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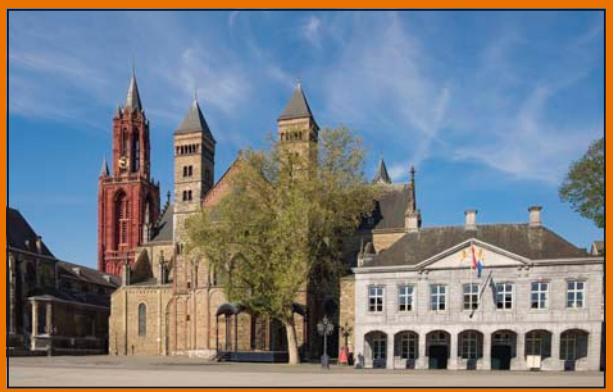

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S1

Impact of Pathology on Breast Cancer Patients

Ⓟ JML Stouthard

Netherlands Cancer Institute, Amsterdam, NL

Breast cancer patients are increasingly interested in shared decision making with regard to their therapeutic options. Furthermore, the impact of the disease is such that most women with breast cancer reconsider important decisions in life. To be able to make these decisions they need to be informed about their prognosis with and without treatment. Although pathologic reports are increasingly clear, consistent and comprehensive, the extent to which they inform individual patients about prognosis and life expectancy is still not very precise. The use of multidimensional tools (such as Predict Online) give some insights in prognosis and benefit of treatment, but focus on the 5-10 years beyond diagnosis. For most women, this time window is not informative enough. During the presentation data of recent publications regarding long term (ie 20 year follow up) outcome for women with hormone sensitive breast cancer will be discussed. Furthermore, new diagnostic information about these long term outcomes will be presented. With these new data, long term prognostication of women with breast cancer can be improved and will add in making individualized decisions about cancer treatment and other important issues in life.

S2

Functional Pathology of ER Positive Breast Cancers

Ⓟ W Zwart

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Purpose of the study: Function studies on Estrogen Receptor (ER) positive breast cancer are typically conducted by the use of cell line models. However, tissue culture conditions are often very different from the actual clinical situation, potentially hampering translational research and preventing the implementation of cell line-based discoveries in the clinical setting.
Methods: Using novel DNA sequencing technologies, functional impact of ER activity can be studied. By implementing chromatin immunoprecipitation followed by massive parallel sequencing, DNA-binding of transcription factors can be studied on a genome-wide scale. We used this technology to determine DNA-binding selectivity of ER in clinical samples, functionally assessing the differential ER-action between patients and cell lines.
Summary of Results: DNA-binding profiles of ER are highly heterogenous between tumours, and many features of ER/DNA binding are shared between tumours and cell lines. Distinct subsets of ER sites had prognostic potential in a cohort of patients treated with aromatase inhibitors in the metastatic setting. Using these DNA-binding profiles, we successfully identified a number of direct-ER-responsive genes that could function as novel drug targets in the metastatic setting.
Conclusions: Many, but not all, key features of ER/DNA interactions are shared between cell lines and human tumours. Using distinct DNA-binding signatures of ER action, novel prognosticators and new drug targets can be identified.

S3

High Quality Breast Pathology of Today and Challenges for Tomorrow

Ⓟ JS Thomas

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Pathology practice has changed substantially in the last 30 years and will continue to do so. These changes have been driven by clinical imperatives, evolving surgical practice, new drugs and breast screening. The latter in particular has driven the quality agenda in breast pathology practice, encouraged true integration of breast pathology services with the effector arms of patient care and has also facilitated the engagement of pathologists in randomised clinical trials and the cutting edge of treatment advances. Where breast services have led other cancer services have tended to follow. Future challenges and opportunities include embracing the full onslaught of digital technology and harnessing its power, grappling with enormous amounts of data from biomarker studies and healthcare systems and giving a rational downstream clinical interpretation. There are exciting opportunities in the field of companion diagnostics with the looming challenge of tumour heterogeneity and its implications.

S4

Limitations of the 2015 WHO Classification of Lung Cancer

Ⓟ E Thunnissen

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The 2015 WHO classification of pulmonary adenocarcinomas contains 6 histologic subtypes, based on two-dimensional (2D) patterns. Interestingly, the artifact of the three-dimensional collapse plays a role in morphology, but is not taken into account in the WHO. Not surprisingly, the 2D described histological criteria did not lead to sufficient worldwide reproducibility, except for very simple straightforward cases, what is unfortunately an infrequent situation in daily practice. In addition, prognostic value of the different subtypes varied widely. Moreover, a difference existed between the judgement of invasion in small adenocarcinomas. In line with these data, measuring invasion in small adenocarcinomas is not performed in a uniform manner. In 2015 a sixth pattern was added in the WHO classification the presence of loose fragments was suddenly assigned with the term “spread though air spaces”. Loose tissue fragments in the lung have been recognized by pathologists for a long time and was by many interpreted as an artifact. However, the first paper adding prognostic relevance to the phenomenon of ‘loose tumour fragments’ was by Onozato et al (2013 PMID 23095504). Since then, several reports supported the concept. In contrast, a recent prospective, multi-institutional study demonstrated the presence of loose tissue fragments in 93% after the knife cuts through the tumour. Large cell neuroendocrine carcinoma (LCNEC) is not defined as one disease. The term LCNEC is actually a diagnostic umbrella term, as tumours from three different lineages appear to fall under this heading: i) overlap cases in morphology between SCLC with slightly more cytoplasm and LCNEC; ii) overlap cases with NSCLC with NE morphology and NE IHC staining and iii) tumours with carcinoid morphology and 11 or more mitoses/ 2mm2. In summary, room for improvement exists in current WHO classification of pulmonary LCNEC and adenocarcinomas due to lack of accurate enough morphological definitions.

S5

Molecular Medicine in Lung Cancer: Insights in Molecular Pathogenesis Driving Better Therapies

Ⓟ RB Büttner

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Traditionally, tumours are classified by histopathological criteria, i.e., based on their specific morphological appearances. Consequently, current therapeutic decisions in oncology are strongly influenced by histology rather than underlying molecular or genomic aberrations. The increase of information on molecular changes however, enabled by the Human Genome Project and the International Cancer Genome Consortium as well as the manifold advances in molecular biology and high-throughput sequencing techniques, inaugurated the integration of genomic information into disease classification. We have therefore introduced multiplex deep sequencing of informative gene sets into routine histopathological diagnostics and molecular pathology. This comprehensive approach integrating morphological and molecular information is currently changing cancer diagnostics in five categories: (1) Somatic genomic or epigenomic alterations acquired during cancerogenesis may be used for disease classification as we show this approach adding important information to conventional morphological classifications. (2) A significant portion of solid tumours depend on oncogenic driver lesions, which provide molecular targets for prediction of effective and selective therapies. (3) Genomic alterations in signal transduction cascades and gene expression pattern may be used as prognostic parameters predicting the need and extent of adjuvant therapy. (4) In the case of multiple syn- or metachronous tumours, genomic profiling assists allocation of metastases from tumours with unknown primary (CUP) and correct staging as multiple small primary tumours and systemic metastases are reliable being discriminated. (5) Finally, mutational profiling of tumour circulating tumour DNA may facilitate monitoring the response of tumours to therapy and development of secondary resistance.

S6

Emerging Biomarkers for Immuno-Oncology in Lung Cancer

Ⓟ KM Kerr

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PD-L1 IHC is by far the most developed biomarker for lung cancer immunotherpay. Each of the five leading PD1 axis inhibitors has been validated in clinical trials with its own PD-L1 IHC assay. Definitions of PD-L1 positivity vary and treatment groups are defined above cutoff values anywhere between 1% and 80% of tumour cells (or in some cases immune cells) expressing PD-L1. The practicalities of providing a clinical PD-L1 testing service are considerable, especially since the test is now regarded as a core, up front test for all patients with advanced stage NSCLC. Efforts to compare different assays show trial validated assays based upon anti-PD-L1 clones 28-8, 22C3 and SP263 appear technically comparable, whilst the SP142 and 73-10 based assays are different. PD-L1 IHC is far from being a perfect biomarker but can improve treatment response rates from around 15% in unselected populations to nearly 50%, at least in some trials. Assessment of tumour inflammation as a biomarker, although not drug-specific, can predict response but there are very few such data in NSCLC. Several trials show mRNA immune gene expression signatures can enrich for response and that this is partially independent of, but no better than, PD-L1 expression. Tumour mutational burden (TMB) has also been used as a biomarker for anti-PD1 axis drugs. There is no consensus on how TMB should be measured and how the treatment group should be defined. Other associated immune-regulatory factors might also be clinically useful but how they should be used is not know, and unproven in trials. It is highly likely that a combination biomarker strategy is more likely to be more effective that testing a single factor, though, for the drugs in question, it seems intuitive that PD-L1 assessment should be part of the equation. This is a rapidly developing field and it is important that practice is driven by evidence. It is also important that the biomarker approaches recommended be both effective and practical.

S7

New Insights in Molecular Pathology of Neuroendocrine Lung Tumours: A Multi-Omics Comparative Analysis

Ⓟ L Fernandez-Cuesta

International Agency for Research on Cancer, Lyon, France

Purpose of the study: Although major advances have been made in the molecular characterization of small-cell lung cancer (SCLC), rare lung neuroendocrine tumours (i.e., large-cell neuroendocrine carcinoma (LCNEC) and pulmonary carcinoids) are still understudied. The purpose of this work was to generate multi-omics data for a series of 20 atypical carcinoids (AC) and compare it with the data we have published for typical carcinoids (TC) and LCNEC. We aimed to (1) characterise at the molecular level the understudied AC, and (2) unravel the molecular mechanisms responsible for the clinical characteristics of this disease in comparison with the other lung neuroendocrine tumours.
Methods: We have performed whole-exome and transcriptome sequencing on 20 AC tumours and matched-normal tissues. Methylation data from 850K Illumina arrays were also generated for these samples, and for 20 TC and 20 LCNEC, which genomes/exomes and transcriptomes had already been characterized.
Summary of results: Our mutational data show that AC present with frequent alterations in chromatin remodelling genes supporting their evolution from TC, but they also have alterations in other cancer-related pathways in agreement with their more aggressive phenotype. Integrative clustering analysis based on RNAseq and methylation data tends to classify carcinoids into four groups, with different clinical and molecular characteristics. When including the LCNEC data, samples from one of the AC groups cluster together with LCNEC, suggesting that AC can display a variety of expression and methylation patterns that may be linked to aggressiveness.
Conclusions: We have identified the molecular pathways that may explain the increase aggressiveness of AC versus TC. Our expression and methylation data supports the existence of a "super-AC" group, which shares molecular characteristics with LCNEC, and that may represent the lung equivalent to the pancreatic grade well-differentiated neuroendocrine tumours.

S8

Hunting for Cancer Cells and Molecules in the Blood

Ⓟ E Schuuring

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Predictive molecular profiling using tumour tissue biopsies or resections to select cancer patients eligible for targeted therapy has become routine practice in diagnostic pathology. However, in many cases tumour tissue sampling is often difficult or tumour biopsies yield insufficient DNA for molecular analysis. In these cases, the analysis of cell-free DNA (cfDNA) derived from plasma has become an alternative method for mutation testing. Plasma-derived cfDNA contains both tumour-derived DNA (ctDNA) and nucleic acids released by normal cells. The mechanism of ctDNA release into the blood is not fully known. The size of ctDNA is on average 160 base pairs due to the specific fragmentation pattern related to apoptosis. To identify rare mutant molecules in a high background of non-mutated cfDNA at range of 0.1%-1%, sufficiently highly sensitive detection methods have to implemented in the Pathology labs. Despite these sensitive methods in ~30% of plasma samples the mutation present in the biopsy cannot be detected. Numerous diagnostic tools for the detection of EGFR, KRAS, NRAS and BRAF mutations in cfDNA are available. The role of cfDNA testing is moving from use in diagnostic research to relevant testing procedures in clinical practice of patients with solid tumours. However, the introduction of this novel methodology into clinical practice can be challenging. The standardization of testing procedures is complex, ranging from plasma collection, transport, processing and storage, cfDNA extraction and ctDNA mutation analysis, to appropriate interpretation and reporting. cfDNA testing is minimally invasive and may be used to monitor tumour progression and response to therapy. Currently, clinical applications of cfDNA are focused on the identification of primary mutations in pretreatment samples and the subsequent detection of resistant mutations upon progression. In the near future, cfDNA testing is expected to significantly change strategies on treatment-decision-making.

S9

National Scale Tumour Whole Genome Sequencing for Personalized Cancer Treatment in the Netherlands

Ⓟ E Cuppen

Hartwig Medical Foundation, Amsterdam, NL

Next-generation DNA sequencing has boosted the promises of personalising cancer treatment. It has now become possible to routinely sequence the complete genome of a tumour from a patient. While patient stratification based on a limited number of genetic measurements is steadily increasing in routine diagnostics, retrospective systematic analyses of genetic information and treatment outcome are still warranted to improve such stratifications, as significant numbers of selected patients for specific treatments are non-responsive, yet may experience severe treatment side effects. In addition, ineffective treatment contributes significantly to the increasing economical burden of novel cancer treatment drugs on health care costs. In 2010, we established the Center for Personalized Cancer Treatment (CPCT) to address this challenge and work towards implementation of DNA-guided therapy into routine care in the Netherlands. In all associated hospitals (currently 47), we have implemented trials to collect fresh-frozen biopsies from tumour metastases before patients start treatment with specific targeted drugs and generate whole genome sequencing data in a centralized sequencing facility based on Illumina Xten. Furthermore, we systematically collect clinical and treatment response data from the treating centres and feed back therapy guidance information, to the treating physician. In collaboration with pharma, we have set up a drug-repurposing study that allows for experimental therapy based on molecular indications (off-label drug use). In this setup, both current and future patients may benefit from comprehensive DNA analyses. Currently, more than 2,500 patients have been analysed by whole genome sequencing (tumour average sequencing depth of 114x, control 38x). All data is made available for research aimed at improving cancer patient care.

S10

From Cytology to Molecular Profiling and the Use of NGS

Ⓟ N D'Haene

Department of Pathology, Erasme Hospital, Brussels, Belgium

In recent years, the management of patients with non-small cell lung cancer (NSCLC) was modified thanks to the development of targeted therapies. The pathologist is now asked to give the most accurate possible diagnosis with associated theranostic information in order to provide the best therapeutic option. Guidelines for NSCLC recommend expanded molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available. This calls for the implementation of methods that probe the mutational status of multiple genes. However, these increased needs are associated with a decrease in sample size. The majority of patients with NSCLC are diagnosed at a late stage and frequently cytology is the only available type of sample. As the numbers of clinically significant genetic variants have increased, clinical testing has evolved, moving from single mutations to multiple hotspot evaluations in multiple cancer genes. The requirements for adopting a test in clinical practice include that (i) the test must be performed on routine samples such as cytological samples, (ii) the test results must be delivered rapidly, and (iii) the test results must be accurate and facilitate clinical decision making. Recently, next generation sequencing (NGS) has begun to supplant other technologies for gene panel sequencing. This technology enables the simultaneous sequencing of millions of short DNA fragments and offers the benefits of lower costs and enhanced sensitivity in mutation detection. In addition to mutations, NGS assays are able to detect fusions/rearrangements and copy number changes in the targeted genes. Moreover, NGS can be performed using DNA from FFPE cell blocks or from smears. Several studies have validated the use of cytological samples for molecular analyses. I will present the clinical applicability of targeted NGS for lung cancer cytological samples.

S11

The Impact of Genetics on Renal Cancer Classification: Revisited

Ⓟ S Fleming

University of Dundee, Dundee, UK

A major paradigm shift in the thinking behind the classification of renal carcinoma occurred in the early 1990's largely prompted by the publication of two papers in the same issue of Histopathology addressing the impact of new genetic data on the classification. The basis was our discovery that the VHL gene was mutated in a large number of renal cancers but only those of the clear cell type whilst other morphological variants exhibited alternative genetic changes. These ideas led to the Heidelberg classification in 1997 in which we proposed that the basis for renal cancer classification should be an understanding of the underlying genetics. Since then we have explored the molecular basis for the remarkably consistent association between genetics and morphology in renal cancer. Discoveries by Ratcliffe demonstrated a role for the VHL protein in oxygen signalling leading us to propose that hypoxia dependent factors drove both the growth and morphology of clear cell cancer. Subsequently we discovered that mutations in genes encoding two members of the Krebs' cycle, fumarate hydratase and succinate dehydrogenase B, resulted in highly specific forms of renal cancer. Whilst there is also a role for cellular hypoxia signalling in the development of these tumours, their morphology differs from that of clear call carcinoma. For these tumour types in we have shown that there is a failure of ATP generation, activation of the AMP dependent kinase and downstream mitochondrial biogenesis, so instead of a clear cell morphology these tumours exhibit numerous giant mitochondria. We have most recently shown that despite the failure to metabolise fumarate and succinate these cell survive and do so by pyruvate carboxylation. This dissection of the genetic and metabolic basis for renal cancer classification, including the latest 2016 WHO Classification, has now led to tumour type specific targeted therapy in which both the diagnostic and experimental pathologist have crucial roles.

S12

Recent Advances in the Biology of Male Breast Cancer

Ⓟ V Speirs

University of Leeds, Leeds, UK

Male breast cancer has been understudied for decades and men who receive a breast cancer diagnosis are treated in exactly the same way as women. This has been based on assumptions that the biology of breast cancer between genders is identical. While this is generally true in terms of histology, transcriptomics studies are starting to identify differences between genders. This has been assisted by the recognition that large numbers of cases are required to move beyond simple observational findings reported from single centres, and is being achieved through international collaborative efforts. I will present an overview of what we have learned about male breast cancer over the last decade and outline how some of these findings may be exploited therapeutically.

S13

Inflammatory Breast Cancer Cells are Characterized by Attenuated SMAD Dependent TGFβ Signalling Leading to Impaired Cell Motility Responses

Ⓟ SJ van Laere

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Inflammatory breast cancer (IBC) is an aggressive form of locally advanced breast cancer with elevated metastatic potential, characterized by the presence of tumour emboli in dermal and parenchymal lymph vessels. In the past, evidence was provided that TGFβ signalling is part of the molecular biology of this disease. To further examine this relationship, TGFβ1 induced cell motility, gene expression and peptide phosphorylation patterns were investigated in a panel of 3 IBC and 3 subtype-matched nIBC cell lines. In addition, a series of tissue samples from 75 and 135 patients with and without IBC was investigated for nuclear expression of total SMAD2, SMAD3 and SMAD4. Finally, SMAD protein expression data were related to gene expression data from patients with available Affymetrix profiles. The cell motility inducing capacity of TGFβ1 was strongly abrogated in all IBC cells (P=0.003). Genes expression profiles post 4 hours of TGFβ1 treatment revealed attenuated expression of SMAD3 transcriptional regulators with concomitant overexpression of MYC target genes in IBC. Assessment of SMAD expression in patient samples demonstrated a near absence of nuclear SMAD3 expression in the primary tumours from patients with IBC (P<0.001) and SMAD3 staining intensity in tumour emboli was even further reduced (P=0.019). A substantial fraction of the IBC signature genes correlated with SMAD3 and these genes (i.e. 21/24; P<0.001) carry evidence in favour of attenuated SMAD3 signalling in IBC patient samples. In conclusion, IBC cells are characterized by attenuated SMAD3 protein expression and transcriptional activity that obliterates the cell motility inducing capacity of TGFβ1. Recent studies revealed that in the absence of SMAD3 expression, epithelial cells acquire a partial EMT phenotype leading to collective invasion which results in a high metastatic potential and favours lymphatic dissemination, thus providing an intriguing explanatory model for the biology of tumour emboli in IBC.

S14

What Should We Do with Tumour Budding in Early CRC?

Ⓟ A Lugli

Institute of Pathology, University of Bern, Bern, Switzerland

Colonoscopy screening programs are leading to increased detection rates of early invasive colorectal cancers (pT1 CRC). Such cancers typically arise from polyps which may be removed endoscopically. Further treatment options include segmental resection or follow-up alone. The probability of nodal metastasis in pT1 CRC is very low (<1%) if no histological risk factors are present, but rises to 35-40% in the presence of multiple risk factors. Therefore, accurate assessment of these factors is essential for the correct identification of at-risk patients while avoiding over-treatment. Tumour budding, defined as the presence of single tumour cells or small clusters of less than five tumour cells at the invasive tumour front is a promising risk factor in pT1 CRC. Indeed, many studies and meta-analyses have demonstrated tumour budding to be significantly and independently associated with lymph node metastases in pT1 CRC (OR range: 4.59 - 7.74). Despite its clinical relevance, tumour budding has not been consistently included in reporting protocols and guidelines, mainly due to the lack of an internationally standardized scoring method. This was the basis for the international tumour budding consensus conference (ITBCC), held in Bern, Switzerland, in 2016. According to the ITBCC statements, tumour budding is an independent predictor of lymph node metastasis in pT1 CRC and should be taken into account along with other clinic-pathological features in a multidisciplinary setting. From a clinical point of view, tumour budding in the scenario of endoscopically removed pT1 CRC is especially relevant and can be used to guide patient management.

S15

Not So Simple Pathology: Issues from the Screening Programme

Ⓟ NA Shepherd

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Colorectal cancer screening is promulgated in many parts of the world and population screening is occurring in many countries, especially Western Europe. The UK, specifically England and Scotland, were the first countries to fully roll out population screening for colorectal cancer. Although, intuitively, it might be thought that the pathology deriving from screening should be straightforward, being mainly that of polyp diagnosis and the biopsy diagnosis and staging of established adenocarcinoma, experience has shown that there are several areas of considerable difficulty and controversy. Particular diagnostic quandaries have been four-fold. Firstly the biopsy diagnosis of adenocarcinoma has generated issues, especially relating to the insistence, certainly in the UK, that a diagnosis of cancer can only be made if submucosal involvement is demonstrated. Serrated pathology has caused many terminological and diagnostic debates and is increasingly seen in screening cases. Standardisation of terminology is advocated in a recent publication of the UK position on serrated pathology terminology. The diagnosis and management of polyp cancers causes major consternation. When to demand a resection after a polyp cancer endoscopic procedure is a subject full of controversy and discussion of the management within a multidisciplinary team-based management meeting is regarded as essential in the UK. Larger adenomatous polyps of the sigmoid colon with epithelial misplacement are selected into FOB-based screening programmes, because they are likely to bleed, and these have provided extraordinary diagnostic challenges. The difficulties have necessitated the establishment of an 'Expert Board' in the UK to deal with these difficult cases. Finally, the quality assurance procedures introduced for screening can ensure a considerable overall improvement in the quality and clinical usefulness of lower gastrointestinal tract pathological reporting.

S16

Implementation of a Nation Wide Strategy for MSI Testing: Challenges and Results

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Background: To improve Lynch syndrome (LS) recognition in the Netherlands, the age-limit for reflex mismatch repair deficiency / microsatellite instability (dMMR / MSI) testing in colorectal cancer (CRC) by the pathologist was raised from 50 to 70 years. Referral for genetic counseling is advised for patients below age 40 and patients with dMMR CRC without MLH1 hypermethylation.
Methods: The Dutch Pathology Registry (PALGA) was used to evaluate dMMR testing in 14 pathology laboratories from January 2016 up to July 2017. Patients referred to two regional genetic centres were linked to PALGA data to evaluate referral rates. Pathology laboratories received feedback on the percentage of correctly tested CRCs.
Results: Of the 55 patients diagnosed below age 40, 28 (51%) were referred for counseling, leading to 4 LS and 2 constitutive mismatch repair deficiency (CMMRD) diagnoses. Of the 3547 patients diagnosed between 40 and 70 years, 2972 (84%) were tested for dMMR. Thirty-two (1%) were MLH1 deficient with unknown hypermethylation status, 162 (5%) CRC showed dMMR with, 81 (3%) without hypermethylation. In the latter group, 19 (50%) of 38 referred patients were diagnosed with LS. 40% of new index patients lacked a positive family history.
Conclusion: Over 10% of patients with CRC below age 40 and 1-2% of those diagnosed between 40 and 70 have LS. An increase of referral rates is essential to further improve the identification of new LS families, of which the majority is not recognized based on young age or family history.
Supported by the Dutch Digestive Foundation with funding from the 'Vriendenloterij'.

S17

Obesity and the Kidney

Ⓟ CE Alpers

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It has been well established that there are growing, worldwide epidemics of both obesity and chronic kidney disease (CKD) which may be linked. Studies originating from obese patients undergoing renal biopsy has led to the identification of the diagnostic entity obesity -related glomerulopathy (ORG). ORG has been defined as a structural lesion of glomerulomegaly and/or focal and segmental glomerulosclerosis (FSGS) associated with partial effacement of glomerular podocyte foot processes in patients with obesity and proteinuria without nephrotic syndrome and for whom an alternate etiology cannot be identified. By definition, a renal biopsy is required to establish this diagnosis. Yet this lesion remains controversial, as the structural changes and functional changes are not unique to this entity. The existence of a glomerulopathy occurs in only a small minority of obese individuals and is not linked to the degree of obesity. It can be argued that ORG is a manifestation of glomerular hyperfiltration, and might best be considered as a structural adaptation to obesity and a risk factor for overt renal disease. Both possibilities will be discussed. Obesity's effects on the kidney may be mediated by a low-level chronic inflammatory state resulting from localized inflammation of adipose tissue. A number of systemic and local cytokines and adipokines have been postulated to mediate the effects of obesity on the kidney. Perhaps the best opportunity to understand obesity's effects on the kidney has come from the emergence of bariatric surgery as an effective therapy producing weight loss and attendant metabolic changes in morbidly obese individuals. Data to date, with some important caveats, suggests bariatric surgery can reduce risk for developing CKD in the obese population; its potential for reversing structural renal injury remains largely unexplored except in anecdotal cases.

S18

Hereditary GI Cancer Syndromes

Ⓟ F Carnerio

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Although most cases of gastric cancer (GC) and colorectal cancer (CRC) are sporadic, a hereditary cause is determined in 1–3% and 3–6%, respectively. The major hereditary GC syndrome is "hereditary diffuse gastric cancer" (HDGC), predominantly caused by germline alterations in CDH1 gene and, in a minority of cases, by mutations in other genes, including CTNNA1. The other hereditary GC syndrome is "familial intestinal gastric cancer" (FIGC) whose cause is currently unknown. Further, hereditary GC develops in the setting of "gastric adenocarcinoma and proximal polyposis of the stomach" (GAPPS), a recently identified hereditary cancer syndrome, caused by germline mutations in the promoter 1B of APC gene. Most hereditary CRC cases are caused by germline mutations or epimutations in the DNA mismatch repair (MMR) genes MLH1, MSH2, MSH6, and PMS2 for non-polyposis cases (Lynch syndrome), and in APC and MUTYH for adenomatous colonic polyposis [Familial Adenomatous Polyposis (FAP) and MUTYH — Associated Polyposis (MAP)]. In addition, several hamartomatous polyposis syndromes exist, including juvenile polyposis syndrome (JPS; SMAD4 or BMPR1A germline mutation), Peutz-Jeghers syndrome (PJS; STK11 germline mutation), and Cowden/PTEN hamartoma syndrome (CS; PTEN germline mutation). Some of these syndromes confer increased risk for extra colonic malignancies, including GC. Furthermore, serrated polyposis is a clinically defined syndrome characterized by multiple serrated polyps in the colorectum and an increased CRC risk, but the genetics are not fully elucidated. Clinical, pathological and molecular features, genetic testing and management recommendations of the main hereditary GC and CRC syndromes will be discussed.

S19

Genotype or Phenotype: What Matters Most in Barrett's Oesophagus?

Ⓟ R Langer

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The classical concept of the progression of metaplastic Barrett's oesophagus to adenocarcinoma bases upon the stepwise accumulation of molecular alterations during this process prompting some authors to propose a cancer progression scheme similar to the well-established adenoma-carcinoma sequence in colorectal carcinoma. Molecular events that play a role in the progression of Barrett's oesophagus are e.g. alterations of cell cycle regulators, growth factors, tumour suppressor genes, adhesion molecules, as well as loss of heterozygosity and DNA aneuploidy. Over time, these events lead to increased cell proliferation and genetic instability and finally progression to cancer. Morphologically, this process is reflected by increasing grades of dysplasia in the metaplastic epithelium, which can be appreciated by histology. Recent publications, though, have shown that several molecular alterations can be found already in non-dysplastic mucosa that does not show any dysplastic changes by morphology, but later progresses to high-grade dysplasia or cancer. In contrast, most cases with low-grade dysplasia never do progress to high grade lesions. Genotypic identification of specific "progressor" signatures may be crucial for the guidance of patients with Barrett's mucosa. Novel technical approaches include cell and tissue based cytologic and histologic techniques allowing comprehensive molecular genetic analysis as additional tool that may even be superior to conventional histology in some cases. Most recently, non-invasive, cell free DNA based methods for the detection of Barrett's patients at risk for progression have been presented. It may be anticipated that early detection of genotypic or phenotypic features that allow the discrimination of patients with Barrett's mucosa at risk for progression will serve as base for individualized surveillance strategies and significantly improve the clinical management of patients with Barrett's oesophagus.

S20

Bone Tumour Syndromes

Ⓟ J Bovée

LUMC, Leiden, NL

In general, the early age of onset, the occurrence of bilateral, multifocal tumours or specific histopathological findings may suggest genetic predisposition. There are a number of rare genetic syndromes that are associated with bone tumours Most of these syndromes have an autosomal dominant pattern of inheritance with variable penetrance. Autosomal recessive transmission is less common. The best known osteosarcoma predisposition syndromes are retinoblastoma and Li-Fraumeni, in which patients carry germ line mutations in the cell cycle regulators RB1 (retinoblastoma), and TP53 or CHK2 (Li-Fraumeni). Cartilaginous tumours can also occur within a hereditary syndrome. The best known syndrome is multiple osteochondromas (hereditary multiple exostoses), which is genetically heterogeneous, with two responsible genes: EXT1 and EXT2. In addition to these known sarcoma predisposition genes, recent next generation sequencing based association studies revealed that about half of the sarcoma patients have putatively pathogenic monogenic and polygenic variations in known and novel cancer genes in their germline, suggesting that hereditary factors contribute to sarcoma development in a much higher percentage of patients than currently thought. Some bone tumours occur within a non-hereditary syndrome and result from a somatic mosaic mutation. In these patients, not the germline, but instead a subset of the normal cells contain mutations. The timing of the mutation during development determines the extent of the disease. For instance, patients with Mc Cune Albright syndrome carry a postzygotic somatic activating mutation in the GNAS1 gene. The early occurrence of the mutation during development affects multiple germ layers and these patients have fibrous dysplasia, endocrine lesions and café au lait pigmentations. When the mutation occurs later during development, affecting only the mesoderm, patients will present with either polyostotic or, when even later, monostotic fibrous dysplasia.

S21

Mimics of Sarcoma

Ⓟ C Fisher

Institute of Cancer Research, London, UK

Non-neoplastic or benign lesions that mimic malignant tumours form one of the most common pitfalls in soft tissue pathology. Their rapid growth, high mitotic activity or atypia can lead to misinterpretation as sarcoma. The most common of these lesions are fibroblastic/myofibroblastic proliferations, including nodular fasciitis, proliferative fasciitis and myositis, ischaemic fasciitis, massive localized oedema, and myositis ossificans and related entities. Other potential pitfalls include pleomorphic lipoma, symplastic leiomyoma, atypical cutaneous fibrous histiocytoma, atypical neurofibroma, and pleomorphic hyalinising angiectatic tumour. Non-mesenchymal soft tissue malignancies such as sarcomatoid carcinoma, especially in viscera or in relation to mucosal surfaces, and melanoma can also mimic sarcomas. Entities can be distinguished by knowledge of clinical history, careful assessment of morphology and use of immunohistochemistry and molecular techniques as required. This presentation will discuss the contemporary diagnosis and differential diagnosis of a selection of these lesions.

S22

MDM2 in Soft Tissue and Bone Sarcomas

Ⓟ RME Sciot

Department of Pathology, University Hospital, University of Leuven, Leuven, Belgium

Murine Double Minute Clone 2 is an oncogene, the most important function of which is to suppress p53 activity. A number of sarcomas have typical MDM2 amplifications. Well differentiated liposarcoma/atypical lipomatous tumour (WDL/ATL). WDL/ATL is characterized by giant marker and/or supernumerary ring chromosomes, both of which contain multiple copies of MDM2, resulting in nuclear MDM2 protein overexpression. There is frequently co-amplification of other genes of the 12q14-15 region, like CDK4, but MDM2 amplification is the main driver. FISH for MDM2 is much more sensitive and specific than immunohistochemistry, an important pitfall being nuclear MDM2 immunoreactivity in histiocytes/lipophages.

Dedifferentiated liposarcoma: Dedifferentiated liposarcoma (DDL) is defined as the transition of WDL/ATL towards nonlipogenic sarcoma, either in the primary tumour or in a recurrence. It also harbours amplifications of 12q14-15, including the MDM2 and CDK4 genes. As opposed to WDL/ATL, DDL shows other genetic changes, as 6q23 and 1p32 co-amplifications.

Intimal sarcoma: Intimal sarcomas are very rare tumours that develop in the wall of large blood vessels, and it is the most frequent primary cardiac sarcoma. On histology, these tumours look like undifferentiated sarcomas and often have a very heterogeneous outlook. There is no specific immunohistochemical marker, but EGFR and nuclear MDM2 expression are classically seen. Amplification of the 12q12-15 region is a hallmark and is accompanied by amplification and activation of PDGFR- alpha (at 4q12) and EGFR (at 7p11).

Low grade osteosarcoma: Low grade osteosarcomas are subdivided in parosteal and low grade central osteosarcoma. On histology, both lesions look very bland, making the diagnosis often impossible in the absence and of imaging features. In this respect, MDM2 and/or CDK4 immunohistochemistry is also of diagnostic use. Indeed, both tumours harbour amplified 12q13-15 regions, including the MDM2 and CDK4 genes.

S23

Diabetic Nephropathy: New insights into Pathogenesis

Ⓟ CE Alpers

University of Washington, Seattle, WA, USA

Diabetic nephropathy is classically thought to be a combined lesion of the glomerular, tubulointerstitial, and vascular compartments of the kidney. Early functional manifestations of diabetic nephropathy- notably proteinuria- have been recognized to be reversible, but loss of GFR and the structural changes of diabetic nephropathy are generally considered progressive and irreversible. The well recognized structural changes of diabetic nephropathy include mesangial sclerosis, tubulointerstitial fibrosis, and arteriosclerosis and arteriolar hyalinosis. More recently recognized changes include the loss of podocytes, a process also thought to be irreversible, and modification of the glomerular endothelial glycocalyx. Using animal models that replicate some of the most prominent features of human diabetic nephropathy, we show that some structural injuries, including podocyte loss, may be reversible. We have studied the effects of multiple therapeutic interventions used for human diabetic nephropathy to test their efficacy for promoting reversal of nephropathy using a unique animal model of type II diabetes. Importantly, as the ob/ob mutation is characterized by leptin deficiency, the BTBR ob/ob mice develop reversal of their diabetes and reversal of their nephropathy with restoration of leptin. These dramatic effects are accompanied by restoration of podocyte number and density in injured glomeruli. This model has allowed us to compare the effects of multiple therapeutic interventions currently utilized to treat patients with diabetic nephropathy or being tested in clinical trials for the treatment of diabetes and diabetic nephropathy and assess their ability to restore podocyte density in cases of established diabetic nephropathy. Our studies demonstrate the potential for therapeutic interventions that can reverse diabetic nephropathy including podocyte loss, and have identified specific sources of podocyte progenitor cells that might be mobilized to achieve this result.

S24

Pathology is Part of Biology

Ⓟ WJ Mooi

VU University Medical Centre Amsterdam, Amsterdam, NL

Pathology is the study of disease. But: what is disease? The enormously heterogeneous group of biological processes that detract from our subjective wellbeing, limit our possibilties and shorten our life span are grouped together as 'disease', but are, essentially, not different from other biological processes. There are no 'normal' and 'abnormal' molecules; similarly, 'healthy' and 'pathogenic' (= disease-causing) molecular interactions and pathways follow the same physicochemical rules. The categorization into 'healthy' and 'pathogenic' is entirely based on the ultimate impact of these biological phenomena on our 'fitness'. Obviously, our fitness being central to the definition of health and disease introduces a non-scientific bias, related to perspective, our perspective. To give an example, the biological success of one organism – *Vibrio cholerae* – to induce watery diarrhoea in the host and thus to enhance the chance of reaching new hosts – is the essence of the disease called cholera, as viewed from the host's – our – perspective. We call it a disease, but *Vibrio cholerae* would call it a great achievement! Another example: mutations in a certain growth factor receptor gene give the basset hound its short legs that make it so effective in small game hunt – and in humans result in the 'disease' called achondoplasia. The enormous advantages in medical science over the past 1,5 century are, to a significant extent, based on biological insights. Ironically, the very same insights blur the borders between health and disease. However, these insights call out to us that disease is not 'bad', and that there is no relation to sin, witchcraft, curses, etcetera, a point that may seem self-evident to us but is anything but self-evident to many across the globe and indeed in our midst.

S25

Extremely Preterm Infants: A Clinicopathological Perspective

Ⓟ E Villamor

Maastricht University Medical Center (MUMC+), Maastricht, NL

Extremely preterm birth is defined as delivery before 28 weeks of gestation and is a major public health issue. Since many major organ systems mature during the final trimester of pregnancy, extremely preterm infants must complete the essential physiologic adaptations to extrauterine life using immature systems. I will focus on the etiopathogenesis of extreme prematurity as well as on the effects of extreme prematurity on the pulmonary and intestinal systems. The pregnancy disorders that lead to very preterm delivery can be divided into two broad groups: placental infection/inflammation and vascular placental pathology. The former group is associated with chorioamnionitis, preterm labor, premature rupture of membranes, placental abruption, and cervical insufficiency. The second group is characterized by the relative absence of inflammation, but presence of histologic features of dysfunctional placentation. This group is associated with gestational hypertensive disorders and the entity identified as fetal indication/intrauterine growth restriction. Bronchopulmonary dysplasia (BPD) is the major pulmonary complication of prematurity. The pathogenesis of BPD involves extreme lung immaturity, treatment-induced oxygen and volutrauma injury, and prenatal and/or postnatal inflammatory responses. BPD pattern of injury involves the interruption of normal lung growth and development, and subsequent reparative processes of impaired alveolization, dysmorphic vasculogenesis, and usually minimal alveolar wall fibroproliferation. Necrotizing enterocolitis (NEC) is a devastating disease of the neonatal intestine. Etiopathogenic factors in NEC include extreme prematurity, formula feeding, hypoxia, mucosal immaturity, intestinal ischemia, and exposure to opportunistic pathogens. These perinatal insults trigger the inflammatory cascade, resulting in intestinal barrier failure and gut-origin sepsis.

S26

Neuroblastoma: Taming of a Double Headed Dragon

Ⓟ R Versteeg

Academic Medical Center, Amsterdam, NL

Neuroblastoma is a pediatric tumour with an often infaust outcome. Initially patients can go in complete remission upon therapy, but many patients develop therapy-resistant relapses. Neuroblastoma show a paucity of gene mutations, which has sparked an interest in their epigenetic regulation. Several tumour types include phenotypically divergent cells, resembling lineage development stages. Here we show that most neuroblastoma include two types of tumour cells with diverging gene expression profiles. Undifferentiated mesenchymal (MES) cells and lineage committed adrenergic (ADRN) cells can interconvert and resemble lineage differentiation stages. Analysis of the epigenetic up-make of isogenic pairs of mesenchymal and adrenergic cells identified a distinct Super Enhancer landscape and transcription factor network for each cell type. Activation of transcription factors could reprogram ADRN cells towards a MES state. Mesenchymal cells were more chemo-resistant in vitro and were enriched in post-therapy and relapsed tumours. They may therefore survive chemotherapy and give rise to relapses. Intra-tumour heterogeneity of neuroblastoma therefore reflects normal developmental stages and may underlie the escape from therapy.

S27

Exploring Neutrophil Function to Delineate Novel Treatments in Acute Respiratory Distress Syndrome

Ⓟ DA Dorward

University of Edinburgh, Edinburgh, UK

Acute respiratory distress syndrome (ARDS) is the frequently fatal outcome of multiple conditions and is characterised by overwhelming inflammation. Initially driven by bacterial infection or sterile tissue injury, dysregulated neutrophil influx, activation and prolonged lifespan results in significant tissue damage and worsening acute inflammation. As ARDS is a neutrophil-dominant condition, manipulation of neutrophils may therefore have therapeutic potential. Neutrophils migrate towards various chemotactic factors but a hierarchy exists with bacterial-derived products dominant in this process. Host-derived mitochondrial DNA (mtDNA) and formylated proteins bear structural resemblance to their bacterial counterparts and have been implicated in sterile inflammation. In ARDS circulating mtDNA is elevated and serves as a powerful predictor of clinical outcome in sepsis while mitochondrial formylated peptides are present in both the circulation and alveolar lavage fluid of ARDS patients. These formylated peptides drive neutrophil chemotaxis and activation. In pre-clinical models of sterile lung inflammation antagonising formylated peptide recognition causes a reduction in inflammation, neutrophil migration and the global burden of disease. An alternative approach is to augment inflammation resolution by reducing neutrophil lifespan thereby promoting a return to tissue homeostasis. Pharmacological acceleration of neutrophil apoptosis through the use of cyclin-dependent kinase inhibitors (CDKi) significantly augments the resolution of inflammation in acute sterile and infective lung injury models. CDKi are also able to over-ride the pro-survival factors present in ARDS to induce apoptosis in neutrophils isolated from ARDS patients. This multi-faceted approach to understanding mechanisms that drive neutrophil recruitment, function and survival in the context of ARDS is creating novel alternative approaches to tackling human diseases including severe lung inflammation.

S28

General Clinical Introduction in Hepatobiliary Disease

Ⓟ J de Bruijne

University Medical Center Utrecht, Utrecht, NL

Liver diseases are a significant cause of global morbidity and mortality. While the predominance of a specific liver disease varies with geographical location, the breadth of hepatic diseases affecting the underdeveloped, developing, and developed countries is phenomenal, with diseases ranging from infectious diseases of the liver to neoplasia and obesity-related illnesses. Hepatobiliary disease includes a heterogeneous group of diseases of the liver and biliary system caused by viral, bacterial, and parasitic infections, neoplasia, toxic chemicals, alcohol consumption, poor nutrition, cardiac failure, metabolic- and autoimmune disorders. Research progress toward unraveling the aberrations of several liver diseases has led to a better understanding of the disease biology with improved diagnostic, prognostic, and therapeutic tools. The treatment depends on the condition and what is affecting the liver and its related biliary system. Treatment plans vary from simple life style modifications to liver resection or liver transplantation, depending on etiology and severity of the disease. Liver biopsy and histologic examination can be key elements to assess the etiology and severity of the liver disease. During this presentation a general clinical overview of biliary tract disease will be given with special attention for the added value of liver histology and the importance of clinical context.

S29

Scoring Systems for Liver Disease, Their Relevance and New Developments in Scoring Biliary Diseases

Ⓟ SG Hubscher

University of Birmingham, Birmingham, UK

This talk will first consider general issues related to scoring systems used in liver disease, before focusing on recent developments in the histological scoring of the two most common autoimmune biliary diseases occurring in adults - primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). Semi-quantitative scoring systems have been widely used to assess the severity of liver damage in liver disease. The assessment of disease severity involves two main components — grading and staging. Grading is a measure disease activity and involves an assessment of ongoing damage (e.g. inflammation), which may predict disease progression, but is potentially treatable. Staging involves the assessment of disease progression (e.g. fibrosis), which has the potential to lead to end-stage liver disease (e.g. cirrhosis) and is less readily reversible. Scoring systems were mainly devised to improve the objectivity and discriminatory power of liver biopsy, particularly for clinical trials. Grading features that can be scored in PBC and PSC include inflammation (portal, interface and lobular) and bile duct injury. The assessment of inflammatory activity (mainly interface hepatitis) is important in the identification of patients who may have a so-called "overlap syndrome" with autoimmune hepatitis. Such patients may benefit from treatment with immunosuppression. In recent years, a system described by Nakanuma et al, which includes semi-quantitative scoring of bile duct loss and CAP deposition in addition to fibrosis, has been shown to more effective than previously-described staging systems in predicting disease outcomes in both PBC and PSC. Due to the lack of other useful surrogate end-points for determining treatment efficacy, histological staging is likely to be increasingly used to assess outcomes in patients entered into clinical trials investigating new therapeutic agents.

S30

IgG4-Associated Cholangitis

Ⓟ J Verheij

Academic Medical Center, Amsterdam, NL

IgG4-associated cholangitis (IAC) is the hepatobiliary manifestation of IgG4-related disease, an autoimmune-mediated inflammatory disease. This disease is associated with elevated IgG4 serum levels and typical histopathological changes in biopsy and/or resection specimens of the affected organs, such as the presence of dense lymphoplasmacellular infiltrates, so-called storiform fibrosis, presence of eosinophils and obliterative phlebitis (partial/complete). IAC occurs often (> 90%) in patients with autoimmune pancreatitis type I (AIP), the pancreatic manifestation of IgG4-related disease. Patients with an IAC are most frequently (80-85%) men older than 50. Professional contact with solvents, oil products, dyes or industrial gases is reported ('blue collar workers'). Clinical presentation consists of jaundice and weight loss. Imaging may show a bile stricture or mass, suggestive for sclerosing cholangitis and/or cholangiocarcinoma. The HISORt criteria (histology, imaging, serology, other organ manifestations, treatment response) are used for the diagnosis of IAC. The final diagnosis of IgG4-related disease requires collaboration between the pathologist and the treating physician. The pathologist evaluates the presence of the different morphological changes, including the number of IgG4 positive plasma cells/HPF, thereby concluding if histology is highly suggestive, compatible or not supportive of IgG4-RD. New diagnostic tests include determination of the IgG4 / IgG quotient in the blood by quantitative RNA polymerase chain reaction (qPCR). The disease responds very well to treatment with corticosteroids. Recurrences of the disease are common and may affect different organ systems.

S31

What's New and Important in Reporting of Uterine Cancers

Ⓟ KM Vroobel

The Royal Marsden NHS Foundation Trust, London, UK

This lecture aimed at trainee pathologists will provide a framework for histopathological diagnosis of endometrial carcinomas and discuss important diagnostic considerations. Problematic areas regarding staging will be included. Attention will be given to new surgical techniques which will have implications in pathological reporting of endometrial cancer specimens. The presentation will also cover additional information to provide in the pathology report based on recent studies, which may further guide consideration of adjuvant therapies.

S32

Challenging Cases in Uterine Pathology

Ⓟ N Wilkinson

University College London Hospitals Foundation Trust, London, UK

A selection of 5 cases will be presented with guidance on approach to specific diagnostically challenging cases. They will cover the diagnosis of endometrial carcinoma and mesenchymal tumours building on and complementing the presentations of the other speakers.

S33

Why is Cancer a Disease of Old People and Sometimes of Children?

Ⓟ JHJ van Krieken

Radboud University, Nijmegen, NL

Cancer is a disease of genes, but only a minority of cancers have a hereditary component. This implies that the alterations in genes that lead to cancer are in the great majority of cases acquired. Acquired through external factors like radiation and toxic agents (cigarette smoke!) or by mistakes in the normal process of cell division during which genes are doubled and split. Although this latter process is very tightly controlled and most mistakes are repaired, it is still results in very rare changes in genes. Because there are billions of cells, trillions of cell divisions and even a multiply of that of potential errors, it is understandable that in every human being abnormalities in the genome increases over time. When these abnormalities are in key genes they can cause abnormal cell growth. Because one mistake is not enough to create a cancer cell it is understandable that cancer is a disease of the elderly. It is also clear that this proces is closely linked to the proces that drives evolution, one can see cancer as the downside of us being human. Sometimes young persons are affected by cancer. There has a variety of reasons. Several hereditary syndromes are known, that result in abnormal genes at very young age (Wiskott Aldrich syndrome, Li Fraumeni syndrome, to name a few). Another situation is for instance radiation to growing organs (thyroid cancer in children in Tsjernobil). Bad luck may be a reason too, but it is quite sure that for such pediatric cancers the reason remains unclear. Finally there syndromes in which a first step towards cancer is hereditary but the other steps accumulated over time. In these syndromes (like BRCA1 and 2 associated breast cancer or Lynch syndrome associated colon cancer) the cancer occurs 10 to 20 years ahead of time.

S34

Alzheimer's Disease: Imaging Neuropathology In Vivo

Ⓟ HIL Jacobs

Maastricht University and Harvard Medical School/MGH, Maastricht, NL

Alzheimer's disease, the most common form of dementia, is characterized by two main pathological hallmarks: the accumulation of extracellular amyloid-beta aggregates and intracellular hyperphosphorylated misfolded tau proteins. These proteins are characterized by a temporal and spatial pattern. Temporally, these proteins start to accumulate on average 20 years before any clinical symptoms are evident and in individuals with genetic risk factors, these patterns occur on average even 10 years earlier. Spatially, the accumulation throughout the brain is not random, autospy studies have shown that these proteinopaties accumulate in specific topographic patterns in the brain, reflecting functional brain networks. Ultimately, amyloid and tau pathology lead to grey matter atrophy and cognitive decline. Neuroimaging studies are now working to further understand the links between amyloid and tau pathology, genetics, other brain changes and cognitive decline. The benefit of in vivo studies is that we can visualize pathology in vivo and track their progression simultaneously with cognitive changes. In the this talk I will show how we can now measure amyloid and tau pathology using specific PET tracers, including their advantages and disadvantages. Using PET and MRI data from 253 participants of the Harvard Aging Brain Study, I will show where autopsy and imaging data overlap and differ in terms of the topography of pathology. Furthermore, I will provide evidence that neurodegenerative processes in the hippocampus (a proxy for tau pathology) are associated with tau pathology in the downstream connected posterior cingulate cortex. Such a potential spread of pathology seems to occur through alterations of properties of specific white matter tracts connecting these regions and is facilitated by amyloid pathology. Finally, I will show that the combination of these events is associated with memory decline.

S35

Forensic Pathology in the Netherlands

Ⓟ B Kubat

MUMC, Netherland Forenisc Institute, Maastricht, NL

The lecture will provide an outline of the structure of forensic medical examination in the Netherlands and address forensic pathology issues in various fields including neuropathology.

S36

Aspirin, Statins and Molecular Pathological Epidemiology of Colon Cancer

Ⓟ MB Loughrey[1]; HG Coleman[2]

[1]Royal Victoria Hospital, Queen's University Belfast, Belfast, UK; [2]Queen's University Belfast, Belfast, UK

Purpose of the study: The association between aspirin or statin use and improved survival after colorectal cancer diagnosis may differ by the tumour molecular profile. As an example of molecular pathological epidemiology, this population-based colon cancer cohort study examined the interactions between (1) PIK3CA mutation status, PTGS2 expression, aspirin use and survival and (2) p53 and HMGCR expression, KRAS mutation status, statin use and survival.
Methods: The cohort comprised 740 stage II/III colon cancer patients diagnosed between 2004 and 2008. Aspirin or statin use was determined through clinical note review. Immunohistochemical assessments were performed on tissue microarrays using a semi-automated approach applying the open source image analysis software QuPath (https://qupath.github.io/). Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals for cancer-specific and overall survival.
Summary of results: Aspirin use was associated with an improvement in cancer-specific survival compared to non-use. This effect was more pronounced in tumours with high PTGS2 expression compared to those with low PTGS2 expression. However, no interaction was observed between aspirin use and PIK3CA mutation status for cancer-specific or overall survival. Statin use was not associated with improved cancer-specific survival in this cohort. Statin use was also not associated with improved survival when the analyses were stratified by tumour p53 expression, HMGCR expression or KRAS status.
Conclusions: Aspirin use was associated with improved survival outcomes in this population-based cohort of colon cancer patients. This association differed according to PTGS2 expression but not PIK3CA mutation status. Statin use was not associated with improved survival in this study.

S37

Molecular Pathological Epidemiology of Lifestyle Factors and Colorectal and Renal Cell Cancer Risk

Ⓟ PA van den Brandt

Maastricht University, Maastricht, NL

In molecular pathological epidemiology (MPE), molecular tumour heterogeneity is taken into account when studying relationships with risk factors, to identify cancer subtypes with distinct etiology or prognosis. The Netherlands Cohort Study (NLCS) is a prospective cohort study designed to evaluate hypotheses in the area of diet, lifestyle and various cancers. At the start of the NLCS in 1986, 120,852 men and women aged 55-69 years completed a questionnaire on diet, physical activity, anthropometry, smoking and other lifestyle factors and family history of cancer (90,000 subjects also provided toenail clippings). The cohort is being followed up for cancer by record linkage to cancer registries and to PALGA, a nationwide database of pathology reports. In 1999, we started collecting FFPE tumour blocks of incident colorectal and renal cell cancer cases from pathology laboratories, through PALGA. After DNA-isolation, this has been used in etiological and prognostic studies with molecularly defined CRC and RCC subtypes. Molecular analyses involved somatic mutations in oncogenes and tumour suppressor genes, as well as DNA-methylation for epigenetic studies. Several risk factors were studied in relation to CRC and RCC risk, stratified by molecular subtype. Specific results of these analyses will be presented. Since 2012, this MPE approach has been extended to more cancers (breast, colorectal, ovarium, oesophagus, gastric cardia, pancreas, invasive bladder cancer) and more cohorts (NLCS, EPIC-NL, NTR, Rotterdam Study and Polygene), in the Rainbow-TMA project. Tumour and normal tissue blocks were collected in 43 pathology laboratories throughout the Netherlands (80% retrieval rate), sectioned and assembled in tissue microarrays (TMAs). After 5 years, TMAs have been created for 78 oesophagus, 91 gastric cardia, 3205 CRC, 64 pancreas, 3516 breast, 581 ovarian and 316 bladder cancer cases. This will enable MPE and biomarker development in large population-based cohort studies.

S38

Strategies for Investigating Etiologic Heterogeneity of Cancer

Ⓟ CB Begg

Memorial Sloan Kettering Cancer Center, New York, USA

Historically, the epidemiology of cancer has been investigated with respect to the tissue site of origin. Thus we have a large literature on the risk factors for breast cancer, lung cancer, colon cancer, and so forth. In recent years, more attention has come to be paid to the possibility that sub-types of these site-specific cancers have distinct etiologies. Research in this field is increasingly being stimulated by the revolution in tumour genomic profiling, whereby tumours may potentially be characterized on the basis of large numbers of tumour markers. These trends pose technical and conceptual challenges for the traditional epidemiologic and statistical tools used to investigate cancer etiology. In this talk I will describe the challenges, and outline some recent methods that are being developed to address them.

S39

Reactive Epidermal and Dermal Changes in Melanocytic Tumours

Ⓟ WJ Mooi

VU University Medical Centre Amsterdam, Amsterdam, NL

More than any other organ of the body, the skin is exposed to the outside world, and may be harmed by, and respond to, a wide variety of physical, chemical, and microbial assaults. Some of these cause disease; others carry clinical relevance largely because they may influence our ability to diagnose of cutaneous disorders, e.g. naevi and melanomas, that are themselves quite unrelated to it. Any treatise on histological diagnosis of melanocytic naevi and melanomas tends to be based on perfect biopsy samples of the various entities, and in the absence of lesions that are unrelated to the entities described and illustrated. In day-to-day diagnostic practice, however, one encounters a variety of confounding factors. These will be discussed and illustrated in this presentation. They include:

1. Reactive changes caused by previous physical trauma. Incompletely removed naevi may recur and may be misdiagnosed as melanoma. However, the reverse mistake, which less commonly receives attention, also occurs: recurrent melanoma inappropriately dismissed as recurrent naevus (melanoma misdiagnosed as 'Ackerman's pseudomelanoma');
2. Chronic solar damage resulting in melanocytic proliferation and atypia that overlaps with the features of paucicellular (parts of) lentigo maligna;
3. Melanocytic naevi presenting in skin affected by bullous dermatoses or interface dermatitides; this may lead to melanoma overdiagnosis, or conversely, lichenoid inflammatory response to melanocytic neoplasia may obscure the melanocytic lesion altogether.
4. True collision tumours (melanocytic naevus or melanoma bordering, or overlapping with, nonmelanocytic (epidermal, adnexal or mesenchymal) tumours.

Awareness of these potential pitfalls will aid the pathologist in arriving at the correct diagnosis – or diagnoses.

S40

Naevoid Pigment Cell Lesions

Ⓟ JJ van den Oord

University Hospitals, KULeuven, Leuven, Belgium

Some benign naevi may be mistaken for melanomas and some types of melanomas may be mistaken for benign naevi. Among the latter, "naevoid melanomas" are most notorious as they resemble compound or dermal naevi, but behave as melanomas. Originally, several variants were described resulting in a heterogeneous and confusing group of "naevoid melanomas". In a recent EORTC-review (Cook et al, 2017), 89 "naevoid melanomas" were reclassified into 2 variants. The first, "papillomatous" variant resembles papillomatous naevus and is characterized by thin rete ridges, many mitoses, Ki67 expression in the neoplastic cells adjacent to rete ridges and lack of maturation; the second, flat or slightly raised "maturing" variant consists of a classical superficial spreading melanoma (SSM) in which the dermal component gradually "matures" towards smaller, atypical cells with "naevoid" appearance. This subtype was previously described as "melanoma with paradoxical maturation" (Ruhoy et al. 2000). Extensive immunohistochemistry in the second, "maturing" variant showed loss of the suppressor of senescence RRM2 and of Ki67 staining in the deep (naevoid) but not in the superficial (SSM-like) component suggesting that the melanoma cells in the dermis have escaped from their arrest of maturation; moreover, the histone-3 methyltransferase WHSC1/NSD2 (that serves as epigenetic regulator of RRM2 transcription) as well as HMB45 and anti-CD44 failed to label the "naevoid" component. Hence, the "maturing" component expresses a phenotype, similar to that of nevi but different from that of conventional melanomas. Finally, one third of patients with "papillomatous" naevoid melanoma developed metastases, whereas no disease progression was noted in patients with "maturing" naevoid melanoma. In conclusion, two subtypes of naevoid melanomas exist, with distinct clinical, histological and immunohistochemical features. Further research is needed to understand the genesis of the "maturing" subtype.

S41

New Melanoma Syndromes: BAP1 and Beyond – Impact on the Pathologist

Ⓟ T Wiesner

Medical University of Vienna, Vienna, Austria

The BRCA1-associated protein 1 (BAP1) - tumour predisposition syndrome (TPDS) is caused by germline mutations in the BAP1 gene and is inherited in an autosomal dominant pattern. The most common manifestations of BAP1-TPDS are multiple BAP1-inactivated melanocytic naevi/tumours of the skin. Beginning in the second decade of life, affected patients usually develop multiple inconspicuous, skin-coloured to reddish-brown, dome-shaped to pedunculated, well-circumscribed papules, predominantly on sun-exposed skin. The number of lesions varies, but usually ranges from a few to more than 50. Histologically, the BAP1-inactivated melanocytic naevi/tumours of the skin are predominantly composed of intradermal melanocytes with varying degrees of atypia, ranging from clearly benign lesions with naevoid cells and minimal atypia (BAP1-inactivated melanocytic naevus) to highly atypical tumours with large epithelioid cells with well-defined cytoplasmic borders, abundant amphophilic cytoplasm, pleomorphic vesicular nuclei and prominent nucleoli (BAP1-inactivated melanocytic tumour). Tumour-infiltrating lymphocytes are often observed. Many of these skin lesions appear as combined melanocytic naevi with areas of small, oval melanocytes (common naevus component) adjacent to the larger, epithelioid melanocytes. The majority of lesions inactivate the wild-type BAP1 allele by various somatic alterations, resulting in lack of nuclear BAP1 expression in immunohistochemistry, and harbour BRAFV600E mutations. In addition to the BAP1-inactivated melanocytic naevi/tumours of the skin, individuals with BAP1 germline mutations have an increased risk of developing uveal and cutaneous melanoma, peritoneal and pleural, clear cell renal cell carcinoma, basal cell carcinoma, and likely other cancer types including cholangiocarcinoma, meningioma, lung adenocarcinoma, thyroid cancer, leptomeningeal melanoma and paraganglioma.

S42

Prostate Cancer Staging and Datasets: The Nitty-Gritty

Ⓟ DM Berney

Barts Health NHS Trust, London, UK

The amount of information that pathologists report in both biopsy and radical prostatectomy reports has increased exponentially over the past decade. Together with the increase in number of biopsies taken this has caused an almost unsustainable increase in workload for urological pathologists. This has resulted in extremely lengthy reports which may be largely disregarded by clinicians, or potentially even misinterpreted. The basis of the lecture will cover the RCPath and International Collaboration on Cancer Reporting (ICCR) guidance for both biopsies and radical prostatectomy specimens as well as ISUP consensus papers on radical prostatectomy processing and European Network of Uro-Pathology (ENUP) surveys of current practice to exemplify what is reported in various regions. For radical prostatectomies the UICC TNM 2018 staging system will be overviewed with changes from the UICC TNM 7th edition and how further developments in staging may be important. Differences between the AJCC and UICC 8th edition will be presented as well as possible future substaging techniques. On a practical basis, the lecture will cover: how biopsy workload may be reduced and made practicable and accessible for clinicians, especially with regard to measurements of cancer extent and assessments of perineural invasion and other non-grading factors such as the reporting of high grade PIN. Practicable methods for radical prostatectomy pathological examination will be reviewed with an emphasis on practices which are time consuming but add little of practicable value in terms of patient prognosis while emphasis is placed on essential metrics for the surgeon. In addition to this recent ENUP work on how clinicians interpret the data we gather will be given to show how pathologists can produce more concise and timely reports with no loss of useful prognostic information.

S43

Intraductal Carcinoma of the Prostate

Ⓟ M Varma

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Intraductal carcinoma of the prostate gland (IDCP) is a lumen-spanning proliferation of atypical prostatic cells within pre-existing ducts that exceeds the characteristics of HGPIN. IDCP generally represents extension of high-volume, high-grade and high-stage invasive prostate cancer along benign prostatic ducts but may rarely occur in pure form without an associated invasive component. Pure IDCP and IDCP associated with invasive cancer (IDCP-inv) are biologically distinct diseases. The former is a rare precursor lesion (analogous to HGPIN) while the latter is in most instances a growth pattern of invasive prostate cancer. It should be noted that most cases of pure IDCP encountered in needle biopsies would represent IDCP-inv with an unsampled invasive component. There is significant controversy regarding the diagnostic criteria for IDCP and whether it should be graded. The criterion "nuclear enlargement >6x normal" is ambiguous as nuclear size may refer to either nuclear area or diameter. WHO 2016 recommends that IDCP should not be graded but it is unclear whether this refers to pure IDCP, IDCP-inv or both. Pure IDCP in needle biopsies should not be graded to avoid risk of being misinterpreted as invasive. The strongest argument for grading IDCP-inv is that the IDCP component was graded in all published studies on Gleason grading, which were based on H&E examination. Issues in the diagnosis and reporting of IDC-P have been discussed in a recent commentary and subsequent correspondence.[1-3]References:

1. Varma M et al. Reporting intraductal carcinoma of the prostate: A plea for greater standardization. *Histopathology* 2017;70:504-7.
2. Khani F, Epstein JI. In response to 'a plea for greater standardization' in intraductal carcinoma of the prostate: Greater standardization requires greater evidence. *Histopathology* 2017;70:1011-3.
3. Varma M, et al. Reply: Greater standardization requires greater evidence: Let's use the available evidence. *Histopathology* 2017;70:1013-4.

S44

Prostate Cancer: Update on Gleason Grading

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Gleason grading is the universally accepted system for grading of prostate cancer biopsies and radical prostatectomies. Since its initial introduction in the late 1960s, major and minor modifications have taken place of which the last one during the International Society of Urological Pathology (ISUP) consensus meeting in 2014. On top of the ISUP 2014 Gleason grading system, various studies have shown the additional value of other pathologic parameters for the prediction of disease outcome. Pathologic features that are not explicitely included in the Gleason score but have prognostic value are: percentage of Gleason grade 4 or 5, presence of invasive cribriform growth and intraductal carcinoma of the prostate (IDC-P). Although the Gleason score still is the most important pathologic factor, the current challenge is to implement these new features in clinical decision-making models. In particular, this shall inflict treatment decisions in men with Gleason score 3+4=7 prostate cancer. In order to get comprehensive insight in the prostate cancer growth patterns actually underlying the two-dimensional H&E cross-sections, we have characterized the three-dimensional (3D) architecture of respective patterns in depth. These 3D reconstructions give completely new insights in the similarities, connections and unique features of the growth patterns underlying the Gleason grading system.

S45

Standards of Training in Pathology Across Europe: Results from an International Survey

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Purpose of the study: European countries have different policies regarding specialist medical training. Our project was created with the aim of providing an up-to-date overview of the different training programs in pathology in each country, as perceived by the trainees. A secondary objective was to assess their personal opinions regarding a possible standardization of pathology certification across Europe.
Methods: A survey was created and sent out to pathology trainees through the mailing lists of the European Society of Pathology (ESP), the British Division of the International Academy of Pathology (BDIAP), the Pathological Society of Great Britain & Ireland (PathSoc) and other European national societies of pathology. The questionnaire assessed the personal and institutional background of the respondents and addressed several issues related to pathology training in Europe, such as workload, training conditions and opportunities, support from senior staff and trainee evaluation. We also inquired about the trainee's opinion on a possible standardization of certification across Europe.
Summary of Results: The survey is currently underway.
Conclusions: Pathology training is heterogeneous across Europe. Workload, responsibilities and support from seniors and staff vary widely between different countries and even inside the same country. This poses difficulties when considering the standardization of certification in pathology across Europe. This survey might identify which areas of training need improvement in the respective countries and contribute to informed decision making regarding future training in pathology.

S46

Standards of Training in Pathology Across Europe: Results from an International Survey

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S47

Discovery Pathology and New Approaches to Treatment

Ⓟ JE Martin

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The advent of augmented intelligence coupled with digital imaging has been hailed as a great replacer of, rather than simply an adjunct to, human interpretation of pathological samples. There remains, and there will continue to remain, a significant role for pathologists in the discovery process in physiological and disease states. Entities and pathological conditions are still being discovered, and this new information can lead to new insights into biological processes and pathways that help to inform therapy developments. This session will focus on the ways in which discovery can inform such developments. The development and results of the largest mutagenesis programme in Europe will be used as an example. Some of the discoveries of this programme have resulted in better understanding of a range of disorders, but also in methods that have then been used for many other studies. Examples of key systematic or serendipitous discoveries will be discussed, including findings of new models of gastrointestinal and neurological disease and other disorders, and of a model of neurodegeneration which led to discovery of the previously unrecognised phagocytic capacity of neurons, and subsequently to a platform method for the delivery of chemotherapy and other agents into a range of tumours. Discovery pathology is alive and well and battling disease.

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