopathologists were inflammatory dermatoses (29%) and fibroepithelial polyp (18%). Gynaecological pathologists received 94% of vulval specimens from gynaecology specialists (and other surgical disciplines) and 6% from physicians. Dermatopathologists received 50% of their samples from gynaecology specialists (and other surgical disciplines) and 50% from physicians.
CONCLUSION: Knowing the origin of a vulval specimen and who reports it may help with interpretation on reporting practice. The data analysis supports that gynaecology specialists generally favour gynaecological pathologists to report their specimens. The wider range of diagnoses made by gynaecological-pathologists on vulval specimens compared to that of dermatopathologists may reflect referral practice.

P150

Myoepithelial neoplasms involving the vulva and vagina: report of four cases

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We report four myoepitheial neoplasms involving the vulva (2 cases) or vagina (2 cases) in patients aged 40-45. Two tumours were composed entirely of ovoid or spindle shaped cells, one entirely of epitheloid cells and in the other, there was a mixture of spindled and epithelioid cells. Small foci of ductal differentiation with squamous metaplasia were present in one case and a minor stromal component, which varied from myxoid to hyalinized, in all cases. In all cases, the tumour cells were positive with epithelial markers (cytokeratins and/or EMA) and the myoid markers, α smooth muscle actin and calponin. Desmin was positive in three cases. S100 and p63 were positive in one of the four neoplasms. On the basis of the nuclear features and degree of mitotic activity, two neoplasms were classified as benign myoepitheliomas and two as myoepithelial carcinomas. Judging by the paucity of cases in the literature, myoepithelial neoplasms appear extremely rare in the vulvovaginal region with only three previous case reports of primary vulval tumours. As far as we are aware, this is the first description of a primary vaginal myoepithelial neoplasms. At these sites, myoepithelial tumours are liable to be misdiagnosed as a variety of other neoplasms since the pathologist may not think of the diagnosis. In reporting these cases, we discuss the criteria for diagnosis and the differential diagnosis.

P151

Bilateral ectopic adrenocortical tissue in the ovary – an incidental finding

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Adrenocortical rests in the ovary and paraovarian tissue occur relatively infrequently, and a limited number of case reports exist. These lesions are more likely to exist in younger patients, and there is a correlation with congenital adrenal hyperplasia. They may present clinically by undergoing change to a functional lesion, or may be discovered incidentally following oophrectomy for other reasons. Although cases of bilateral testicular adrenocortical rests have been described, there are no detailed accounts of bilateral ovarian adrenocortical rests in the literature.

We describe here a case of bilateral adrenocortical rests in a 65 year old patient, who underwent laparotomy and bilateral salpingo-oophrectomy for suspected ovarian carcinoma. Ectopic adrenocortical tissue was present microscopically in the paraovarian fat of both ovaries, and stained positively for inhibin on immunohistochemistry. Both ovaries and both fallopian tubes also contained papillary serous carcinoma separate from the rests. The rests were not visible on pre-operative CT imaging. The patient did not complain of any virilising symptoms or display any virilising signs, suggesting the lesions were non-functional.

It is important to recognise that adrenocortical rests can be bilateral, and can occur both in the ovary and in the pelvic ligaments. These lesions are often benign, but care should be taken to ensure they are not confused with functional adrenocortical adenomas or malignant steroid cell tumours on microscopy.

P152

The outcome of patients with borderline changes in endocervical cells (BCE)

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Borderline changes in endocervical cells (BCE) pose perhaps the greatest challenge to the cytologist. It is a rare diagnostic category which is not well defined morphologically. Moreover, no statistics on incidence or follow up are available since the national data collection system does not differentiate between borderline changes in squamous and endocervical cells. It is believed that this subgroup is associated with significant histological abnormality. Consequently, in 2004 the NHSCSP altered the management of patients diagnosed with BCE, recommending referral to colposcopy on the first occurrence. In our department, the BCE group is recorded as a subgroup within the borderline category, enabling us to retrieve follow up data.
AIM: To determine whether the cytological diagnosis of BCE is associated with abnormal histology in a significant number of patients.
METHOD: A retrospective data collection over a two year period revealed that 35 out of 104623 (0.03%) patients were diagnosed as BCE. Colposcopic findings, subsequent cytology and histology results were recorded and analysed.
RESULTS: Of the 35 women with BCE, 8 (23%) had subsequent abnormal histology. These were both squamous and/or glandular in type. Of these, 5 (14%) had CIN2 or more or HG CGIN. Reasons for false positive diagnoses included polyps, papillary cervicitis and microglandular hyperplasia.
CONCLUSION: This audit confirms that BCE is associated with significant pathology in 14% and that the recent change in management, recommending referral to colposcopy on the first occurrence, is justified.

P153

Testing the indicators of survival with endometrioid carcinoma of the ovary

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Prognostic indicators of ovarian carcinomas include the age, stage, histological type, grade, tumour rupture and ascites. Patients with endometrioid carcinoma (EC), representing 16-25% of ovarian carcinomas, have better prognosis and 10% - with tumours arising simultaneously in the ovary and uterus - have particularly good sur vival advantage. We have compared the survival data for EC of the ovary from the old and recently published studies. In 1952 Kistner summarised the cases published under a name adenoacanthoma or adenocarcinoma with squamous metaplasia. One of his 5 patients died almost 16 years after the surgery. In 1982 Eifel described a follow-up of 16 treated cases of concurrent uterine/ovarian EC none of which died of this neoplasm. In Zaino's series (1984) deep myometrial invasion indicated poor prognosis of the synchronous EC. Storey's analysis (2008) of 1261 ovarian carcinomas, 21% of which were EC, showed the stage, debulking and age as independent predictors of survival after platinum-based treatment, whilst Kline's study (1990) of 145 patients with EC suggested the histological type was a useful predictor. Our case, age 63, presenting with metastasizing EC, whose simultaneous ovarian/uterine EC remained undiscovered for 5 years despite imaging, survived for 17 years and died of septicaemia, confirms such conclusion. At autopsy fibrosed metastases showed well differentiated squamous component - possibly more reliable indicator of slow progression of this neoplasm, overlooked in retrospective studies.

P154

Prophylactic bilateral salpingo-oophorectomy in women at increased risk of ovarian carcinoma: the experience of a regional gynaecological oncology centre and a reminder of why we do it

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BRCA mutations are associated with an increased risk of ovarian carcinoma. Women with a BRCA mutation or with a strong family history of ovarian carcinoma may therefore be offered prophylactic bilateral salpingo-oophorectomy (BSO).

We have reviewed the pathological features of the 31 prophylactic BSO specimens received in our department over a three and half year period between August 2006 and March 2009.

58% were removed from women with a known BRCA mutation. Of the remainder there was a strong family history of ovarian carcinoma in 16%, and of both ovarian and breast carcinoma in 10%. Furthermore, 48% of these women had a personal history of breast carcinoma. The median age at the time of surgery was 51 years (range 33 to 70 years).

In situ carcinoma (CIS) of serous type was present at the fimbrial end of the fallopian tube in a single case. One case showed focal atypia of the tubal epithelium not amounting to CIS. The remaining tubal specimens (94%) were normal. 100% of the submitted ovaries were normal or showed benign pathology, most commonly cortical inclusion cysts (42%).

CIS of the tubal epithelium, in particular of the fimbrial end, is increasingly accepted as the precursor lesion to ovarian serous carcinoma, as well as tubal carcinoma. Furthermore, malignancies arising at the fimbrial end of the tube have the propensity to disseminate widely, as we illustrate with a case presentation.

P155

Accuracy of reporting atypical complex hyperplasia on endometrial biopsy: an audit

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BACKGROUND: The diagnosis of atypical complex hyperplasia (ACH) is made according to the degree of endometrial architectural and cytological atypia observed by the reporting pathologist. Previous study has shown that only a small proportion of these cases are reported as ACH on subsequent hysterectomy specimen.
AIM: To analyse the correlation between endometrial biopsy and hysterectomy result for ACH and to determine if clinical or pathological features influence reporting.
METHOD: All cases (57) of ACH with a subsequent hysterectomy over a 5-year period were reviewed. The following features were noted: age, menopausal status, endometrial thickness, clinical suspicion, and the presence of architectural and cytological atypia.
RESULTS: In the majority of cases no clinical information was given. Where available, the age ranged from 36-78 years and 68%, 5% and 16% were postmenopausal, peri-menopausal and pre-menopausal respectively. Nineteen percent of cases used the departmental synoptic report. In cases remaining, architectural atypia, cytological atypia, and both features were described in 71%, 5% and 5% of reports respectively. In the hysterectomy specimen, ACH, endometrioid endometrial carcinoma and benign pathology were diagnosed in 35%, 46% and 16% of cases respectively. Of the latter cases, the majority were small pipelle samples.
CONCLUSION: Our study shows a high correlation between ACH on biopsy and in subsequent hysterectomy, in keeping with published literature. The lack of clinical information on request forms may contribute to those discrepant cases along with small sample size. Pathologists should consider asking for a repeat sample more readily in those cases.

P156

A 20 year retrospective analysis of cervical adenocarcinoma in women less than 40 years

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BACKGROUND: Cervical cancer is second most common cancer in women under 35 years. About 2,800 women are diagnosed with cervical cancer in the UK each year. There has been recent discussion about decreasing the age of cervical screening and introduction of HPV vaccines for girls aged 12/13.
AIM: To assess the prevalence and histology of cervical adenocarcinoma in women less than 40 years diagnosed in our institution between 1988 and 2009.
METHOD: Cases of adenocarcinoma were retrieved from the co-path database using the snomed codes. All available pathology reports were reviewed for each patient. The tumour was classified into various histological subtypes, stage, differentiation, lymphovascular invasion and extent of lymph node involvement.
RESULTS: The search revealed a total of 54 cases. The number of women under 25 years were 3(5.5%), between 26-30 years were11 (20.3%) and between 31-40 years were 40(74.2%). 10(18.5%) showed well differentiated tumour, 19(35.2%) moderate differentiation and 15(27.8%) showed poor differentiation. Differentiation was not mentioned in 10(18.5%) cases. The percentage of villoglandular carcinoma was 7.4%, Endometriod 3.7%, Carcinofibroma and clear cell type was 1.9% each. Evidence of lymphovascular invasion was seen in 3 and lymphnode involvement was found in 2 cases.
CONCLUSION: In our analysis we found that cervical adenocarcinoma affects a substantial number of young women with 25.8% under 30 years of age. The HPV vaccine programme will possibly help in decreasing this incidence.

P157

A single institution experience of cervical squamous cell carcinoma in less than 40 year olds over a period of 20 years

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AIM: To study the incidence and associated factors of cervical squamous cell carcinoma (SCC) diagnosed in our institution between 1988 and 2009 in women less than 40 years of age.
METHOD: The cases were retrieved from the co-path database using the SNOMED codes. The histopathology reports were reviewed for each case. The cases were analysed with respect to the age, grade, and lymphovascular invasion.
RESULTS: A total of 68 cases were retrieved. The age range was 23 to 39 years. 4(6%) patients were less than 25 year old.
48 (70%) cases of invasive SCC (NOS), 13 (19%) cases of micro invasive SCC, 6 (9%) cases of invasive large cell non keratinising SCC and 1 (2%) case of SCC with neuroendocrine differentiation were noted. 24 (35%) cases showed poor differentiation, 18 (27%) cases with moderate differentiation, 1 (1.47%) case was well differentiated and in 25 (37%) cases the grade was not mentioned. 39 (57%) cases were associated with CIN3, 1(1.47%) case each of CIN1 and CIN2 were noted. 1(1.47%) case showed associated CIN3, CGIN, and SMILE. Another case showed CIN3 and CGIN. 19 (28%) cases showed lymphovascular invasion. No lymphovascular invasion seen in 21(31%) cases and it was not mentioned in 28 (41%) cases.
CONCLUSION: In our study approximately 6% of patients less than 25 years were diagnosed with cervical SCC. This gives food for thought for decreasing the age of the cervical screening programme.

P158

Investigating the early and late morbility in infants with severe acidosis

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BACKGROUND: A consequence of child hypoxia is pH change in the child's blood. The pH of the blood of the umbilical cord artery (UCA) is probably the most important parameter for the well-being of the infant. Severe acidosis of the newborn is associated with severe child sequelae and disabilities of the child (e.g. cerebral palsy, seizures) that are also an important topic in law court.
DESIGN: In nine years 24.378 births were registered at our University Hospital. In 80 infants (0.33%) an UCA-pH of <7.0 was found. 39 were preterm babies, 34 babies born at term, 5 infants were postterm babies. 21 of these infants died (33% of preterm babies and 21% of babies born at term). An autopsy was performed in all cases.
RESULTS: The most frequent causes of an UCA pH <7 were pathologic cardiotocography (39%), abnormal placentation site (19%), severe prematurity (13%), and dystrophy (10%). Causes of death were mostly prematurity, multiple congenital anomalies, pneumothorax, and sepsis. In 6 infants (10%), who survived, there was severe psycho-motoric impairment. In 29 infants there were no sequelae. In preterm babies with severe acidosis there was an increased early morbidity and mortality. The long-term prognosis of the majority of the babies was surprisingly good.
CONCLUSION: According to our data, the UCA pH – as sole parameter – is probably not an exclusive prognostic factor for all babies. The direct association between UCA pH <7 and psycho-motoric disabilities is under investigation.

P159

Characteristics of histopathological features of placental villi in pregnant women living at high altitude

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AIMS: The placenta is an important functional unit for gas transfer between mother and fetus. The trophoblast layer interposed between maternal and fetal blood plays an active role for the correct functionality of the placenta. It has been suggested that fetal growth retardation (FGR) and an increase of fetal morbidity or mortality rate may occur at high altitude. In this study, we investigated the histopathological features of the placenta in fetuses with FGR born to pregnant women living at high altitude.
METHODS: Twenty placentas from women living at high altitude with fetuses with FGR and twenty placentas from age-matched women not living at high altitude with fetuses with FGR were compared for maturation disorders of the villous tree and abnormalities of vasculogenesis by routine histology and histochemistry.
RESULTS: Subchorionic fibrin deposition and intervillous fibrin deposition were found in both groups, but the incidence of chorangiosis was significantly higher in the case group than that in the control group (11 out 20 vs. 3 out of 20; p=0.0187). There was no evidence of chorangiomas in both groups and the number of syncytial knots was not substantially different in the two groups.
CONCLUSIONS: The incidence of chorangiosis seems to be increased in the placenta of FGR from women living at high altitude. The use of cross-sectional investigations may be needed to confirm this data.

P160

Solid-pseudopapillary tumour of the pancreas (Frantz-Tumour): case report

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AIMS: Solid-pseudopapillary tumours of the pancreas are considered very rarely occurring neoplasms. The occurrence in childhood is also considered special. If the majority of these tumours are actually benign, very few pancreatic malignancies have been reported.
METHODS: A 12 years old female patient was admitted to the hospital because of upper abdominal pain, which was persistent for 3 weeks. Physical examination of the abdomen was unremarkable and routine laboratory parameters were at normal ranges. Abdominal ultrasound showed a well-defined tumor, which was partially cystic and measured 8 cm in the longest diameter. There was no indication of metastases. The tumour was also investigated by computed tomography and magnetic resonance imaging studies. The tumour was diagnosed as solid-pseudopapillary neoplasm of the pancreas. The girl underwent surgery with the aim to perform a radical surgical procedure.
RESULTS: The clinical diagnosis was confirmed by histology and immunohistochemistry. Neither short-term or long-term surgical complications, nor metastases have been recorded in the follow-up (more than five years).
CONCLUSIONS: Solid-pseudopapillary tumours of the pancreas are rare tumours. Diagnosis is based on the fact that these tumours particularly affect young girls and radiological findings show a tumour with solid and cystic parts. The surgical treatment is sufficient and no chemotherapy is usually necessary. tumour enucleation should be carried out with the aim of radical resection, but also preserving the pancreas function.

P161

Quantitative analysis of the sensory and sympathetic innervation of the perinatal human pancreas

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AIMS: To define the peripheral sensory and sympathetic fibers involved in transmitting and modulating pancreatic pain in the perinatal human pancreas.
METHODS: Immunohistochemical detection was used to examine the sensory and sympathetic innervation of the head, body and tail of the normal human fetal pancreas using specimens from 15 fetuses (13-36 weeks of gestation) following intrauterine death or legal interruption of pregnancy. Myelinated sensory fibers were labeled with an antibody raised against neurofilament (NF) and post-ganglionic sympathetic fibers were labeled with an antibody raised against tyrosine hydroxylase (TH). Choline acetylase (ChAT) at cholinergic synapses was labeled with a conventional antibody.
RESULTS: NF. TH, and ChAT immunoreactive fibers were present in parenchyma of the head, body and tail of the pancreas at variable density, but the relative density of both NF and ChAT expressing fibers seemed to be increasing head>body>tail, whereas for TH, a relatively even distribution was observed. In addition to this set of sensory and sympathetic nerve fibers that terminate in the pancreas, there were large bundles of en passant nerve fibers in the dorsal region of the pancreas that were associated with the superior mesenteric plexus.
CONCLUSIONS: These data suggest that the pancreas receives a significant sensory and sympathetic innervation during fetal life. Understanding the factors and disease states that may alter the distribution of nerve structures can be of significance for the development of therapies in pancreatic disorders of child and adulthood.

P162

Postmortem karyotyping in perinatal pathology – a local review

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OBJECTIVE: To assess the success rate of karyotype cultures in terminations of pregnancies for fetal anomalies (TOPs) and intrauterine deaths (IUDs).
METHOD: A random sample of 100 post-mortem records with tissue submitted for karyotyping was reviewed. The karyotype culture rate for TOPs and IUDs was determined, together with the time interval between delivery and sample retrieval.
RESULTS: 33 TOPs (mean: 19 weeks) and 67 IUDs (mean: 28 weeks) were identified. The failure rates within the TOP and IUD groups were 9 (27%) and 42 (63%), respectively. The most frequently cultured tissues directly post-delivery were umbilical cord (37%) and placenta (15%). The most frequent post-mortem tissue was cartilage (24%). In the TOP group, the mean interval in the successful karyotype group was 4 days (range 0-12 days, median 0 days) versus 8.5 days (range 0-21 days, median 8 days) in the failure group. Of 13 TOP cord samples, only one failed. In the IUD group, successful karyotyping was achieved after an interval of 3 days (range 0-14 days, median 0 days) versus 3 days (range 0-11 days, median 0) in the failure group. Aneuploidy was identified in 6% of TOPs and 1.7% of IUDs.
CONCLUSION: The high failure rate for karyotype studies in TOPs relates directly to delayed sampling, Prompt post-delivery cord sampling is thus recommended. Routine sampling in non-anomaly IUDs can detect aneuploidy.

P163

Giant cell tumour and central giant cell reparative granuloma of the skull: do these represent ends of a spectrum? A case report and literature review

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Giant cell tumour (GCT) of bone is an uncommon primary bone neoplasm typically occurring at the epiphyses of long bones in young adults. They are considered to be of low grade malignant potential, with approximate local recurrence rates of 25%, and 2% of patients develop pulmonary metastases. These tumours appear very rarely in the skull, with those few reported cases arising predominantly in the sphenoid and occasionally the temporal bones. They demonstrate benign histological features, but are locally aggressive and surgical excision is the treatment of choice. It is widely believed that giant cell tumours should be distinguished from other giant cell lesions, importantly central giant cell reparative granulomas (CGCG) which are thought to have a lower recurrence rate and for which no cases of malignant transformation or metastases have been reported. Investigators have noted that giant cell lesions in the skull bones may be unique and that GCT and CGCG may be part of a spectrum of a single disease process. We present a case of a giant cell tumour of the temporal bone which illustrates and re-emphasises this concept and review the literature on these lesions.

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Abstract withdrawn

P165

A benign recurrence of a supratentorial pilocytic astrocytoma in an adult

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Pilocytic astrocytoma is a slow growing low grade (World Health Organization Grade1) glioma of childhood and located mainly in the midline structures, the brainstem and the cerebellum. This is different from the other gliomas at histological, biological and molecular level. Pilocytic astrocytoma in supratentorial location is rare in adults. The review of literature contains little data about the pilocytic astrocytomas in adults.
METHODS: A 58 years old female presented with a recurrence of pilocytic astrocytoma of the parietal lobe 25 years after initial removal. Computed tomography showed a well enhanced and circumscribed cystic tumour with a mural nodule. Histology confirmed the same microscopic features as original tumour, WHO Grade I pilocytic astrocytoma.
DISCUSSION: Supratentorial pilocytic astrocytoma in adults are uncommon tumours. They are biologically similar to childhood pilocytic astrocytomas. Currently, there are no certain histological criteria to predict recurrences in these tumours and the extent of surgical resection has prognostic importance. A review of literature summarizes the recurrence of adult pilocytic astrocytomas.

P166

Immunohistochemical profile of ephrin A4 expression in human osteosarcoma

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Ephrin receptors and ephrin ligands constitute one of the largest groups of tyrosine kinases. The division of ephrin receptors into type A or type B is determined by their ligand binding specificities. Ephrin A4 as a ligand has a broad capacity to bind and stimulate different subtypes of ephrin A receptors. Little is known about the role of ephrins generally and ephrin A4 particularly in osteosarcoma. Ephrin A4 was immunohistochemically assessed on archival material from 46 primary osteosarcoma cases, 10 metastatic pulmonary lesions and 20 normal control bone specimens. Ephrin A4 was expressed in 100% of normal bone specimens, in 84.4% of primary osteosarcoma cases and in all metastatic pulmonary lesions. Cytoplasmic and nucleocytoplasmic patterns of ephrin A4 immunoreactivity were observed with the predominance of the latter pattern in normal bone (100%) and in 43.5% of primary osteosarcoma cases, which showed a higher intensity of expression compared to normal bone ($p<0.05$). The cytoplasmic pattern is the only staining pattern seen in metastatic cases, which may suggest its role in enhancement of invasion and metastasis. The differences in the distribution of the two patterns of ephrin A4 may indicate a different biological activity of this molecule depending on its localization. The nuclear localization of ephrin A4 requires further investigation to clarify the mechanism and the significance of the nuclear trafficking of ephrin A4.

P167

Expression of HIF -1α and VEGF in cutaneous and soft tissue smooth muscle tumours

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Hypoxia is established to be a key factor influencing the pathophysiology of malignant growth. Amongst effects, hypoxia modulates the expression of many genes through the induction of hypoxia-inducible transcription factors. HIF-1 is a heterodimer consisting of α and β subunits. HIF-1α expression is related to cellular oxygen status and under hypoxic conditions, the degradation of HIF-1α is suppressed, and its accumulation used as an intrinsic marker of hypoxic response. Neoangiogenesis, driven by a variety of angiogenic factors, plays an essential role during development and progression of malignant tumours. Vascular endothelial growth factor (VEGF) and its receptors are recognised as being central in the angiogenic process during malignancy.
Malignant smooth muscle tumours are high grade, aggressive neoplasms which grow rapidly, with early metastasis and frequent recurrence. Their benign counterparts have limited growth with low recurrence.
To date few studies have examined hypoxia in smooth muscle tumours or related hypoxia and angiogenesis to biologic behaviour, and thus this was the aim of this study .
23 benign and 35 malignant smooth muscle tumours were examined and subjected to HIF -1α and VEGF immunohistochemistry and multispectral image analysis, along with microvessel density assessment. The results show an increased expression of HIF -1α and VEGF in malignant compared to benign tumours, and show that angiogenesis is markedly increased in sarcomas in line with HIF and VEGF expression
The results suggest that leiomyosarcomas show cellular adaption to hypoxic conditions, and these changes are more pronounced than in benign leiomyomas.

P168

Matrix metalloproteinase expression in cutaneous and soft tissue smooth muscle tumours: an immunohistochemical study

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Benign and malignant tumours are differentiated biologically by their ability to become invasive and metastasize by degrading and remodelling extracellular matrix, crossing basement membranes and promoting angiogenensis. Enzymes involved in ECM remodelling include matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). The upregulation of certain MMPs (notably 2 and 9) has been demonstrated in a number of carcinomas and in a lesser number of sarcomas and their use as a biomarker in colorectal tumours is under investigation.
We have used immunohistochemistry and multispectral image analysis to objectively assess the expression of MMPs 1,2 and 9 in a series of 23 leiomyomas and 35 leimyosarcomas diagnosed in our department between 1991 and 2007, to compare the benign and malignant tumours and relate this to a number of histological and clinical parameters including microvessel density, and clinical outcome.
Our results show an at least threefold increased expression of MMP 1, 2 and 9 by malignant compared to benign smooth muscle tumours. Higher grade sarcomas were also associated with greater MMP expression compared to their lower grade counterparts. The leiomyomas expressed similar amounts of TIMP1 to the leiomyosarcomas but less TIMP2. Higher grade malignant tumours also showed a microvessel density of over twice that of the benign group (47 vs 20/HPF).
Our results suggest that in common with other malignant tumours the ability of smooth muscle tumours to become invasive may be related to over expression and increased activity of matrix metalloproteinases involved in the regulation of ECM turnover.

P169

IL-1 regulates cytokine production in the intervertebral disc

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Intervertebral disc degeneration is a major cause of low back pain, and the inflammatory cytokine interleukin 1 (IL-1) has been implicated in its pathogenesis. With increased production of the IL-1 agonists and their receptor IL-1RI during degeneration without any increase in the antagonist. IL-1 has also been shown to result in the increased production of degradation enzymes seen during degeneration and can inhibit the normal synthesis of matrix molecules. However to date, there is little information on the regulation of other cytokines by IL-1 in disc cells.

Bovine nucleus pulposus cells were expanded in monolayer culture for 2 wks prior to transfer to alginate culture for 2 weeks to allow re-differentiation. Alginate cultures were then treated with 0 or 10ng/ml IL-1β for 48hrs and conditioned media collected. Media was then subjected to BioRad Bioplex analysis of a number of cytokines, and concentration calculated using standard curves.

IL-1 stimulation of disc cells resulted in significant increases in a number of catabolic cytokines including: TNFα (214 fold), IL-4 (31 fold), IL-6 (14 fold), IL-8 (6 fold), IL-17 (6 fold), IFNï□§ (41 fold) and VEGF (3 fold) ($P<0.05$).

The increased synthesis of these cytokines following IL-1 stimulation could result in a further increase in matrix degradation, induction of inflammatory cell infiltration and vascular in-growth, all of which contribute to the pathogenic pathways seen in the intervertebral disc during degeneration.

P170

Cannabinoid receptors are expressed in degenerate intervertebral discs: a possible therapeutic target

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Low back pain is a common and debilitating disorder which has significant economic consequences. Intervertebral disc (IVD) degeneration has been implicated as a major cause of this disorder. Interleukin 1 (IL-1) is increased during disc degeneration and results in an increase in degradation enzymes (matrix metalloproteinases (MMP) and ADAMTSs) and a decrease in normal matrix synthesis. In articular cartilage cannabinoids have been shown to inhibit IL-1, and thus the aim of this study was to investigate if cannabinoids could be used to inhibit the IL-1 induced changes seen during disc degeneration.

Polymerase chain reaction (PCR) was used to investigate expression of cannabinoid receptors in cells derived from degenerate human discs. In addition bovine nucleus pulposus cells were treated with IL-1 in the presence of a synthetic cannabinoid agonist (WIN-55(212) and MMP3 gene expression analysed using Quantitative real time PCR.

We demonstrated that human disc cells from degenerate IVDs express both cannabinoid receptor 1 and 2, and so may potentially respond to cannabinoids. In addition WIN-55(212) inhibited the 5 fold increase in MMP 3 gene expression stimulated by IL-1.

This study has demonstrated that human IVD cells express the cannabinoid receptors and that the synthetic cannabinoid (WIN55(212) can inhibit responses induced by IL-1. Together this data is suggestive of a possible therapeutic role for cannabinoids in human IVD degeneration.

P171

An unusual osteochondroma arising from the hamate: a case report

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Osteochondromas arising from the carpal bones are rare. In the carpal bones, osteochondromas usually arise from the scaphoid. We report a case of an unusual single multilobed ostechondroma arising from the hamate which was successfully excised, with no evidence of recurrence.

CASE REPORT: A 14 year boy presented with a slow progressive mass over the dorsal-ulnar aspect of his dominant right wrist for the past three years. He gave no history of trauma. This was the only such mass in the patient and there was no history of similar lesions in the family. Examination revealed a well defined fixed prominent bony hard mass over the dorsal-ulnar aspect of his wrist, which was non tender. In addition to the dorsal-ulnar mass, an ill defined bony hard mass was also palpated over the volar-ulnar aspect of his wrist. He had no ulnar nerve symptoms. Anteroposterior radiographs of the wrist showed a bony lesion in relation to the hamate, triquetrum and pisiform. CT scan showed three bony masses branching out from a single stalk from the hamate, thus giving arise to a single multilobed osteochondroma. The masses were surgically excised. Two masses were covered with smooth cartilage with a bluish tinge and another was covered with creamy coloured glistening cartilage. Histopathological examination confirmed the diagnosis of osteochondromas.

CONCLUSION: Ostechondrmas either arising from the hamate or multilobed osteochondrmas arising from the carpal bones has not been reported in literature and due to its rarity we present this unusual case.

P172

Granuloma annulare-like reaction in a red tattoo

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We describe a case of a 28-year-old female who was referred to our department with an unusual reaction 4 months following a red and black "winged heart" tattoo to her right wrist. Initially she noted several erythematous raised papules, within the red heart of the tattoo which progressed to a confluent raised plaque with a shiny granulomatous surface. At the same time, similar changes were noted confined to the red pigmentation in two smaller older tattoos on her abdomen.

A 4mm punch biopsy taken from the wrist showed classical features of granuloma annulare including palisaded granulomas with necrobiotic centres surrounded by palisaded histiocytes and Langhan's type multinucleate giant cells. The wrist lesion was managed with surgical excision

There is only one previous case report of a Granuloma Annulare-like tattoo reaction in a 7 month old tattoo. Granuloma annulare can result from trauma, drugs and vaccination. It is possible that the reactions may simply be due to the traumatic process of tattooing, however it is limited to red areas within the tattoos and occurred simultaneously in three tattoos of different ages. The dye itself contains mercuric sulphide, ferric hydrate, cadmium suphide and more recently synthetic azo dyes. Further work is needed to identify the specific agents responsible.

This is likely to represent an unusual hypersensitivity reaction to a component of red tattoo dye. It was refractory to conventional treatments and required surgical excision.

P173

Clinicopathological correlation of cutaneous metastases: an analysis of 159 cases

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Cutaneous metastasis is a bad prognostic sign and usually occurs as a late event in a disseminated disease. Occasionally, it may be the presenting sign of an underlying hidden malignancy. They frequently present as solitary skin nodules mimicking primary skin tumours. We reviewed the histological reports of 207 patients coded as skin metastasis. 48 cases were excluded due to miscoding. This resulted in 159 patients (89 females, 70 males) with an average age of 68 years (36 - 94). The commonest primary site of origin was skin (n=36) followed by the gastrointestinal tract (n=30), breast (n=25), urogenital tract (n=11), gynaecological tract (n=9), lung (n=8), nasopharynx (n=4), salivary gland (n=1) and conjunctiva (n=1). Cutaneous metastasis was the first presentation of internal malignancy in 34 cases. The most common sites involved were head and neck (n=43) followed by chest (n=32) and abdomen (n=27). In 6 cases the site of metastasis was not recorded. Fifteen cases presented with multiple cutaneous metastases. The average interval between primary malignancy and cutaneous metastases was 40 months (1 - 192). The majority of metastases were adenocarcinomas (n=86) followed by malignant melanoma (n=33). Most of the metastatic adenocarcinomas originated from the gastrointestinal tract. Immunohistochemical results were available for 18 cases of unknown primary. These were helpful in narrowing the differential diagnosis and the most frequently used antibodies were AE1/3, CK7, CK20, CEA, S100 and TTF-1.

P174

Auricular ossificans associated with a primary cutaneous Merkel cell carcinoma, basal cell carcinoma and actinic keratosis: a case report

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Auricular ossificans (ectopic ossification) is a phenomenon in which normal cartilaginous structures of the ear are replaced by bone, leading to rigidity and petrifaction of the auricle. The aetiology is not entirely understood, although it has been suggested that various injuries, including frostbite, trauma and Addison's disease may trigger the metaplastic process. The condition, which is most commonly seen in relation to severe cold injury, is very rare, with only 14 cases described in the English literature.

We report a case of a 75 year old man who presented with a unilateral ulcerated nodule on his left pinna. It was found, histologically, to be a Merkel cell carcinoma which was confirmed by immunohistochemistry. Further re-excision of his carcinoma revealed a nearby multifocal basal cell carcinoma and patchy actinic keratosis. An unusual finding was the presence of ossification in the underlying cartilage, in close proximity to the Merkel cell carcinoma. In his past medical history, he had been treated with radiation therapy for a brain neoplasm when he was aged 10 years.

To our knowledge, this is the first described case of auricular ossificans in association with primary skin malignancies in the form of Merkel cell carcinoma and basal cell carcinoma.

P175

The differentiation of canine cutaneous round cell tumours

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The accurate diagnosis of poorly differentiated canine cutaneous round cell tumours is challenging due to similar histological features. Immunohistochemistry can be applied to classify these tumour types further. The differentiation of these tumours is important diagnostically due to marked differences in the clinical progression and treatment options. A panel of antibodies were applied (CD3 for T-lymphocytes; CD79a for B-lymphocytes; CD117 for mast cells; lambda light chain for plasma cells; Mac 387 for histiocytes and Melan-A for melanocytes) to formalin-fixed, paraffin-embedded sections of 67 unclassified canine cutaneous round cell tumours and 17 cases with a definitive morphological diagnosis. Of the 67 unclassified cutaneous tumours, 51 received a definitive diagnosis based on the immunohistochemical staining pattern and histological appearance. In 29 of the 67 unclassified cases the original diagnoses matched the revised diagnoses. In these cases the use of immunohistochemistry allowed further tumour differentation and a more specific diagnosis to be achieved. For the 22 remaining cases, the revised diagnosis indicated that the original diagnosis did not include the correct differentials. The Mac 387 antibody selected for the differentiation of histiocytomas did not label Langerhans' cells preferentially and an alternative immunohistochemical marker for histiocytes is needed. The panel of antibodies selected for this study proved useful in the diagnosis of mast cell tumours, plasmacytomas, T and B-cell lymphomas, and melanomas, confirming that immunohistochemical analysis, when used in conjunction with histological appearance can be a helpful diagnostic tool in more accurately classifying poorly differentiated round cell tumours.

P176

The reporting of skin melanomas in Cardiff. Our audit experience over the last 16 years

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The introduction of the minimum datasets for cancers has changed the reporting of skin melanomas. The dataset for malignant melanoma was published in 2002. However in Cardiff a proforma for reporting of melanomas has been used since 1999 which fulfilled the dataset requirements.
Previous audits have shown an increase in turnaround time; in 1992 the turnaround was 5.8 days, in 1994, 7.8 days. In 2005 the turnaround time was between 7 to 9 days for skin cancer specimens, reflecting the increase in melanoma incidence and histopathology workload. Previous audits have also shown an improvement in the quality of the reports.
The NICE guidlelines say that all reports should be generated within 2 weeks. This has been used as the gold standard to compare the reporting times to.
In the most recent audit, 30 cases were selected from 2008 from the database at the University Hospital of Wales, along with all 19 cases of melanoma reported at the University Hospital Llandough in 2008.
The mean turnaround time at UHW is 12.4 days (median 10, range 5-53). At Llandough the mean time is 18 days (median 10, range 3-81).
The majority of outlying cases at both sites were ones which required expert review or further stains.
The proforma is being completed to nearly 100% accuracy in all areas.
This shows that at both sites the mean turnaround time is slightly longer than the target and has increased over time, but the median hits the 2 week guideline.

P177

A case of clear cell Atypical Fibroxanthoma: characterization and diagnostic pitfalls

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Atypical Fibroxanthoma (AFX) is a pleomorphic dermal tumour of probable fibrohistiocytic or myofibroblastic origin which some consider to be a superficial variant of malignant fibrous histiocytoma. It associated with a good prognosis as it has a very low risk of recurrence or metastasis. It most often presents as a solitary nodule in the head and neck region of the elderly, often in the context of sun damaged skin. AFX includes several variants and among the rarest, is the clear cell AFX. We describe a case of clear cell AFX, the tenth in the literature to date, and discuss the diagnostic difficulties posed by a pleomorphic clear cell dermal tumour. Clear cell AFX is a diagnosis of exclusion dependent upon prior consideration of a variety of other lesions which may show similar clear cell change. The differential diagnosis includes clear cell variants of primary skin tumours, such as squamous cell carcinoma, skin adnexal tumours, or melanocytic proliferations but it must also include metastatic lesions with clear cell change. Notably, we describe the remarkable morphological similarity in this case of clear cell AFX to renal cell carcinoma. This finding is in accordance with one other case report of clear cell AFX retrieved from the literature. We emphasise the importance of excluding metastatic clear cell carcinomas when faced with such a dermal lesion and discuss the use of immunohistochemistry to aid in the definitive diagnosis.

P178

Erythema Elevatum Diutimun and Granuloma Faciale – are these separate disease entities or are they part of a pathological spectrum?

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A 76-year old male presented in February 2008 with a one-year history of a 3 x 3cm plaque on his right parietal scalp. This was firm, pruritic, erythematous nodular and had flecks of pigment throughout. It was excised and left to heal by secondary intention. Several months later new asymptomatic lesions appeared at the scar edge, which resembled the original plaque.

Microscopy showed an ill-defined lesion involving the dermis and subcutis. This was composed of spindle cells and collagenous tissue and contained a heavy, mixed inflammatory cell infiltrate with a predominance of neutrophils. There was evidence of a leukocytoclastic vasculitis with associated fibrinoid necrosis. A Grenz zone was absent. Immunohistochemistry highlighted background staining for smooth muscle actin and a proliferation of small vessels throughout the lesion. The spindle cells were negative for CD34 and factor VIII. The patient was treated with Dapsone, and had a good clinical response.

The clinical presentation was that of granuloma faciale (GF), however the histological features were more in keeping with erythema elevatum diutinum (EED). The scalp is an unusual site for EED which usually occurs as multiple lesions on the limbs. The patient responded to Dapsone in a way that would be expected for patients with EED. This case is of a patient with a clinical presentation of GF, but a histological picture of EED, raising the question of whether EED and GF should be considered as the same pathological spectrum of disease.

P179

A case of rare cutaneous presentation of Kikuchi-Fujimoto Disease

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We present a case of a 19 year old Chinese woman who had recently arrived from China, with a clinical history of fever, facial rash and generalised lymphadenopathy. A punch biopsy of the facial lesions showed a superficial and deep perivascular inflammatory infiltrate with interface dermatitis and epidermal basal vacuolar degeneration. The infiltrate comprised histiocytes and lymphocytes with abundant atypical blasts. There was prominent apoptotic debris and epidermal necrosis with no neutrophil polymorphs. Immunohistochemistry highlighted rich predominantly CD8+ T-cell infiltrate with abundant CD68+ histiocytes. The differential diagnosis included cutaneous T-cell lymphoma and systemic lupus erythematosus (SLE). A lymph node excision biopsy was required which showed the classical morphological and immunophenotypic features of Kikuchi-Fujimoto disease (KFD). The serology for SLE was negative. The patient fully recovered after a short course of steroids and was disease free upon 3 month follow up.

We conclude that the cutaneous manifestations of KFD are infrequent, clinically diverse and could be diagnostically misleading. Few cases are described in the literature. The histological features of KFD in the skin are closely reminiscent of the lymph node changes but interface dermatitis and lymphoid atypia can point to a diagnosis of SLE or cutaneous lymphoma. Accurate diagnosis depends on close clinicopathological correlation with simultaneous skin and lymph node biopsies.

P180

Is one transverse section from an excised skin tumour sufficient?

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AIMS: To determine whether a single transverse section from a skin tumour is sufficiently robust in determining Breslow's thickness and the completeness of excision in terms of the deep and lateral resection margins, using malignant melanoma as an example, and a surrogate for non-melanoma skin tumours.
MATERIALS AND METHODS: Sixty cases of malignant melanoma were identified from the hospital histology database. Selection criteria included primary invasive cutaneous melanoma with two or more tissue slices available for analysi; punch biopsies and metastases were excluded.
Two sections of each specimen were analysed by a histopathologist or a senior pathology trainee and two medical students. Breslow's thickness and distance to the deep and both lateral resection margins were measured using a graduated 1: 100 objective micrometer.
RESULTS: The differences in deep and lateral excision margin measurements between each the two sections were strongly significant ($p < 0.0001$ at 95% CI). Analysis of the second section increased the stage of the tumour in 45% of cases, in one case increasing the stage from 1 to 3.
In 10% of cases an involved margin was found in one of the two sections, indicating the need for re-excision.
CONCLUSION: The results of this study indicate that more accurate excision margin measurements and tumour staging will be obtained if more than one section of a skin tumour is examined. We recommend that two or more transverse sections are taken from all malignant skin lesions in order to more accurately define prognosis and future management.

P181

Rare presentation of extracranial meningeal tumours

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Ectopic mengingothelial lesions are extremely rare in the skin and subcutaneous tissues, thought to arise from arachnoid cells misplaced during fetal development along the skull sutures. They are present at birth or occur during childhood. Immunohistochemically, the tumour cells show expression of vimentin and epithelial membrane antigen (EMA), thus closely resembling the staining pattern for meningioma. Clinically, the lesions are well-circumscribed, solitary nodules of uncertain nature.

This study presents two unusual cases of heterotopic meningeal tumours occurring on the scalp of an elderly female of 75 years (case 1) and a baby girl aged 1 years (case 2). Both cases showed a solitary, infiltrative lesion expanding the dermis, unrelated to previous trauma. The lesion in case 1 was composed of nests and cords of a neoplastic proliferation of a single cell tell type staining positive for EMA. The lesion in case 2 was characterized by an admixture of a cellular, EMA positive spindle cell formation surrounding blood vessels and prominent collagen fibres. A macroscopically identified cyst stained positive for glial fibrillary acidic protein (GFAP), thus indicating a glial element. Both cases exhibited mild nuclear pleomorphism. No mitotic activity was noted.

In view of the microscopical findings we concluded that case 1 represented a primary cutaneous meningioma at an unusual age, and case 2 an ectopic meningothelial hamartoma with a cystic glial component. However, the most important factor lies in their distinction from other, more aggressive neoplasms, such as metastatic carcinoma or adnexal tumours.

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MicroRNA 21 expression and its role in cutaneous melanoma

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The relationship between microRNA-21 (miR-21) and PTEN was assessed. Eighty-one clinical melanocytic tumour samples were retrieved. MiR-21 was assessed by Q-PCR and PTEN by immunohistochemistry alongside assessment of NRAS and BRAF mutation status. Congenital naevi and cutaneous melanoma had higher MiR-21 expression than common acquired naevi ($p<0.001$). BRAF and NRAS mutant melanomas showed no significant difference in miR-21 expression. The miR-21 expression in melanomas with low nuclear PTEN was higher than melanomas with high nuclear PTEN ($p=0.043$), but cytoplasmic PTEN showed no effect on miR-21 expression. Thicker and ulcerated melanomas had higher miR-21 expression ($p=0.02$ and 0.024 respectively). Plasma miR-21 in seven metastatic melanoma patients was higher than in five healthy volunteers ($p=0.032$) and there was correlation between miR-21 in the plasma and the corresponding melanoma tumour tissue ($p<0.001$). These results suggest that miR-21 is important but not sufficient for melanomagenesis, and is associated with down-regulation of nuclear PTEN; miR-21 seems to be found in both BRAF and NRAS mutant melanomas, to be associated with important clinical prognostic indicators and can be detected at increased levels in the plasma of patients with metastatic melanoma. This study implicates miR-21 in melanocytic tumourigenesis.

P183

Dermatopathology cut-up at Leicester Royal Infirmary

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OBJECTIVE: To compare blocks taken at cut-up with those recommended by the Departmental Handbook.
METHODS: I observed the cut-up of 124 skin specimens by Consultants, Specialist Registrars and Specialist Trainees. These included punch and incisional biopsies, re-excision of melanomas, and complex specimens requiring orientation. Non-compliance was defined as any deviation from the Departmental Handbook. This was further sub-divided into high risk, low risk and generation of extra laboratory work. High risk was defined as an event directly impacting on diagnosis and included poor orientation of small specimens in which there was no further tissue available for assessment. Low risk events included having to return to a specimen to take extra blocks, thus resulting in delayed diagnosis. Those specimens in which blocks were taken extraneous to the requirements of the Handbook were classed as creating extra work for the laboratory.
RESULTS: Of 124 specimens, 24 were punches, 13 incisional, 57 complex and 12 re-excision of melanoma. 37 specimens (29.8%) were non-compliant with protocol. 2 were high risk (1.6%), 11 low risk (8.8%) and 24 (19.3%) created extra laboratory work.
Given the Department deals with approximately 1000 skin specimens a month, in real terms this would account for 290 being incorrectly processed per month. High risk events could occur in 16 of these cases, low risk in 88 and extra work would be generated in 193 specimens.
CONCLUSION: There was marked variation seen in cut up protocol resulting in significant additional laboratory workload and, in some cases, affecting the diagnostic process.

P184

Mohs Micrographic Surgery – the validity, workload and cost implications of involving the histopathology department?

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INTRODUCTION: There is currently no published literature with regard to the processing and reporting of paraffin sections following Mohs surgery , or the validity of doing so. However the practice of processing paraffin sections remains widespread in many UK pathology departments.
This audit aims to demonstrate with objective evidence that this process is labour intensive, lacks cost effectivity and above all contributes nothing towards patient management. This consideration is important in the modern day world of pathology where so many extra demands are placed upon the workforce within a pathology department .
METHODS: 361 Mohs micrographical surgical cases in one year were reviewed. The margin status's between the dermatologist and the reporting pathologist were compared . Following this the RCPATH workload scores were used as a tool to determine the effort expelled in reporting these specimens, as well as the cost implications for the laboratory.
RESULTS: There was 1 case out of the 361 whereby there was discrepancy regarding margin involvement between the pathologist and dermatologist. The total number of extra paraffin blocks was 1613 at a technical cost of £4100. The workload units per year amounted to 7240 which equated to 91 hours of time per consultant, per year.
DISCUSSION/CONCLUSIONS: If the dermatologists are as good as the pathologists why do the latter need to be involved?
What is the validity of processing the paraffin sections in all Mohs cases?
Can a UK national standard between dermatology and pathology departments be implimented?

Abstracts

Invited Speakers

S1

An introduction to genomic instability and chromosome structure

R Waters[1]
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The stability of our genomes is tightly regulated to prevent excessive mutations which can lead to genetic disease and cancer. However, some mutation must occur, as evolution relies on it. Hence a delicate balance is required.

Each human body is subjected to 1018 DNA damages per day, and unrepaired damage results in mutation. As a result, all organisms have a range of mechanisms to repair such damage to reduce the potential mutational load. These pathways have been highly conserved throughout evolution. They include the reversal of DNA damage, its removal from DNA by excision repair processes, the tolerance of DNA damage during DNA replication and recombination mechanisms. The absolute need for such mechanisms is highlighted by the fact that defects in DNA repair are related to a number of human cancer-prone and immune deficient conditions.

We know a considerable amount about how these pathways operate on damage in naked DNA. However, in humans there is 2 metres of DNA packaged into each cell nucleus; we know far less about how these mechanisms access the packaged genome and whether they can operate equally on different regions of our genome where the packaging varies. Furthermore, to date we have focussed on the extreme effects of DNA repair defects, yet we have little idea as to whether there are lesser variations in capacity amongst the so called "normal" population. These events have implications for molecular diagnostics related to mutational risk assessment and to the efficacy of cancer therapeutics that damage DNA.

S2

Replication of damaged DNA and cancer protection

AR Lehmann[1]
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Although cells have many ways of removing different lesions from their DNA, damage often persists until the cells replicate their DNA. An important pathway by which cells are able to tolerate this unrepaired DNA damage during replication is translesion synthesis (TLS). In this process DNA is synthesized past the damaged bases by specialized DNA polymerases, most of which belong to the Y-family. These polymerases have an open structure which allows them to accommodate damaged DNA bases in their active sites. Deficiency in one of these polymerases, pol eta, is responsible for the variant form of the highly skin cancer-prone disorder xeroderma pigmentosum. Regulation and control of the Y-family polymerases is mediated by important motifs in the C-terminal third of the polymerases. These motifs are required for their correct localisation and for protein-protein interactions. The sliding clamp accessory protein PCNA plays a crucial role in regulating TLS. When the replication fork is blocked, PCNA becomes ubiquitinated. This increases the affinity of Y-family polymerases for PCNA, because they all contain both PCNA-binding and ubiquitin-binding motifs. Localisation of the polymerases in replication factories and interaction with PCNA are complex and highly dynamic processes.

S3

Telomeres, genome stability and human disease

DM Baird[1], M Tankimanova[1], BT Letsolo[1], R Jones[1], R Capper[1], B Britt-Compton[1], J Rowson[1], TT Lin[1], C Fegan[1], C Pepper[1]
[1]*Cardiff University*

Telomeres provide the end-capping function that allows the chromosomal terminus to be distinguished from double-stranded DNA breaks. Telomere erosion acts as a cell division "counter", imposing a proliferative lifespan barrier that must be overcome to allow the progression to malignancy. This tumour suppressive function is paralleled by the ability of dysfunctional telomeres to trigger genomic instability, whereby the loss of the capping function leads to telomere fusion events; the resulting cycles of anaphase-bridging, breakage and fusion result in genomic rearrangements, such as non-reciprocal translocations, that typify early-stage neoplasia. We have developed single-molecule approaches to characterise telomere length and fusion. We have been using these technologies to study in detail the dynamics of telomeres and the mechanisms underlying telomeric instability and fusion.

We have shown that gradual telomere erosion is consistent with the end-replication problem and that this is superimposed by additional mutational mechanisms that create severely truncated telomeres. We have also provided a definition of the length at which telomeres become dysfunctional and undergo fusion, as well as mechanistic insights into the fusion process.

We are now applying our understanding of telomere dynamics gained in vitro, to examine the role that telomere dynamics may play in the progression of neoplastic conditions. Data concerning these aspects of our work will be presented, focusing in particular on chronic lymphocytic leukaemia.

S4

Clinical aspects of human genomic instability syndromes: common cancer predisposition

G Evans[1]
[1]*St Mary's Hospital Manchester*

Inherited predisposition to cancer has been recognised for many years. In particular rare dominantly inherited families have been described caused by genes that often show a syndromic predisposition such as those that cause neurofibromatosis or familial adenomatous polyposis. It was assumed that the apparently more common predisposition to common cancer such as breast/ovarian cancer and Lynch syndrome would also be due to typical tumour suppressor genes. However, discovery of BRCA1 and BRCA2 that cause a high risk of breast and ovarian cancer and the mismatch repair genes that underlie Lynch (Hereditary non Polyposis Colorectal cancer-HNPCC) syndrome has show that these genes are actually DNA repair genes and the mechanism of action is loss of a vital repair pathway that leads to tissue specific accumulation of DNA damage when gene function is lost. The combined frequency of inherited mutations is about 0.5% for the BRCA genes and 0.1% for the MMR genes. They still have their action by loss of the normal copy (recessive at cellular level), but their action in families is shown by a high penetrance tumour predisposition. Intriguingly targeting either DNA damage or disabling another repair pathway is now showing immense promise in tumour therapy for these disorders. Methotrexate is being in trials for MMR deficiency and PARP inhibitors for BRCA deficiency.

S5

Defective biological responses to DNA damage and human disease

E Friedberg[1]
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Humans are endowed with multiple mechanisms for coping with the potentially mutagenic and lethal effects of DNA damage. These protective mechanisms include (i) several distinct DNA repair modes collectively referred to as excision repair, during which various types of genomic insult are physically removed from the genome, (ii) several repair processes collectively referred to as DNA damage reversal that reverse damage, thereby restoring affected nucleotides in DNA to their normal chemistry, (iii) several distinct modes by which arrested DNA replication is relieved without removing or reversing the damage, collectively referred to as DNA damage tolerance. Inherited defects in these biological responses to DNA damage can lead to several hereditary diseases, including xeroderman pigmentosum (XP), thrichothiodystrophy (TTD), Cockayne sydrome (CS) and the combined CS and XP complex. This lecture will briefly review these biological responses to DNA damage and describe the principal features of these diseases.

S6

Lymphoma diagnosis and classification – WHO and beyond

S Dojcinov[1]
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Lymphoma classification developed through frequent changes ultimately resulting in entity based, “REAL” classification in 1994. This new approach relied on recognition of morphological features, immunophenotypes, genetic markers and specific clinical characteristics. This necessitated application of immunocytochemistry, flow cytometry, conventional cytogenetics, interphase FISH and molecular clonality studies in an integrated laboratory setting, together with wider clinicopathological correlation. The subsequent WHO classification, based on the same principles, has recently been updated. Diagnostic criteria are clarified and new entities are introduced highlighting particularly the significance of the clinical presentation (e.g. cutaneous follicular lymphoma, primary diffuse large B-cell lymphoma (DLBCL) of the CNS, primary cutaneous DLBCL of leg type, LBCL arising in HHV8 associated multicentric Castleman disease). New categories are introduced to highlight diagnostic “grey zones” between DLBCL and Burkitt lymphoma and DLBCL and classical Hodgkin lymphoma respectively, rationalising management of these contentious cases. Better understanding of EBV and immunosuppression associated lymphoproliferations resulted in the addition of entities such as EBV positive T-cell lymphoproliferative disorders of childhood and EBV positive DLBCL of the elderly. New entities are still emerging and classification changes will continue with a greater influence of gene expression analysis and requirement for its routine diagnostic application. Further classification changes might be based around common therapeutically relevant cellular pathways, facilitating targeted, entity specific clinical management. To keep pace with the new changes, proactive preparation with appropriate training and timely introduction of new technology is needed. However, “good old” morphology will remain, for still some time, the key to diagnosis.

S7

Airborne mineral particles, properties, deposition patterns in the lung and disease

F Pooley[1]
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The size, shape and density of airborne mineral particles are the properties which will determine their ability to be inhaled and penetrate deeply into the lungs. They also influence the pattern of deposition throughout the respiratory tract but more importantly the lung parenchyma. This presentation will illustrate how mineral particles as different as coal and asbestos can be inhaled ,deposited in the lung and retained to produce deposition patterns which can be related to the aerodynamic size distribution of each dust. The results illustrate how variations in the size of specific mineral particles can alter their potential to cause disease. The health hazard represented by an exposure to a mixed mineral dust can be assessed from a characterisation of the particles it contains. This will enable strategies to be designed for atmospheric dust control purposes and reduce the health effects produced as a result of exposure to airborne mineral particles .

S8

Pathways in colorectal carcinogenesis

M Arends[1]
[1]*University of Cambridge, Pathology Department*

Colorectal carcinogenesis involves transit from normal mucosa via adenomas to carcinomas. Cancer formation is associated with characteristic genetic changes that occur at a relatively high frequency, including mutations to APC (~80%), p53 (40-50%), K-ras (30-50%) and PI3K (15-35%), or deletions of SMAD4/2 on chromosome 18 (~60%), or alterations to the DNA mismatch repair (MMR) genes (~15%), amongst others. Recent large-scale sequencing studies have identified a much larger number of genes that are mutated in colorectal cancer, but at a lower frequency. Mutation of APC (inherited in familial adenomatous polyposis) and/or loss of APC are seen in adenomas and this represents the major pathway of adenoma formation. Progression to carcinoma is often associated with chromosomal instability and acquired genetic and epigenetic alterations. A second pathway involves transition from hyperplastic polyps to serrated adenomas to carcinomas, usually with evidence of microsatellite instability (MSI) due to MMR deficiency. MSI is associated with mutations to repetitive sequences in other genes (e.g. Bax, TGFBRII, etc) and accounts for cancer susceptibility in Lynch (HNPCC) syndrome patients with germline MSH2 or MLH1 mutations. Around 15% sporadic colorectal cancers show MSI mostly due to MLH1 promoter methylation. Overlapping with these two major carcinogenic pathways is the phenomenon of CpG Island Methylator Phenotype (CIMP), whereby promoter methylation transcriptionally silences certain genes (e.g. MLH1, MGMT, CDKN2A/p16, MINT31, etc) and associates with BRAF mutation. The molecular changes in the different carcinogenic pathways often affect a similar range of signalling pathways.

S9

Getting the most from a resection specimen

ID Nagtegaal[1]
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Quality assessment and assurance are important issues in modern health care. For the evaluation of surgical procedures, there are indirect parameters such as complication, recurrence, and survival rates. These parameters are of limited value for the individual surgeon, and there is an obvious need for direct parameters. In addition to the established factors such as circumferential margin involvement and involvement of the distal margin, macroscopic evaluation of colorectal resection specimens has found its place in the pathological workup. The value of the evaluation of the planes of mesorectal resection in rectal cancer specimens has recently been confirmed in a large trial with 1156 patients. When a superior plane of surgery was achieved, local recurrence risks were significantly lower.

Recently, a macroscopic evaluation method for colon cancer has been described. In the single centre study of 400 patients, the plane of surgery was associated with survival, this was especially marked in stage III tumours. These developments have further established the important role of the pathologist in the multidisciplinary evaluation of colorectal cancer patients.

S10

Pathology-guided colorectal cancer treatment

T Maughan[1]
[1]*Cardiff University*

The pathologist plays a central role in management of colorectal cancer by making the diagnosis, identifying background disease states, staging the tumour and identification of molecular features which guide therapy. Identification of background disease gives insight into causation and guides the need for more extensive surgical resection or more intensive surveillance. The mismatch repair phenotype is important as a prognostic marker of survival, a predictive marker of response to 5-FU chemotherapy and a screening tool for HNPCC.

In the earliest T stage tumours the Kikuchi staging system correlates most closely with risk of nodal involvement. Poor risk Stage II disease can be identified from serosal involvement, extramural vascular invasion, perforation through tumour and incomplete excision. The presence of adequate (>12 nodes) nodal harvest is also crucial to be certain that occult nodal involvement has not been overlooked. Microarray signatures to detect poor risk stage II disease from FFPE are not yet in widespread clinical use to select patients for chemotherapy.

The finding that kras mutation identifies patients who gain no benefit from inhibition of EGFR signalling has opened the door to molecular geneticists in colorectal cancer diagnostics. Prediction of response to conventional chemotherapy agents is more difficult. Identification of germline polymorphisms (in UGT1A1) has not been confirmed. The presence of topo-isomerase 1 (the molecular target of irinotecan) has been associated with benefit from both irinotecan and oxaliplatin, while low topo-1 expression showed no significant benefit. The era of molecularly guided therapy in colorectal cancer is just beginning.

S11

DNA methylation in the progression and early detection of colorectal neoplasia

AEK Ibrahim[1]
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Colorectal cancer is the second leading cause of cancer-related deaths in the UK. Its evolution from histologically recognizable pre-invasive lesions to carcinoma is now known to be associated with stepwise changes in gene function, and to involve several pathways and a variety of genetic and epigenetic mechanisms[1-4]. Understanding these events is crucial for the development of better strategies for both treatment and screening.

In the colorectal group at Addenbrooke's hospital, I have mapped DNA methylation changes across the spectrum of pre-invasive and invasive colorectal neoplasia, using both low and high throughput approaches to reproducibly and quantitatively assess DNA methylation at the single CpG dinucleotide level.

CpG methylation of targets identified is shown to be quantitatively cumulative during neoplastic progression from normal mucosa to adenoma to carcinoma and these DNA methylation changes are correlated with changes in expression of the genes examined as well as a DNA methyltransferase. Two of these DNA methylation targets are potential biomarkers and are shown to discriminate normal DNA from neoplastic DNA with 100% sensitivity (95% CI: 93.2-100.0) and 90.5% specificity (95% CI: 69.6-98.8). These findings have implications for and are discussed in the context of bowel cancer screening strategies.

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S12

"So when I am an Accredited Specialist Expert …"

S Dicken[1]
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In 2008, the Department of Health published a consultation document entitled: The Future of the Scientific Workforce.
Modernising Scientific Careers: The Next Steps.

The document reviews the key contribution of science to healthcare; The challenges of modern healthcare; Highlights the for change in the health care science workforce, and details the vision for healthcare science.
Proposals for modernising scientific careers and the benefits for these proposals are described.

This presentation reviews the Modernising Scientific Careers publication. The proposed changes to training and careers are designed to allow employers to optimise the skill mix and effectiveness of their workforce.

The stages of training and career pathways for healthcare science are defined as Healthcare Science Assistants (HCSA;) Healthcare Scientist Practitioners (HCSP) and Healthcare Scientists (HCS).
The MSC publication identifies the educational pathway for healthcare science workers and identifies the educational framework which will accompany its implementation.

There will be development of a BMedSci which will be available for the healthcare science workforce.
These changes have implications on the biomedical science so it is appropriate that the MSC proposal takes notice of the views expressed during consolation.

These issues include concerns regarding lack of clarity about implementation; the need to completely review training pathways especially when well established, successful programmes are already in place, i.e with Biomedical Science. There are also concerns with regard the introduction of a broad based, 2one size fts all" BMedSci degree.

S13

Cancer causing lipids

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We have previously shown that Hodgkin's lymphoma (HL) cells produce two small bioactive lipids, sphingosine-1-phosphate (S1P) and lysophosphatidic acid (LPA). We have also shown that infection with the lymphomagenic Epstein-Barr virus (EBV) is sufficient to increase S1P and LPA levels; an effect that is mediated by at least three latent viral genes through distinct cellular pathways. S1P and LPA are potent mediators of the transformed phenotype in a variety of cancer types and have recently been implicated in the development of several lymphomas and leukaemias. These observations are of interest because monoclonal antibodies directed against S1P and LPA are now being evaluated in mice and non-human primates having been shown to be effective in vitro against several cancer cell types. More recently, we have investigated the expression of several enzyme regulators of these small lipids in primary tissues. Importantly, we have also established the methodology for the demonstration by immunohistochemistry of both S1P and LPA in histological sections. This will enable us to determine for the first time the impact of their detection on clinical outcome and treatment response in malignant lymphomas

S14

Bone marrow trephine biopsies - time for a national technical EQA?

A Ramsay[1]
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Bone marrow trephine biopsies are commonly used for the identification, staging and detection of relapse in haematolymphoid malignancy. The histological findings in these biopsies can be critical to patient care, particularly where there is a dry tap or a haemodilute aspirate. Since trephine biopsies contain bone, soft tissue and haemopoietic elements, the latter having several different components, analysis requires sections with well-preserved morphology that can also be used for immunohistochemical analysis.

Despite the critical nature of such biopsies, there is little consensus on the technical aspects. Fixation can be in 5% formalin or aceto-zinc formalin. Decalcification may use weak organic acids, Gooding and Stewart's decalcification fluid, calcium chelation or even inorganic acids. The tissue can be embedded in paraffin wax or in plastic, sections can be cut at at a variety of thicknesses and different strategies are used for taking levels and sections for immunohistochemistry. Many laboratories are moving to rapid processors or short processing schedules, and on the diagnostic side there is an increasing requirement for both PCR and FISH-based molecular techniques.

The situation seems to be calling out for a national EQA scheme that would operate in a similar manner to the current UK NEQAS schemes for cellular pathology techniques and immunohistochemistry. By collecting data on the methods used in UK laboratories and by independently assessing the results, both for morphology and immunohistochemistry, it should be possible to identify the best practice for the technical aspects of bone marrow trephine biopsies.

S15

Pathology: the patients' champion in bowel cancer

N West[1]
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Large bowel cancer is the third commonest malignancy in the UK with around 35,000 new cases annually and the second commonest cause of cancer-related mortality with 16,000 deaths. Pathologists play a major role in bowel cancer care and provide important quality control feedback to other members of the multidisciplinary team. This has contributed to a marked increase in survival over the last 30 years following subsequent improvements in surgery, radiology, oncology and pathological reporting.

Studies have shown that large differences in outcome exist between different surgeons and different centres suggesting that surgical differences account for a proportion of this effect. Pathologists led the discovery of the importance of the circumferential resection margin and plane of surgery in rectal cancer and have provided important evidence to generate a change in practice.

Pathologists continue to drive further improvements in survival though better reporting, earlier detection, identification of predictive markers and by influencing the type and quality of surgery. The new NHS bowel cancer screening programme is estimated to reduce mortality by 10% through the earlier detection of tumours. The identification of patients with wild type k-ras allows us to select those more likely to respond to anti-EGFR therapy. New evidence generated by our unit demonstrates that changing the way surgeons operate in colonic and low rectal cancer may further improve outcomes by around 10%. These measures could lead to over 3000 extra lives saved per year in the UK and many more if translated around the world.

S16

Muscle histochemistry pilot scheme for EQA

J Vickers[1]
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Muscle biopsies are performed to confirm a clinical diagnosis, distinguish between nerve and muscle disorders, identify a metabolic defect of muscle, diagnose disease of connective tissue and blood vessels, detect inflammation of muscle or rule out muscle disease. With occassional exceptions it is the essential element in the assessment of patients with suspected myopathy. Although the British Neuropathological Society run an EQA scheme for Neuropathologists whose primary aims are both educational and to identify poor performance in interpretive skills by comparison with their peers, departments operate without a specific technical EQA scheme. Following discussion at PATHSOC in 2007, support was given to initiate a pilot scheme in order to ascertain whether or not there was a genuine requirement.

Assessments were based on predetermined criteria against four chosen histochemical techniques which were H&E, GMT, NADH, and COX. Up to 14 centres submitted slides for each assessment. These were assessed by volunteer assessors which included Biomedical Scientists and Neuropathologists.

In conclusion it is obvious that the preparation of muscle biopsies is technically demanding. The pilot scheme emphasised this as marks were deducted for preparation, cryotomy, staining and finishing. Poorly prepared tissue can lead to difficulties in subsequent reporting. The aim of the presentaion is to ascertain a need for an established scheme. It will allow for specialised departments to be confident that the standard and quality of work being produced is equal to that of thier peers and allows regular scrutiny of performance.

S17

Osteoarticular pathology: pilot EQA scheme

J Smith[1]
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Hard-tissue histology (bone and cartilage) poses significant difficulty to the laboratory as blocks selected for microscopy must often be sawn from the gross specimen, and virtually all must be decalcified pre-processing to paraffin wax. Decalcification, usually be exposure to acid, effects the staining properties of the cut section, be the stain tinctorial, empirical or immuno-histochemical.

At the outset the primary question addressed by the six participating labs was whether bone work was sufficiently different to "the rest" to merit its own scheme; on the basis of the processes used to produce sections that are fit for purpose in every way it was agreed that OA work did merit its own scheme.

Four H&Es, two from the participants archive, and two from material supplied from a pool assembled by participants are assessed each run; sections submitted are assessed using the General Scheme criteria, plus an additional microscopical assessment of adequacy of decalcification. Sections are assessed by two persons, one of whom has expertise in OA histology.

Following the first run, agreement was reached as to the nature of the material supplied from pool; each lab would receive two fixed blocks of bone from different specimens, to decalcify, process, section and stain H&E. This change was introduced to eliminate variation in staining occurring as a result of differences in decalcification procedures between participants.

Results of the first run: range 5/10 to 9/10, mean scores varying from 6.50 to 8.00

S18

Lister: Pathologist

R MacSween[1]
[1]*University of Glasgow*

Lister is universally recognised for introducing the concept of antisepsis(asepsis) into surgical practice in the 1860s.He held pathology in high regard and wrote in1857 "We stand in need of the beacon light of correct pathology to steer a safe course amid the various conflicting opinions which assail us".He was an accomplished microscopist, taught by his father who was elected FRS for his contributions to the development of achromatic lenses. During his time as a lecturer in Professor Symes Dept. of Surgery at Edinburgh in the 1850s Lister prepared a series of 'case reports' now archived in the library of the Royal College of Surgeons of England. These contain clinical details and drawings,extended macroscopic descriptions of resected specimens highlighted by superb water colour illustrations and with some cytological details derived from unstained free-hand sections examined by camera lucida.I will demonstrate some of this material which should be of interest to all Society members. These reports show that Lister was a surgical pathologist of distinction and an excellent artist.

S19

Was Homer a pathologist?

R Marshall[1]
[1]*Peninsula Medical School, Royal Cornwall Hospital*

This study looks at descriptions of wounding and death in Homer's Iliad and considers what relevance they have to modern medical practice.

Much scholarship has been expended in assessing how anatomically and pathologically accurate Homer's descriptions are – could a spear thrust to the centre of the forehead dislodge both eyeballs? Could the shaft of a spear lodged in the mediastinum quiver with each beat of the heart? The detail and accuracy of some of Homer's descriptions even led to the suggestion that he was Surgeon-General in the Agamemnon army.

A different reading of the text would ask whether the question of accuracy is relevant. Homer constructed his story within the knowledge and narrative demands of his age. Today, we are not practising pathology that is in some sense 'right' but are bound by our own age's constructs of knowledge. Our students' knowledge of the internal body is one based on books, models and the web. Their knowledge will be of virtual bodies and virtual pathology, probably well-suited to practising medicine that will also be largely virtual.

Where Homer's descriptions seem wrong – the warrior killed by a blow severing the large vessel running from the neck down the centre of the back, for example, - we want to ask 'Surely, he had the opportunity to examine cadavers?' We find ourselves asking the same question today. Perhaps the question will seem as inappropriate in a hundred years time as it is of Homer now.

S20

An international evidence-based clinicopathological classification of IgA nephropathy: the Oxford Classification

ISD Roberts[1], D Cattran[2], HT Cook[3], R Coppo[4], J Feehally[5], S Troyanov[2]
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[3]*Hammersmith Hospital, London,* [4]*University of Turin, Italy,* [5]*University of Leicester*

A new classification for IgA nephropathy has been developed by an international working group. Clinical data were obtained on 206 adults and 59 children with IgA nephropathy, median follow-up 5 years. Patients were from 8 countries on 4 continents; Asia (62), Europe (94), Americas (109). Renal biopsies were scored by multiple renal pathologists for 24 histological variables.

Six reproducible histological lesions were identified. Four predicted renal outcome independent of clinical variables: mesangial hypercellularity, segmental glomerulosclerosis, endocapillary hypercellularity, and tubular atrophy/interstitial fibrosis.

The predictive value of pathology variables on rate of renal function decline was not influenced by age. Endocapillary proliferation (ECP) was the only lesion influenced by immunosuppression; in patients with ECP who received immunosuppression, the rate of renal function decline was -1.5+/-8.3 ml/min/1.73m2/yr, versus -5.4+/-1.1 ml/min/1.73m2/yr in those who did not receive immunosuppression (p=0.006). There was no interaction with ethnicity, other than ECP. The rate of renal function decline associated with ECP in Asian subjects was significantly better compared to Caucasians. However, Asian patients with ECP were more likely to receive immunosuppressive therapy (42% versus 22% in Caucasians, p=0.002).

An approach to reporting biopsies with IgA nephropathy is recommended. The summary line should include a MEST score: mesangial proliferation ≤0.5 (M0), >0.5 (M1); endocapillary hypercellularity absent (E0), present (E1); segmental glomerulosclerosis absent (S0), present (S1); tubular atrophy/interstitial fibrosis <25% (T0), 26-50% (T1), >50% (T2).

S21

When should a renal pathologist order electron microscopy? The evidence

GA Herrera[1]
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The crucial role that electron microscopy plays in renal pathology continues undisputed. By allowing recognition of findings not identifiable under the light microscope, electron microscopy has contributed immensely to the understanding of medical renal diseases and has proven to be of unquestionable diagnostic value. Customarily, a sample is submitted for ultrastructural evaluation in every diagnostic renal biopsy that is performed. The role of electron microscopic evaluation in transplant renal biopsies is still debatable but many have agreed that even in that setting ultrastructure can provide useful information at least in selected situations. The percentage of cases in which electron microscopic evaluation adds important information, that is either key for establishing or confirming a diagnosis or provides additional important data that affects patients' management has remained quite stable over the years, as reported by several authors analyzing large numbers of renal biopsies over a span of 30 years. This figure; however, changes depending on the renal biopsy service that is surveyed. Another important factor that needs to be recognized is that in approximately 10% of the cases, the renal pathologist makes a diagnosis based on light and immunofluorescence data felt to be sound, only to find out later, when the electron microscopic findings become available that the initial impression was totally or partially incorrect, or that additional clinically useful information needs to be added to the initial interpretation.

S22

Application of electron microscopy within drug discovery

A Bigley[1]
[1]*AstraZeneca*

Transmission electron microscopy is employed as an important complementary tool to the light microscope, providing significant data for the pathological assessment of safety in both drug discovery and development.
To further elucidate on changes observed at light microscope level, for example in staining characteristics, such as basophilia or eosinophilia, or morphology, such as vacuolation or hypertrophy, electron microscopy is required to relate these to a target organelle or early toxicological features.

Electron microscopy is valuable in the characterisation of ostensibly minor changes to cell organelles, such as peroxisomes, mitochondria and endoplasmic reticulum when correlated with alterations in metabolic enzymes, where early toxicological effects may be related to drug class and action. Indeed, electron microscopy is employed as the 'gold standard' in the identification of xenobiotic induced phospholipidosis, especially in relation to the evaluation of cationic amphiphilic compounds.

Immuno-electron microscopy may also be employed in the evaluation of tissue antigens, for example, in the validation of safety biomarkers, which is an important adjunct to normal tissue identification and protein localisation by immunohistochemistry.

S23

Advances in clinical electron microscopy, 1963–2000: a personal view

R Griffin[1]
[1]*Ex-University of the West of England, Bristol*

A diagnostic electron microscope (EM) service commenced at Southampton in 1964. The service expanded. Advances critical to the rise of the EM as a diagnostic tool are considered in this presentation. The EM of the 1960's demanded a high level of operator expertise and service support to maintain its optical performance and function. Improvements were made and instruments became easier to use. Specimen preparation became easier and surer.

Crucial to the advancement of EM as a service was the introduction, in 1965, of machines to make glass knives used to cut ultrathin sections. Previously, glass knives were made by hand using hand tools. Knife production was unreliable. In another critical step, glutaraldehyde replaced osmium tetroxide as the primary fixative. Fixatives containing osmium tetroxide are hazardous and require laboratory containment. Ultramicrotomes improved with thermal regulation of section thickness and superior optical equipment. Gradually, resins for embedding improved until consistent results were possible.

Alongside technical improvements were advances in the recognition of the value of EM. Particularly in renal pathology, neuropathology, classification of tumours especially lymphomas and disorders of blood cells and platelets. Negative staining methods made rapid identification of viruses possible. The usefulness of the EM was extended by the techniques of x-ray microanalysis and immunocytochemistry.

Qualifications in Electron Microscopy awarded by the Institute of Biomedical Science have advanced career development for Biomedical Scientists in EM laboratories. Previously, those working in EM laboratories were disadvantaged. Career and promotion prospects for Biomedical Scientists were linked to the large major pathology disciplines .

S24

Diploma of Expert Practice in ultrastructural pathology

P Tarpey[1]
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2008 saw the first submissions for the Diploma of Expert Practice in Ultrastructural Pathology from Biomedical Scientists working in the field of electron microscopy.
Prior to examination, the candidates are required to submit a portfolio The Institute expect that this portfolio "will demonstrate a range of competencies, skills, experience and an overall reflective approach". As a member of the Examining Board for this award I am presenting my views on the required content of submitted portfolios to demonstrate completion of training in ultrastructural pathology. The presentation also has examples of evidence, which I would expect to see, to demonstrate knowledge and skills in the areas of Personal and Professional Development, Education and Training and Management

S25

External quality assurance for diagnostic electron microscopy: the Australian experience

J Stirling[1]
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Diagnostic electron microscopy (EM) is in a difficult phase due to closure of laboratories and staff retirements; monitoring of quality is critical if negative impacts on patient care are to be avoided. RCPA Quality Assurance Programs Pty Ltd (RCPA QAP) undertook an EM pilot survey in 2006, now an internationally accredited (ILAC G13) annual fee-for service program with 20 participants. The program has two sections. The first covers technical-scientific proficiency: specimen preparation, artefact recognition, microscope performance, imaging and micrograph interpretation. Participants submit micrographs, complete a technical questionnaire and identify artefacts. The second tests diagnostic accuracy and is aimed at pathologists; micrographs are provided for diagnostic interpretation.

In 2006, 87% of responses in t he technical-scientific section were 'satisfactory'; results for 2007 were similar. In 2008 the spread of scores was broader with 74% 'satisfactory'. Diagnostic accuracy scores varied (concordance of interpretation with an expected diagnosis): (2006) thin basement membrane nephropathy 79%; (2007) post infectious glomerulonephritis 100% and cryptosporidiosis 95%; (2008) diffuse diabetic glomerulopathy with Kimmelstiel-Wilson nodules 68% and primary ciliary dyskinesia 76%, ~50% of respondents failed to identify the tip and base of a normal cilium.

Results indicate that technical-scientific expertise is declining. Anecdotal evidence suggests this may be because inadequately trained junior staff are being given responsibility for EM laboratories. In respect to diagnostics, 'classic' features are identified, more unusual cases are problematic.

QAP is an essential part of responsible practice with a significant educational role that can improve outputs.

S26

Molecular morphology employing quantifiable internal reference standards

C Taylor[1]
[1]*University of Southern California*

In order fully to realize the potential of immunohistochemistry (IHC) it will be necessary radically to change the mindset of pathologists, from the current practice of regarding IHC as a 'special stain', to accepting it as a tissue based immunoassay, having the characteristics of precision and quantification of an enzyme-linked-immunosorbent assay (ELISA), with which it is analogous. As an essential step to accomplishing this goal it is proposed to develop a system of Quantifiable Internal Reference Standards (QIRS).

An IHC stain, in principle, is identical to an ELISA test performed in the clinical laboratory. It is a curious oversight of pathologists, that principles and reagents used in one environment (serum-ELISA) are universally accepted as providing a quantitative result, but when applied to formalin paraffin tissue sections (IHC), constitute only a qualitative stain, that at best may be subject to a crude semi-quantitative score.

The key difference, comparing IHC and ELISA, is lack of 'proper performance' of the former. The missing elements in IHC, as currently practiced, are lack of control of sample preparation (including fixation), inconsistent validation of reagents and protocols, incomplete automation, non-standardized image analysis, and absence of calibration or reference standards. Of these deficiencies the last is most critical. The proposed development of Quantifiable Internal Reference Standards (QIRS) is described, as providing a viable approach to establishing IHC as a reproducible, quantitative, tissue based immunoassay.

S27

Tissue proteomics: a way forward to quantitative biomarker analysis

KF Becker[1]
[1]*Technical University of Munich, Pathology*

Molecular medicine is currently migrating from genomics to proteomics. Recently, much progress has been made for protein analysis of archival tissues, including formalin fixed and paraffin embedded (FFPE) material. We focused on utility of full length proteins extracted from FFPE tissues for Western blot and reverse phase protein microarray analysis. In a pilot study for applying the new technology, we asked whether the p38-mitogen activated protein kinase (MAPK) and/or the AKT - glycogen synthase kinase-3 (GSK-3beta) pathways are involved in the regulation of the E-cadherin repressor Snail in human endometrial carcinomas.

Proteins were extracted from 17 FFPE primary endometrioid endometrial carcinomas. 25 antibodies were used to precisely quantify signalling end points using protein lysate microarrays spotted onto nitrocellulose-coated glass slides. All antibody specificities were validated by Western blot analysis.
Expression of activated EGFR (epidermal growth factor receptor, Tyr1086) and p38-MAPK (Thr180/Tyr182) correlated with increased levels of Snail protein. These data suggest that EGFR and p38 MAPK activation may be involved in the stabilisation of Snail protein in primary endometrial cancers, possibly resulting in down-regulation of E-cadherin.

Our vision is that monitoring phosphorylated proteins in archival clinical tissues may allow us in the near future to infer the activity levels of proteins in a particular pathway as starting point for the design of individual therapy regimens without changing the routine clinical workflow for tissue analysis.

S28

The Human Tissue Act and research

P Furness[1]
[1]*University Hospitals of Leicester*

The Human Tissue Act 2004 makes it a criminal offence to use human tissue in research, or to store human tissue for research use, unless certain conditions are met. Human tissue is defend as anything containing human cells, but excludes human cells that have proliferated in vitro.
To use human tissue is lawful if 'appropriate consent' for use is available, or if the sample was obtained from a living person, the person from whom the sample came is 'not identifiable' to the researcher and an appropriately constituted research ethics committee has approved its use in research without consent.
Storage for research use is lawful either if a Human Tissue Authority licence for such storage is available or if the sample is being stored as part of an ongoing REC-approved project.
There are special provisions in relation to the analysis of DNA without consent. Remarkably, these do not apply to collections of DNA after extraction from human cells.
Unfortunately, these superficially straightforward statements are complicated by the need to define terms such as 'research', 'appropriate consent', 'not identifiable', 'appropriately constituted research ethics committee' and 'storage'. Questions arise as to whether some preparations contain human cells or not. There are uncertainties around storage that is incidental to acquisition and transportation. These problems will be explored in the light of Human Tissue Authority guidance on the subject.
The law in Scotland is different and will not be addressed, but problems in relation to the import and export of tissues will be considered.

S29

Ethics in research

P Furness[1]
[1]*University Hospitals of Leicester*

This presentation will concentrate exclusively on the ethics of research using human tissue, and mainly on the arguments that are relevant to an REC approving the use of human tissue samples in research where 'appropriate consent' is not available.
The different ethical status of pre-mortem and post-mortem samples will be reviewed.
In relation to pre-mortem samples, an argument will be proposed based on the assumption that tissue removed from the living may be regarded as 'discarded' by the patient once diagnostic procedures are completed. This stance will be justified by the observation of universal NHS practice.
The need for consent will then be analysed not as a method to enhance patient autonomy, but as a basis which can legitimise actions that might otherwise be regarded as causing an insult or injury. On this basis it is possible to construct a logical justification to distinguish situations where the use of human tissue in research does and does not require consent, and to identify situations where consent must be study-specific or may be generic. Arguments will also be considered around the durability of consent, the amount of information that must be given if consent is to be valid and the ethics of removing fresh tissue for research before there has been time for laboratory examination for the benefit of the patient.
These arguments have been accepted by several NRES committees, so it is to be hoped that their inclusion in research ethics applications will facilitate REC approval.

S30

Normal biology and new insights into breast cancer

B Gusterson[1]
[1]*Glasgow University*

Studies of normal development have had enormous impact on our understanding of cancer. The discovery of nerve growth factor by Rita Levi-Montalcini and and epidermal growth factor by Stanley Cohen, led to *in vitro* culturing of skin for burns patients and the blocking of growth factor signalling pathways in targeted treatments of cancer with dugs such as herceptin and gefitinib.

The main development of the breast takes place during puberty, when in the mouse the rate of migration of the epithelium is 1mm/day. Isolated epithelial cells from a virgin adult have the capacity to develop into a complete mammary gland. This post - natal development produces a unique system in which to study the control of morphogenesis, epithelial migration and stem cells. Studies of the normal cell lineages have important implications to current hypotheses on the molecular classification of breast cancer. BRCA1 is important in mammary development where it may act as a regulator of the stem cell compartment, whilst mutations result in a morphology similar to sporadic breast cancers that lack ER/PGR and HER2. This has raised the possibility that some sporadic triple negative cancers may be more responsive to DNA damaging agents and EGFR inhibitors.

Recent data suggests that the normal breast and breast cancers share similar migratory mechanisms to those in brain development. Using both studies of individual molecules, such as reelin and pathways analysis of the pubertal and involuting gland have revealed novel insights into invasion and metastasis.

S31

Prostate cancer: from screening the masses to tailored treatment for the individual

MD Mason[1]
[1]*Cardiff University*

A decade ago, the uncertainties around prostate cancer management stemmed from the knowledge that many men had indolent disease that would not threaten their health, while some men had aggressive disease that was incurable. The roles of screening and of attempted curative treatment were unproven, and opinions were held with disproportionate conviction. The biology of prostate cancer was ill-understood, despite over 50 years' of experience with androgen suppression. Are we any further on today? We now believe that radical surgery may, sometimes, improve survival, but does it need to be performed immediately, or only on disease progression? Recent randomised trials of PSA screening have just been reported; their results are discordant, but current calculations suggest that 48 men must be treated in order to save 1 life. Specific chromosomal aberrations such as the TMPRSS-2/Erg gene fusion may both drive the development of the disease, and also define its behavior. New markers, such as sarcosine could have utility in diagnosis, prognosis, and even as therapeutic targets. Recent clinical data with drugs such as Abiraterone teach us that many men with so-called *hormone-refractory* disease may actually have *hormone super-sensitive* disease. The major challenges in prostate cancer management are to learn how to better target screening and curative treatment to those men who need it, and to develop better treatments for men with advanced disease. Understanding the biology will be a pre-requisite to achieving these goals.

S32

Quality control of the diagnostic process: the pivotal role of histopathology

DF Griffiths[1]
[1]*Cardiff University*

There is no formal prostate cancer screening program in the UK, nevertheless the majority of biopsies and subsequent resections seen by histopathologists are the result of opportunistic or self referred PSA screening. This process should be subject to the same quality control as a planned screening program; histopathology is the source of a number of key variables that can assess the possible effectiveness of screening; and some of these depend on the quality of the histopathological process itself.

The proportion of cancer to benign diagnoses in biopsies (controlled for presentation PSA) is a key indicator. Evidence suggests that if this is below 0.35 it may indicate poor biopsy method or inadequate laboratory processing. Measuring the total length of prostate core examined on the histological slide can assess this. Routine measurement of this could act as a running quality measure to intercept problems before they become apparent as adverse outcomes.

A number of quality measures are available on the examination of radical prostatectomy specimen including nature of resection at posterior fascia, incidence of capsular incisions, the relative proportions of "insignificant' cancers, significant T2 cancers and T3 cancers, and the rate of margin positivity and lymph node metastasis. These are all dependant on consistent processing and can indicate both the quality of surgery and the appropriateness of selection for treatment.

These pathological variables; together with clinical and biochemical covariates can offer a screening program a robust quality management system.

S33

Processing and reporting the radical prostatectomy specimen

L Egevad[1]
[1]*Karolinska University Hospital, Stockholm, Sweden*

The International Society of Urological Pathology (ISUP) organized a Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens in Boston, USA in March 2009 with 116 voting delegates from 23 countries.
The meeting recommended that the prostate should be weighed independent of seminal vesicles and measured in three dimensions. The sagittal cone method should be used both at apex and base. Cases with biopsy diagnosed cancer but no cancer found in the radical prostatectomy specimen should be staged pT0. Substaging of pT2 was controversial and although no specific recommendations were issued, many speakers argued for a revision. Zonal location of index tumour should be reported and also a measure of tumour size (such as volume, diameter or percentage).
Location of extra-prostatic extension (EPE) and margin positivity should be categorized as Posterior, posterolateral, lateral, anterior at either the apex, mid, base. EPE should be quantitated, but there was no consensus on the method.
Bladder neck involvement is best considered pT3a, in line with the upcoming TNM revision. Cancer invasion into the intra-prostatic portion of the seminal vesicles should not be considered seminal vesicle invasion. The diameter of the largest lymph node metastasis is the best outcome predictor for metastatic deposits and should thus be reported. The extent of a positive margin should be given as millimeters of linear involvement.
These recommendations will serve as an important aid for future revisions of staging systems and local guidelines but also emphasize the need of futher studies in some controversial areas.

S34

The histological assessment of the prostate biopsy

M Varma[1]
[1]*University Hospital of Wales, Cardiff*

Recent years have seen an inexorable increase in the number of prostate needle biopsies due to increases in both the number of men undergoing biopsy as well as the number of biopsies performed on each patient. Despite advances in special techniques such as immunohistochemistry, morphology remains the cornerstone of prostate biopsy assessment. Hence, a thorough understanding of the rationale behind prostate biopsy reporting protocols as well as a systematic approach to evaluating prostate needle biopsies is essential.

This presentation will highlight the unique features of prostate needle biopsy interpretation, explaining how it differs from assessment of TURP specimens as well as needle biopsies from other sites such as the breast. A practical approach to reporting prostate biopsies will be outlined with emphasis on the clinical significance of various morphological diagnoses. The nebulous diagnostic category “suspicious for malignancy” will be shown to be heterogeneous with at least three different groups that differ greatly in their clinical significance. The current raging controversy regarding the classification of atypical intraductal proliferations including intraductal carcinoma of the prostate will be addressed. Various malignant mimics of benign prostatic lesions and benign mimics of prostate cancer will be discussed with particular emphasis on newer “entities” such as PIN-like prostate cancer, partial atrophy and diffuse adenosis. A morphology based approach to the use of immmunohistochemistry to establish the diagnosis of prostate cancer will also be described.

S35

Morphological and molecular techniques for identifying the tigers in the cattery: current status and future directions

DM Berney[1]
[1]*Barts and The London School of Medicine*

The prediction of the behaviour of low grade/stage prostate cancer remains challenging. Data can be gathered from retrospective conservatively treated cohort studies and current active-surveillance cohorts. New biomarkers must give information in excess of currently known parameters to improve the prognostic model. Nearly all studies show that Gleason grading remains the most powerful predictor of behaviour. However as a result of immunochemistry for basal cell markers and the ISUP 2005 consensus conference, there have been recent proposed changes to Gleason grading which need to be applied in a consistent fashion.

Further morphological observations may refine our ability to predict disease progression. Evidence based reviews have shown that the presence of peri-neural invasion and cancer extent may give prognostic information. Numerous immunohistochemical markers have shown promise, but only a few have been assessed in pre-treatment biopsies, at the point when therapeutic decisions are made. Ki-67 is the most promising marker at present, which has the advantage of being in widespread use. However translation into clinical use for any immunochemical biomarker is a huge challenge and has to achieve intra-laboratory and intra-observer consistency.
The recently described translocation TMPRSS/ERG may be studied in formalin fixed tissue. Data on the prognostic significance of this translocation is contradictory, and it may be that overall genetic instability is the best molecular marker for outcome.

The use of standardised retrospective cohorts with long outcome data or mature prospective studies with sufficient material for assessment are vital for biomarker development.

S36

The advent and impact of novel prognostic and predictive markers

R Osamura[1]
[1]*Tokai University School of Medicine, Japan*

Prognostication and therapeutic implementation has been emphasized more extensively in recent surgical pathology practice. This lecture focuses on the novel prognostic, predictive and therapeutic markers.
1. Mammalian target of rapamycin (mTOR) & AKT in ovarian and breast cancers
From our studies, p-mTOR was detected in the clear cell carcinoma(CCC) of the ovay with poor prognosis and suggested mTOR-targeted therapy such as everolimus (Miyazawa et al 2009). Noh et al.(2008) suggested that over 50% of breast cancer patients could be potential candidates for rapamycin treatment. Phosphorylation of Akt kinase was significantly higher in triple-negative breast cancers which follow poor prognosis(Umemura et al 2007).
2. MGMT expression in pituitary adenomas
Half of the patients with progressive, regrowing nonfunctioning pituitary adenomas exhibit low 0(6)-methylguanine-DNA methyltransferase (MGMT) expression and are potential candidates for treatment with temozolomide (TMZ) (Widhalm G et al 2009). Immunohistochemically. MGMT has been localized in the pituitary tumor cells(Takei et al.2009).
3. Somatostatin receptor (SSTR) in prostatic cancer SSTR2a is the target for somatostatin analogue(SA) in neuroendocrine carcinomas. Our study (Tang et al.2009) showed expression of SSTR2a in 12% of prostatic cancer which was related with the histological grade (Gleason) and tumor stage. SSTR2a is a prognostic factor and may be the target for SA in prostatic cancer.
It is expected that more prognostic and therapeutic markers will be exerted in diagnostic immunohistochemistry for appropriate patient care.

S37

Atmospheric particles and lung disease

R Maynard[1]

[1]*Health Protection Agency, Didcot*

Until about 1990 many people thought that air pollution as a problem for health was over. This was not the case: it is now accepted that short term and long term exposure to current, rather low, levels of air pollution shorten life expectancy, contribute to the development of atheromatous arterial disease, trigger asthma attacks, cause a reduction in birth weight, impair lung development and increase the number of people admitted to hospital for treatment of both heart and lung disorders. Interestingly the effects on the cardiovascular system seem more serious than those on the lung. Rather surprisingly air pollution does not seem to contribute to the development of asthma: at least this remains uncertain. It is now thought that inhaled particles lead to the generation of free radicals in the lung and that the induced inflammatory response causes a release of cytokines and other mediators that have widespread effects. Changes in heart rhythm, in clotting factors and in weakening of the shoulder region of atheromatous plaques have all been suggested. That such effects could be produced by such small inhaled doses of particles seemed unlikely until the “ultrafine hypothesis” was proposed in 1995. This has led to a surge on interest in effects of particles of less than 100nm aerodynamic diameter and to the science of nano-toxicology.

Presenters' Index

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