UKI NETS 11th National Conference
25 November 2013

The Royal College of Physicians
London, UK

Abstract Marking Panel

Alan Anthoney (Leeds, UK)
Simon Aylwin (London, UK)
Dr Tu Vinh Luong (London, UK)
Prakesh Manoharan (Manchester, UK)
Nick Reed (Glasgow, UK)

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UKI NETS

Euro House
22 Apex Court
Woodlands
Bradley Stoke
Bristol, BS32 4JT, UK

Tel: +44-(0)1454 642277
Fax: +44-(0)1454 642222
Email: enquiries@ukinets.org
Website: www.ukinets.org

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Programme

CPD

UKI NETS 11TH NATIONAL CONFERENCE has been approved by the Federation of the Royal Colleges of Physicians of the United Kingdom for 6 category 1 (external) CPD credits.

08:30	**Registration, Coffee and Poster viewing**
09:25	**Welcome and opening remarks** *Nick Reed (Glasgow, UK)*
09:30 – 11:00	**Session 1 – Pancreatic NETS –who when and how to intervene?** *Chair: Graeme Poston*
09:30	Imaging assessment of the incidental pancreatic mass *Dylan Lewis (London, UK)*
09:50	Management of pancreatic primary in presence of metastatic disease *Massimo Falconi (Torrette-Ancona, Italy)*
10:10	Localisation of insulinoma *Karim Meeran (London, UK)*
10:30	Surgical approach to the pancreas and parathyroid in patients with MEN1/VHL *Barney Harrison (Sheffield, UK)*
10:50	Open Floor Q&A
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	For the motion *Juan Valle (Manchester, UK)* Against the motion *Harpreet Wasan (London, UK)*

12:15 – 12:50	**Session 2b – Management dilemmas - Gastroenterological aspects of gut NET** *Chair: Alan Anthoney (Leeds, UK)*
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14:00	A Case Study of a Functional Syndromic Patient *Nikie Jervis (London)*
14:15	PERT *Elizabeth Bradley (Cambridge)*
14:30	A Case Study of an Insulinoma Patient *Margaret Roberts (Manchester)*
14:45	Q&A *Philippa Davies & Barbara King*
14:00 - 15:00	**Session 3b – TRANSNET – translation advances in neuroendocrine tumours** *Chair: Tim Meyer (London, UK)*
14:00	The implications of tumour heterogeneity for treatment of cancer *Charles Swanton (UK)*
14:30	What can circulating tumour DNA tell us *Tim Forshew (Cambridge, UK)*

15:00 - 16:00 **Session 4 - Oral communications**
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Rebecca Dobson (Liverpool, UK)

OC2 Metabonomic profiling – a novel approach in neuroendocrine neoplasms
James Kinross (London, UK)

OC3 Serial Assessment of Metastatic Neuroendocrine Tumours: Factors Associated With Progression of Carcinoid Heart Disease & Death
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OC4 Lymph Node Involvement to Predict Survival in Pulmonary Neuroendocrine Tumours – A Single Centre Experience.
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OC5 A randomized, double-blind, placebo-Controlled study of Lanreotide Antiproliferative Response in patients with gastroenteropancreatic NeuroEndocrine Tumors (CLARINET)
Martyn Caplin (London, UK)

OC6 Metastatic Phaeochromocytoma/ Paraganglioma is predominantly associated with inherited mutations in the SDH complex
Bahram Jafar-Mohammadi (London, UK)

16:00 **Tea, exhibition and poster viewing**

16:20 – 16:35 **Rare Diseases TRC - Cancer call NIHR**
Raj Thakker (Oxford, UK)

16:35 – 17:15 **Session 5 International Speaker – 'Chatterjee' lecture**
Chair: Nick Reed (Glasgow, UK)

16:35 Molecular genetics of phaeochromocytoma in 2013
Anne-Paule Gimenez-Roqueplo (Paris, France)

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Juan Valle (Manchester, UK)

17:25 – 17:30 **Closing remarks**
Nick Reed (Glasgow, UK)

17:30 – 18:30 **Evening Reception and Awards Ceremony**

18:30 **Close**

Speaker Biographies

Anne-Paule Gimenez-Roqueplo (Paris, France)

Organization : Université Paris Descartes
Job title: Professor of Genetics
Website: http://parcc.inserm.fr/spip.php?rubrique8
Anne-Paule Gimenez-Roqueplo (MD, specialized in Endocrinology, PhD) is Full Professor in the Department of Genetics (Assistance Publique- Hôpitaux de Paris- Hôpital Européen Georges Pompidou) and at Paris Descartes University. She is the leader of an academic research team entitled "Genetics of paraganglioma and pheochromocytoma" within the INSERM Unit 970 at the Paris Cardiovascular Center at HEGP (PARCC@HEGP), Paris, France. Her research is dedicated to the genetics of paraganglioma and pheochromocytoma (PGL/PCC). Her group established the genetic testing recommendations for patients with PGL/PCC, demonstrated that the identification of a germline SDHB mutation is the first high risk factor of malignancy and of poor prognosis and showed that SDHx-related PGL/PCC are characterized by a stimulation of the hypoxia-angiogenesis pathway and by a hypermethylator phenotype. Her group develops an integrative genomic approach and different animal and cellular experimental models of malignant PGL/PCC. Her researches are supported by ANR (National Research Agency), the European Union Seventh Framework Programme (FP7) and the Ligue Nationale contre le Cancer (Programme Cartes d'identité des Tumeurs). She is the past chairman of the Pheochromocytoma-Paraganglioma Research Support Organization (PRESSOR), the head of the Pheochromocytoma working group of the European Network for the Study of Adrenal Tumors (ENS@T) and member of the ENS@T steering committee. She coordinates the National French registry for SDH-related paraganglioma (PGL.R). She is member and/or expert in genetics of endocrine tumors for different societies (Société Française de Génétique Humaine, Société Française d'Hypertension Artérielle, Groupe des Tumeurs Endocrines, ENS@T) or expert centers (Institut National du Cancer networks: COMETE-Adrenal Cancers, RENATEN-Neuroendocrine Tumors, PREDIR-Von Hippel Lindau disease and renal cancers; Hypertension ESH Hypertension Excellence Center) in Europe.
Anne-Paule Gimenez-Roqueplo is an editorial board member of the JCEM.

Barney Harrison (Sheffield, UK)

Barney Harrison is Consultant Endocrine Surgeon at the Royal Hallamshire Hospital and Honorary Senior Lecturer at the University of Sheffield. His training in endocrine surgery was with Malcolm Wheeler in Cardiff with and in Lille with Charles Proye.

He is past Secretary and past President of the British Association of Endocrine & Thyroid Surgeons, and currently a member of Council of the International Association of Endocrine Surgeons

His special interests include minimally invasive adrenal surgery, audit and standards of care in endocrine surgery.

Charles Swanton (London, UK)

Charles completed his PhD in 1998 at the Imperial Cancer Research Fund Laboratories on the UCL MBPhD programme before completing his medical oncology and Cancer Research UK funded post-doctoral clinician scientist training in 2008. Charles was appointed Medical Research Council and Cancer Research UK senior clinical research fellow and Group Leader of the Translational Cancer Therapeutics laboratory at the CR-UK London Research Institute in 2008 focussing on personalised cancer medicine through an understanding of mechanisms of drug resistance, intratumour heterogeneity and genomic instability. He combines his laboratory research with clinical duties focussed on biological mechanisms of drug resistance in lung and breast cancer. Charles worked as a consultant medical oncologist at the Royal Marsden Hospital with an interest in early phase drug development for the treatment of specific subtypes of metastatic solid tumours (2008-2011). Charles has had lead and corresponding author publications in Nature, Cancer Cell, PNAS, Lancet Oncology and The New England Journal of Medicine. Charles is a member of several translational research scientific committees including the Cancer Research UK Sciences Committee and ESMO translational working group. He leads the scientific aspects of the EU Framework Program 7 PREDICT consortium. According to Thomson Reuters, his paper in NEJM in 2012 was the most highly cited in biomedicine in 2012. Charles was made Fellow of the Royal College of Physicians in April 2011 and was appointed to the Chair in Personalised Cancer Medicine at the University College London Cancer Institute and Consultant Medical Oncologist at UCL Hospitals, Thoracic Oncology Unit in November 2011. Charles is the Chief Investigator of the CR-UK TRACERx national lung cancer evolution study to decipher clonal evolution through the disease course and is director of the CR-UK UCL Lung Cancer Centre. Charles was recently promoted to the tenured position of Senior Group Leader at the CR-UK London Research Institute and was awarded the Royal College of Physicians Goulstonian lecture and Graham Bull Prize for Clinical Sciences in 2013.

Dylan Lewis (London, UK)

Dr Dylan Lewis has been a Consultant in Hepatobiliary, Transplant and Trauma Imaging and Intervention at King's College Hospital for just over 3 years. His special interests include imaging and treatment of liver malignancy (primary and metastatic), intervention relating to liver transplantation, liver and pancreatic trauma and adrenal imaging.

Elizabeth Bradley (Cambridge, UK)

Elizabeth Bradley has been practising as a Clinical Dietician in the NHS since 2009, having graduated from Leeds Metropolitan University Post Graduate Diploma in Nutrition and Dietetics. Elizabeth started her career as a graduate Dietician at the Royal Brompton Hospital in London, where she worked in cardiothoracic surgery and paediatric Cystic Fibrosis. Elizabeth later moved to the Heart of England NHS Foundation Trust where she worked as a nutrition support Dietitian, covering Intensive care, gastro-surgery and oncology.

Currently working at Addenbrookes Hospital, Cambridge University Hospital NHS Foundation Trust as a pancreatic Dietician , Elizabeth's current role involves providing nutritional advice to patients that have undergone pancreatic surgery and/or have pancreatic cancer, including neuroendocrine tumours. Elizabeth is also a member of the Nutrition Interest Group of the Pancreatic Society of Great Britain and Ireland.

Harpreet S Wasan (London, UK)

Dr Harpreet Wasan leads the gastrointestinal oncology clinical research programme at Hammersmith Hospital, Imperial College London. Dr Wasan has been involved in many clinical trials and is chief investigator of the UK MRC COIN-B CRC trial, Co-CI for The FOXFIRE trial (a phase III randomised CRC liver-metastases specific, radioembolisation study) and CUP-ONE, a global clinico-translational study of 'Cancer of unknown primary'. He was also co-chief investigator of the pivotal, advanced Biliary cancer (ABC02) trial. He is involved in UK National Cancer Research Institute (NCRI) committee of the advanced colorectal cancer and the HPB sub-groups, as well as the inaugural past chair of the West London Colorectal Cancer (CRC) Network. More recently, he has set up a clinico-translational science laboratory to complement the trials in personalised cancer medicine, including an integrated liver haemodynamic programme as a novel predictive functional biomarker. He is involved in developing the upcoming UK national CRC personalized medicine trial FOCUS4, and CI for the '4b' cohort.

John Ramage (London, UK)

John Ramage is Honorary Consultant Physician at the Institute of Liver Studies at Kings College Hospital and Lead Clinician for Kings Health Partners NET centre which includes Kings, Guys, St Thomas's, Kent Oncology Centre and Hampshire Hospitals. He is treasurer of the UK and Ireland Neuroendocrine Tumour Society and on the Advisory board for the ENETs. He is a member of the EORTC Quality of life Group, through which he pursues research into Quality of Life in Cancers. His main research interest is in Quality of Life and symptoms scores in Neuroendocrine tumours of the small bowel and liver.

Juan W Valle (Manchester, UK)

Juan Valle is Professor and Honorary Consultant of Medical Oncology in the Manchester Academic Health Sciences Centre (Institute of Cancer Studies). He is based in the Department of Medical Oncology at The Christie NHS Foundation Trust within the Gastrointestinal Disease Group and treats cancers of the pancreas, liver and biliary tract, neuroendocrine tumours and colorectal cancer. He is Head of Service for The Christie Neuroendocrine ENETS Centre of Excellence.

Professor Valle is a member of the UK National Cancer Research Network (NCRN) Upper Gastrointestinal Clinical Studies Group and member of the hepatobiliary, and pancreatic subgroups; in addition he is Chair of the Neuroendocrine Subgroup. He has been awarded a number of grants for research leading to numerous publications and presentations and national and international meetings and is a peer-reviewer for a number of international medical journals.

He is a member of ASCO (American Society of Clinical Oncology), ESMO (European Society of Medical Oncology), UKI NETS (UK and Ireland Neuroendocrine Tumour Society) and ENETS (European Neuroendocrine Tumour Society).

Karim Meeran (London, UK)

Professor Karim Meeran did his undergraduate and postgraduate training in London, and then proceeded to an academic career at Imperial College. He is a Fellow both of the Royal College of Physicians and the Royal College of Pathologists. He has become the Training Programme Director for Metabolic Medicine and Endocrinology in London.

He has over 100 peer reviewed articles. He has an active research programme looking both at patients with clinical problems resulting from Neuro endocrine Tumours as well as those with pituitary disease as well as an interest in Multidisciplinary working.

He runs a successful Multidisciplinary Endocrine Symposium every year, the next one being on Friday December 6th 2013. Details are on http://metmed.info

Margaret Roberts (Manchester, UK)

Margaret Roberts has worked in the Endocrine Department for the past 14 years, with a background as an Oncology Nurse and up until recently working as theSenior Research Nurse.
Margaret's role leads on both Neuro-Endocrine Tumours and Acromegaly, as well as on many other projects. Recently Margaret was promoted to the Senior Sister within the unit, which oversees endocrine patients. The unit also run joint clinics with oncologists dealing with Neuro- Endocrine and adrenal patients as well as geneticists for MEN patients and familial endocrine diseases.
Margaret has a vast amount of experience of working with Neuro-Endocrine patients and has dealt with a number of patients with Insulinomas, Margaret will be talking today about one specific patient with insulinomas.

Mark Pritchard (Liverpool, UK)

Prof Pritchard studied Medicine at Manchester University (BSc (1st class Hons) in Medical Biochemistry, 1988, MB.ChB (with Hons), 1991). After junior hospital posts (MRCP(UK) 1994), he returned to the University of Manchester to train in Gastroenterology and performed research on the genetic regulation of apoptosis in the GI tract with Profs J. Hickman and C. Potten (Digestive Disorders Foundation and MRC Clinical Training Fellowships leading to PhD, 1999). In 2000 he moved to the University of Liverpool as a clinical lecturer to complete clinical training in Gastroenterology. Following this he was awarded an Advanced Fellowship for Clinicians from the Wellcome Trust (2002-6) to study apoptosis in the stomach. He was awarded the ASNEMGE Rising Star award in 2007 and the Sir Francis Avery Jones Research Medal of the British Society of Gastroenterology in 2008. He was appointed Clinical Senior Lecturer at the University of Liverpool in 2006, Professor in 2009 and Head of the Department of Gastroenterology in 2010.

His main focus of research is studying factors which influence the pathogenesis of gastric and colorectal cancer and gastrointestinal neuroendocrine tumours, in particular the importance of apoptosis and of the gastrin family of peptides. He is an honorary Consultant Gastroenterologist at Royal Liverpool University Hospital where his main clinical role is managing patients with neuroendocrine tumours, especially those associated with hypergastrinaemia, as part of Mersey Regional Neuroendocrine Tumour Multidisciplinary Team.

Massimo Falconi (Torrette-Ancona, Italy)

Dr. Massimo Falconi is currently Associate Professor of Surgery and Chairman of the Pancreatic Unit at the University Politecnica delle Marche in Ancona, Italy. He studied medicine at the University of Verona, specializing in general surgery, gastroenterology and endoscopy. A member of many medical societies, including IAP, EPC, and EHPBA, Prof. Falconi is currently on the executive committees of ENETS and IAP. He has written almost 280 peer-reviewed articles and his impact factor calculated on the basis of JCR 2010 is more than 1000 and his *h* index on Scopus and Isi Web of Science is 49 and 45, respectively.

Nikie Jervis (London, UK)

Miss Jervis is the Team Lead Senior Clinical Nurse Specialist (CNS) for Hepatobiliary Cancers at King's College Hospital, London; a role she has held since November 1999. This role incorporates her position as the lead NET CNS for the trust, through which she instigated a "one-stop" MDT NET clinic . The resulting holistic clinic facilitates joint review and care planning (NET physician, Oncology, CNS and HPB Surgery).

Miss Jervis also runs a nurse-led service for the administration of medication and review of care while patients are receiving somatostatin analogues. This facilitates home-care delivery and GP–referral-team liaison for ongoing treatment.

Miss Jervis teaches at both hospital trust and university level, and is currently involved in working on national nursing guidelines for the symptom care of patients with NETs, as well as reviewing Trust held information for NET patients. She has previously been involved in the production of guidelines for primary-care givers,as well as authoring a book chapter in a published textbook for Liver Disease and contributing to clinical articles.

Tim Forshew (Cambridge, UK)

Tim is a Senior Research Associate at the University of Cambridge. He focuses on the development of techniques for the analysis of cancer mutations. His current research is based on detecting low frequency mutated cancer DNA found cell free in body fluids such as blood and urine. As part of this work he was in the team that first demonstrated detecting solid tumour mutations through next generation sequencing of blood plasma. In his previous position he studied the genetics of childhood brain tumours and for this work he won the 2009 Jeremy Jass Prize for Research Excellence in Pathology.

Abstract Section

Oral Communications (OC1 – OC6)

Posters (P1 – P48)

Oral Communications

OC1 & P2

The Variability In Screening For Carcinoid Heart Disease in the United Kingdom and Republic of Ireland

Rebecca Dobson[1,3], Juan Valle[2], Malcolm Burgess[3], Graeme Poston[3], Daniel Cuthbertson[1,3]

[1]University of Liverpool, Liverpool, UK, [2]The Christie NHS Foundation Trust, Manchester, UK, [3]Merseyside Neuroendocrine Tumour Grou, Liverpool, UK

Introduction: Screening for carcinoid heart disease (CHD) is an important aspect of the management of neuroendocrine tumours (NET). Screening is advocated in international guidelines, although details of the mode and frequency are not well-defined. We sought to map current practice for CHD screening in specialist NET centres throughout the United Kingdom and Ireland.

Methods: Thirty-five NET centres were invited to complete an on-line survey about size of NET service, patient selection for CHD screening, and the method and frequency of screening.

Results: Twenty-eight centres responded (80%), representing a total caseload of over 5500 patients: 11% screen all NET patients, 14% screen all midgut NETs, 32% screen all patients with liver metastases and/or carcinoid syndrome and 43% screen all patients with syndrome or raised 5-hydroxyindoleacetic acid (5HIAA). Mode of screening included clinical examination, echocardiography and biomarker measurement: 89% of centres perform echocardiography, either once at baseline (24%), ad-hoc (28%), annually (36%) or less than annually (12%); three centres use a scoring system to report their echocardiograms. Biomarkers for CHD screening are used by 50% of centres (chromogranins, plasma/urinary 5HIAA or NT-proBNP) at varying time intervals. The commonest biomarker used was NT-proBNP (35% of centres).

Conclusion: Screening for CHD differs widely across the UK and Ireland, with variations seen in the population screened and in the frequency and mode of screening. Evidence-based guidelines with explicit recommendations for frequency and mode of screening would help to address these variations and improve screening for CHD.

OC2 & P5

Metabonomic profiling – a novel approach in neuroendocrine neoplasms

James Kinross, Panagiotis Drymousis, Beatriz Jimenez, Andrea Frilling

Imperial College London, London, UK

Background: Identification of personalized biomarkers that can predict tumor behavior and therapeutic outcome is an unmet need in neuroendocrine neoplasms (NEN). A metabonomic phenotyping strategy was developed as part of a pilot study to define a diagnostic metabolic phenotype for NEN.

Methods: 28 NEN patients were prospectively recruited: small bowel (SBNEN) n=8, pancreatic NEN (PNEN) n= 10 and others n=10 (Mean age 49.4 years (26-81) M:F = 17:11).There were 17 healthy controls. Urine samples were subjected to ^{1}H Nuclear Magnetic Resonance (NMR) spectroscopic profiling using a Bruker Avance 600MHz spectrometer (Bruker, Rheinstetten, Germany). Acquired spectral data were imported into SIMCA (v.13.0.1, Umetrics AB, Umeá, Sweden) and MATLAB (v.7.12.0.635, MathWorks, Natick, USA) for supervised and unsupervised multivariate analysis.

Results: Partial least squares-Discriminant Analysis (PLS-DA) could differentiate between NEN and healthy samples with accuracy (R^2Y = 0.79, Q^2 Y = 0.53, AUC 0.90).Orthogonal-PLS-DA was able to distinguish between SBNEN and PNEN (R^2Y = 0.91, Q^2 Y = 0.35). Subclass analysis also demonstrated class separation between functional and non-functional NEN (R^2Y = 0.98, Q^2 Y = 0.77, AUC 0.6) and those with metastases (R^2Y = 0.72 , Q^2 Y = 0.41, AUC 0.86) due to variations in hippurate metabolism ($p<0.0001$).

Conclusions: Metabonomic analysis suggests that subgroups of NEN may possess a stratified metabolic phenotype. Metabolic profiling could provide novel biomarkers for NEN.

OC3 & P10

Serial Assessment of Metastatic Neuroendocrine Tumours: Factors Associated With Progression of Carcinoid Heart Disease & Death

Rebecca Dobson[1,2], Malcolm Burgess[2], Mark Pritchard[1,2], Juan Valle[3], Brian Keevil[4], Joanne Adaway[4], Uschi Hofmann[5], Alan Anthoney[6], Graeme Poston[2], Daniel Cuthbertson[1,2]

[1]University of Liverpool, Liverpool, UK, [2]Merseyside Neuroendocrine Tumour Group, Liverpool, UK, [3]The Christie NHS Foundation Trust, Manchester, UK, [4]University Hospital of South Manchester, Manchester, UK, [5]Huddersfield Royal Infirmary, Huddersfield, UK, [6]St James' University Hospital, Leeds, UK

Introduction: Carcinoid heart disease (CHD) is a complication of metastatic neuroendocrine tumours (NETs). We sought to identify factors associated with CHD progression and death in patients with metastatic NETs.

Methods: Consenting **p**atients underwent prospective serial clinical, biochemical, echocardiographic, and radiological assessment. Patients were classified as CHD progressors (defined as an increase in the degree of tricuspid regurgitation, or an increase in the degree of tricuspid leaflet thickening/immobility), non-progressors or deceased. Multinomial regression was used to assess the univariate association between variables and disease progression.

Results: A total of 133 patients were included (2816 patient years), with a median follow up of 27 months. 13 patients developed CHD or had progression of existing valvular disease. Baseline median levels of both biomarkers were significantly different between groups:

All patients (n=133)							
	CHD + (n=27)			**CHD – (n=106)**			
Biomarker	**Died (n=12)**	**Progressors (n=9)**	**Non-progressors (n=6)**	**Died (n=14)**	**Progressors (n=4)**	**Non-progressors (n=88)**	**P value**
BNP	962	375	125	211	86	75	<0.001
5HIAA	6429	2519	413	353	952	280	0.002

Every 100 nmol/L higher 5HIAA yielded a 6% greater odds of disease progression (OR 1.06, 95% CI: 1.02, 1.11; p=0.006) and 8% greater odds of death (OR 1.08, 95% CI: 1.03, 1.12; p<0.0005). CHD progression occurred more frequently in those with a deterioration in symptoms (69% v 2%, p<0.005).

Conclusion: In patients with metastatic NETs, CHD is a significantly adverse prognostic indicator: associated with poor symptom control, biochemically more severe disease and reduced progression free and overall survival.

OC4 & P17

Lymph Node Involvement to Predict Survival in Pulmonary Neuroendocrine Tumours – A Single Centre Experience.

Vanessa Clay[1], Rebecca Stein[3], Erick Piarino[3], Deborah Lam[2], Zena Salih[1], Piotr Krysiak[2], Kandadai Rammohan[2], Wasat Mansoor[1]

[1]The Christie Hospital, Manchester, UK, [2]University Hospital South Manchester, Manchester, UK, [3]The University of Manchester, Manchester, UK

Introduction: Pulmonary carcinoid tumours belong to a spectrum of neuroendocrine neoplasms, they account for only 1-2% of all lung malignancies. This study aimed to examine lymph node (LN) status as a prognostic factor within these well differentiated tumours, specifically; Typical (TC) and Atypical Carcinoid (AC) tumours, presenting to a single centre.

Methods: A retrospective review of 94 patients treated at the Christie Hospital between 2005 and 2013 was carried out. All cases were identified as either TC or AC according to the WHO criteria. Median follow up time was 21 months (1-149 months). The Chi-square test was used for statistical analysis.

Results: There were a total of 73 (77.7%) TC and 21 (22.3%) AC tumours identified.

Significantly more ACs demonstrated LN involvement at the time of diagnosis (66.7%) than TCs (19.2%, p= 0.00008). As such far fewer ACs were suitable for surgical treatment (57.1% vs 83.6% p=0.0104).

Furthermore, Kaplan Meier survival curves demonstrated that LN positive AC patients had a statistically significant survival disadvantage in comparison to LN negative AC patients(p=0.027). In contrast, TC tumours demonstrated no significant survival difference between the LN positive and negative groups (p=0.125).

Conclusion: This study serves to highlight the more aggressive nature of ACs in comparison to TCs. It also suggests that LN status is of paramount importance within the AC group and is a useful prognostic marker. We suggest that the more aggressive nature of AC tumours and the significance of positive LN status support the consideration of adjuvant chemotherapy for these patients.

OC5 & P29

A randomized, double-blind, placebo-Controlled study of Lanreotide Antiproliferative Response in patients with gastroenteropancreatic NeuroEndocrine Tumors (CLARINET)

Martyn Caplin

Royal Free Hospital, London, UK

Background: The antiproliferative role of somatostatin analogs (SSAs) in GEP-NET patients is still limited, with only one previous prospective trial showing efficacy in patients with midgut tumors and limited liver tumor burden. This is the first large-scale, multinational, phase 3 trial to prospectively evaluate antiproliferative effects of the SSA lanreotide Autogel in a large population with non-functioning GEP-NET, including pancreatic and gastrointestinal tumors.

Methods: CLARINET was a randomized, double-blind, placebo-**C**ontrolled study of **L**anreotide **A**ntiproliferative **R**esponse in patients with GEP-**NET**. In total, 204 patients ≥ 18 yrs, with well or moderately differentiated (Ki67 < 10%) non-functioning GEP- NETs, with no hormone-related symptoms, and who had not received SSAs, interferon, chemoembolization or chemotherapy in the last 6 months, were treated with lanreotide Autogel 120 mg (n=101) or placebo (n=103) every 4 weeks for 96 weeks or until progressive disease (PD) or death. The primary endpoint was progression free survival (PFS; i.e. time to progression using RECIST, or death). Regular CT scans at baseline and at restaging throughout the study were centrally assessed. Secondary endpoints included % of patients with PD or death, and safety. The final analyses in the intent-to-treat and safety populations are presented. The study was sponsored by Ipsen. CT.gov NCT00353496; EudraCT 2005-004904-35.

Results: At enrolment, primary tumor locations were pancreas (45%), midgut (36%), hindgut (7%) and unknown (13%). Most had stable disease (96%) and were treatment-naïve (81%); 22% of patients had Ki67 3%–10% (WHO grade 2), 33% had hepatic tumor load >25%. Two years of treatment with lanreotide showed significantly prolonged PFS over placebo: median PFS was not reached with lanreotide vs 18 months with placebo (hazard ratio 0.47; 95% CI 0.30–0.73; p=0.0002). At end of 2 years of treatment, 62% of lanreotide treated patients vs 22% of placebo treated patients had not progressed or died. Lanreotide showed favourable safety/tolerability consistent with its known safety profile. Treatment-related AEs with lanreotide vs placebo occurred in 50% vs 28% of patients (most frequent event was diarrhea, 26% vs 9%), and few of these were serious events (3% vs 1%). Few AEs led to study withdrawal (3 vs 3 patients).

Conclusions: Lanreotide Autogel 120 mg can substantially prolong PFS for GEP-NET patients. These data offer new and compelling evidence for the antiproliferative effect of lanreotide.

OC6 & P44

Metastatic Phaeochromocytoma/ Paraganglioma is predominantly associated with inherited mutations in the SDH complex

Bahram Jafar-Mohammadi[1], Louise Izatt[2], Klaus-Martin Schulte[3], Paul Carroll[4], Barbara McGowan[4], Jack Powrie[4], Benjamin Whitelaw[1], Salvador Diaz-Cano[5], Simon J B Aylwin[1]

[1]Department of Endocrinology, King's College Hospital, London, UK, [2]Department of Clinical Genetics, Guy's and St Thomas's Hospital, London, UK, [3]Department of Endocrine Surgery, King's College Hospital, London, UK, [4]Department of Endocrinology, Guy's and St Thomas's Hospital, London, UK, [5]Department of Histopathology, King's College Hospital, London, UK

Phaeochromocytomas (PCC) and Paraganglioma (PGL) are neural crest tumours arising from the chromaffin producing cells of the adrenal medulla or sympathetic/parasympathetic system respectively. Recently, in part due to advances in high throughput sequencing, our understanding of the genetic predisposition to these tumours has greatly increased. To date, thirteen genes have been implicated in the pathogenesis of these conditions (ten available for testing at our centre). We aimed to determine the frequency that metastatic PCC/PGL was associated with mutations in known susceptibility genes.

The genetic profile of all individuals diagnosed with metastatic PCC and PGL in our centre was ascertained and compared to individuals with PCC/PGL without evidence of metastasis. 82 individuals with a diagnosis of PCC or PGL fulfilled the criteria for genetic testing in the past 5 years. This included 16 individuals with metastatic disease. Among the patients with confirmed metastatic disease 13/16 (81%) had a genetic mutation identified in *SDHB*, *SDHA* or *SDHD* predisposing to PCC and PGL. However, among those patients with no metastatic disease identified to date, only 42% (29/69) had a genetic mutation identified (p=0.001). Among the subjects with metastatic PCC, 11/13 had mutations (85%) in *SDHB.*

Our results imply that the identification of a mutation in the known PCC/PGL susceptibility genes confers an increased metastatic potential and also subjects with metastatic disease are most likely to harbour mutations in *SDHB*. Subjects with metastatic PGL/PCC are highly likely to have a genetic predisposition. In addition, identification of those individuals with PGL/PCC with a genetic mutation should be considered at high risk for harbouring tumours with metastatic malignant potential.

Posters

P1

Improved survival in Midgut Neuro-endocrine tumours with liver metastases: the East Anglia Experience

Nadeera De Silva, Thankamma Ajithkumar, Francesca Swords, Gaurav Kapur

Norfolk and Norwich University Hospital, Norwich, UK

Purpose: UKINETS data for midgut neuroendocrine tumours (mNETs) with liver metastasis shows a median survival of 7.69 years from diagnosis, and 5.95 years from the diagnosis of liver metastases. We analysed the survival of our patient cohort to compare with the UKINETS data.

Materials and Methods: 52 patients were diagnosed with metastatic mNETS in our centre between 2002 and 2011. We performed a retrospective analysis, and present the data on 35 patients who presented with or developed liver metastases from a histology proven mNET during this period.

Results: The mean age at diagnosis was 65 years and 50% female. 14 patients presented with symptoms of the carcinoid syndrome. 26 patients had liver metastases at presentation and 9 developed liver metastases during follow-up. All patients were discussed in a specialist NET MDT. Primary tumours were resected in 24 patients. All patients received treatment with somatostatin analogues. 40% of patients received some form of liver directed therapy: hepatic metastatectomy in 5; RF ablation in 6; and trans-arterial chemo embolization in 3. Systemic chemotherapy was delivered to 9 and interferon alpha to 2. 4 patients were referred for Peptide Receptor Radionuclide Therapy (PRRT). Median follow-up was 5.5 years for all patients (95% CI: 2.8-7.8), and 4 years after diagnosis of liver metastases (95%CI: 3.2-4.8). Survival analysis of all patients showed a 5- and 10-year survival of 82.5% and 64.2% respectively, with median survival still not reached. 5-year survival after the diagnosis of liver metastases was 72% with median survival still not reached.

Conclusion: Excellent long-term survival can be achieved for patients with mNETS and liver metastases with an aggressive treatment strategy led by a specialist MDT. Our early adoption of somatostatin analogues and active consideration of liver directed therapy may account for these results.

P2 & OC1

The Variability In Screening For Carcinoid Heart Disease in the United Kingdom and Republic of Ireland

Rebecca Dobson[1,3], Juan Valle[2], Malcolm Burgess[3], Graeme Poston[3], Daniel Cuthbertson[1,3]

[1]University of Liverpool, Liverpool, UK, [2]The Christie NHS Foundation Trust, Manchester, UK, [3]Merseyside Neuroendocrine Tumour Grou, Liverpool, UK

Introduction: Screening for carcinoid heart disease (CHD) is an important aspect of the management of neuroendocrine tumours (NET). Screening is advocated in international guidelines, although details of the mode and frequency are not well-defined. We sought to map current practice for CHD screening in specialist NET centres throughout the United Kingdom and Ireland.

Methods: Thirty-five NET centres were invited to complete an on-line survey about size of NET service, patient selection for CHD screening, and the method and frequency of screening.

Results: Twenty-eight centres responded (80%), representing a total caseload of over 5500 patients: 11% screen all NET patients, 14% screen all midgut NETs, 32% screen all patients with liver metastases and/or carcinoid syndrome and 43% screen all patients with syndrome or raised 5-hydroxyindoleacetic acid (5HIAA). Mode of screening included clinical examination, echocardiography and biomarker measurement: 89% of centres perform echocardiography, either once at baseline (24%), ad-hoc (28%), annually (36%) or less than annually (12%); three centres use a scoring system to report their echocardiograms. Biomarkers for CHD screening are used by 50% of centres (chromogranins, plasma/urinary 5HIAA or NT-proBNP) at varying time intervals. The commonest biomarker used was NT-proBNP (35% of centres).

Conclusion: Screening for CHD differs widely across the UK and Ireland, with variations seen in the population screened and in the frequency and mode of screening. Evidence-based guidelines with explicit recommendations for frequency and mode of screening would help to address these variations and improve screening for CHD.

P3

Binding of *Helix Pomatia* agglutinin glycoproteins is a predictor of poor survival in adrenal cancers.

Phakanant Chaichanavichkij[3], Gregory Sadler[1], Susan Brooks[2], Radu Mihai[1], Parameswaran Rajeev[1,3]

[1]Department of Endocrine Surgery, Oxford Radcliffe Hospitals, Oxford, UK, [2]Department of Cellular Biology, Oxford Brookes University, Oxford, UK, [3]St Mary's Hospital, Newport, Isle of Wight, UK

Background: Adrenocortical cancers (ACCs) are rare endocrine cancers with poor outcomes if untreated. Binding of the lectin Helix pomatia agglutinin (HPA) is associated with poor prognosis in many human cancers but not previously studied in ACCs.

Methods: Lectin histochemistry was performed on archival paraffin wax embedded specimens of adrenocortical tumours excised between 2000 – 2012 at a tertiary referral centre. Demographic data, histological data, recurrence of disease, local invasion and mortality data were recorded. The aims of the study were to assess alteration in cellular glycosylation, detected by HPA binding in adrenal cancers and to determine if such altered glycosylation carries any prognostic significance.

Results: Analysis was performed on 39 samples of benign adrenal tissue (adenoma and normal) (n=8), metastases into adrenals (n=9) and 22 patients with ACC, of whom 10 had functional tumours (9 Cushing's, 1 Conn's).

Normal and benign adrenal tumours showed no binding with the lectin HPA. In the ACC group, no difference was seen in terms of local recurrence, invasion or metastatic disease between HPA-positive and negative tumours. HPA binding was associated with advanced disease and greater mortality. Patients with positive HPA binding (n=11) survived a mean of 21 months (range 2-55 months) whilst all but one patient with negative HPA binding (n=11) were alive at time of the study (range 36-108 months follow up) (p=0.0015).

Conclusion: This is the first study showing that HPA-binding glycoproteins are synthesised by adrenal cancers. Positive HPA binding in adrenal cancer is a predictor of both aggressive disease and poor prognosis.

P4

Nurse Led Assessment and treatment delivery clinics: results of Patients Satisfaction Survey

Graham Dilks, Gaurav Kapur

Norfolk and Norwich University Hospital, Norwich, UK

Background: Patient with Neuroendocrine Tumours (NETs) receiving Somatostatin analogues in our hospital were traditionally treated in the chemotherapy day unit. A dedicated Clinical Nurse Specialist (CNS) led clinic was established to review and administer treatment for these patients The aim of the survey was to assess the impact and benefit of the service on patients

Methods and Aims: Patient satisfaction survey forms were given to 48 patients attending the clinic each month. Completed forms were returned by 41. 29 of these patients had received treatment in the chemotherapy day unit prior to the nurse led clinic, and 12 patients had only been seen in the CNS clinic.

Results: All patients felt that the Specialist Nurse in the clinic had more time to answer questions and discuss their feeling and concerns (100% versus 68%). 89% of patients were seen within 15 minutes compared to 48% on the day unit. 97% of patients felt that the CNS was able to ask questions on their behalf to their consultant compared to 41% by nurses on the day unit. All patients were familiar with their key worker compared with 27% on the day unit.96% of patients had a better understanding of their condition and felt better able to cope with some or all of their symptoms since attending the CNS led clinic. When given a choice of their place of treatment between the CNS led clinic, Chemotherapy Day Unit or the GP, 79% would choose the CNS led clinic to have their treatment.

Conclusion: Patients attending the nurse-led clinic had a better understanding of their condition and were better able to cope with their symptoms. The role of a dedicated CNS has shown to be an important factor in delivering individualized care and promoting effective communication between the patient, nurse and consultant.

P5 & OC2

Metabonomic profiling – a novel approach in neuroendocrine neoplasms

James Kinross, Panagiotis Drymousis, Beatriz Jimenez, Andrea Frilling

Imperial College London, London, UK

Background: Identification of personalized biomarkers that can predict tumor behavior and therapeutic outcome is an unmet need in neuroendocrine neoplasms (NEN). A metabonomic phenotyping strategy was developed as part of a pilot study to define a diagnostic metabolic phenotype for NEN.

Methods: 28 NEN patients were prospectively recruited: small bowel (SBNEN) n=8, pancreatic NEN (PNEN) n= 10 and others n=10 (Mean age 49.4 years (26-81) M:F = 17:11).There were 17 healthy controls. Urine samples were subjected to ^{1}H Nuclear Magnetic Resonance (NMR) spectroscopic profiling using a Bruker Avance 600MHz spectrometer (Bruker, Rheinstetten, Germany). Acquired spectral data were imported into SIMCA (v.13.0.1, Umetrics AB, Umeá, Sweden) and MATLAB (v.7.12.0.635, MathWorks, Natick, USA) for supervised and unsupervised multivariate analysis.

Results: Partial least squares-Discriminant Analysis (PLS-DA) could differentiate between NEN and healthy samples with accuracy (R^2Y = 0.79, Q^2 Y = 0.53, AUC 0.90).Orthogonal-PLS-DA was able to distinguish between SBNEN and PNEN (R^2Y = 0.91, Q^2 Y = 0.35). Subclass analysis also demonstrated class separation between functional and non-functional NEN (R^2Y = 0.98, Q^2 Y = 0.77, AUC 0.6) and those with metastases (R^2Y = 0.72 , Q^2 Y = 0.41, AUC 0.86) due to variations in hippurate metabolism ($p<0.0001$).

Conclusions: Metabonomic analysis suggests that subgroups of NEN may possess a stratified metabolic phenotype. Metabolic profiling could provide novel biomarkers for NEN.

P6

Role of Ki-67 proliferative index in the assessment of patients with neuroendocrine neoplasias regarding the stage of disease

Helen Miller, Rasphal Flora, Panagiotis Drymousis, Duncan Spalding, Andrea Frilling

Imperial College London, London, UK

Introduction: The Ki-67 index is the basis for grading of neuroendocrine neoplasias (NEN) originating from the gastro-entero-pancreatic system (GEP-NEN). The correlation of the Ki-67 index with tumor staging remains poorly addressed. We aimed to determine the usefulness of the Ki-67 index in assessing malignant potential of GEP-NEN.

Methods: A retrospective review of a database of patients with GEP-NEN seen at out institution between 2000 and 2012 was carried out. Immunohistochemical staining for Ki-67 was performed on sections from paraffin embedded tissue blocks. Ki-67 index was determined according to standard criteria. Correlation of Ki-67 index with clinical data was carried out.

Results: The study included 161 GEP-NEN patients. Of these 151 had a G1/G2 NEN and 10 a G3 tumour. There were 73 female and 88 male patients, with a median age of 61 years (21-91 years). Metastatic disease was seen in 46.1% (53/115) of G1 tumors, 77.8% (28/36) of G2 tumors and 100% (10/10) of G3 tumors (p=0.0002). When stratified according to the primary site, metastatic disease was documented in 42.5% of PNEN and in 91.9% of small bowel NEN. Assessment of Ki-67% for a subset of cases at metastatic sites as well as primary tumor site showed discrepancies in 35.3% of cases.

Conclusion: Ki-67 index is not helpful in predicting the stage of a G1/G2 NEN. Different disease sites mat express heterogeneous Ki-67 levels.

P7

Extent of surgical resection in metastatic gastrinoma – a case report

Yong Yong Ling, Preeshila Behary, Raj Tanday, Raghunath Kadiyala, Agnieszka Falinska, Jeannie Todd

Department of Endocrinology, Hammersmith hospital, London, UK

We present a 41 year old Polish gentleman who has MEN-1 gene mutation (pX317X) with abdominal pain due to Zollinger-Ellison syndrome. He has multiple gastrinomas within the pancreas and duodenum, primary hyperparathyroidism with osteoporosis and pituitary microadenoma with hyperprolactinaemia and hypogonadotrophic hypogonadism. He had computed tomography, magnetic resonance imaging, endoscopic ultrasound and gallium-DOTATE PET/CT which demonstrated 5 octreotide-avid lesions in the pancreas measuring up to 3cm and 2 additional lesions in the duodenum (D2/D3). There was a 1.8cm liver lesion which could represent a metastasis.

A radical pancreatoduodenal resection with locoregional lymphadenectomy was the only treatment option which was potentially curative. However in view of the potential risk of perioperative morbidity and postoperative pancreatic insufficiency, a total pancreatic resection was not advisable. Following the neuroendocrine tumour (NET) MDT discussion, he underwent a resection limited to the gastrinoma at the pancreatic head which had been growing on interval scans to reduce risk of future metastatic progression. Intraoperatively, there was no evidence of lymph node or hepatic metastases. Histology confirmed neuroendocrine tumour (pT1 G2 vascular invasion). At 6 months follow up, his gastrin level was 385pmol/L (on PPI) and MRI demonstrated stable NET lesions.

PPIs and surgery are the mainstay treatment for gastrinoma, especially tumours >2cm. However, there is no clear consensus regarding the extent of surgery (including hepatectomy) in patients with multiple NETs. This case highlights that surgery should be tailored to individual patients based on disease load and co-morbidities and where possible to preserve pancreatic function for improved quality of life.

P8

What is the best Management of asymptomatic pancreatic tumours in MEN1?

Preeshila Behary, Raj Tanday, Raghunath Kadiyala, Agnieszka Falinska, Yong Yong Ling, Jeannie F Todd

Imperial NHS TRust, London, UK

This is a case discussion of a 49 year old lady with an asymptomatic non-functioning pancreatic lesion in the context of MEN 1.

She was first diagnosed with primary hyperparathyroidism 6 years ago and underwent a total of 3 parathyroidectomies over 4 years. Genetic testing confirmed MEN1 Syndrome.

Screening investigations revealed normal pituitary function and MRI and normal fasting gut hormones. However, initial MRI of her abdomen showed a 1.5 cm pancreatic tail lesion. One year interval MRI revealed no major growth. However gut hormone profile remained normal and the patient is asymptomatic. Ga68 DOTATATE was consistent with a gallium avid pancreatic tail lesion.

Discussion:

Pancreatic islet tumours occur in 30% to 80% of patients with MEN1 and over 80% of those are functional. The management of functional pancreatic tumours is well established and normally involved surgery; however this is less so for Non-Functioning Pancreatic Endocrine tumours (NFPETs) in MEN1. Some argue for early surgical removal of tumours >1cm as prophylaxis against tumour growth and malignant potential. Others advocate a conservative approach for NFPETs <2 cm as the mortality and morbidity of pancreatic resection outweigh the low risk of metastases and death in such scenario. It has been reported that small asymptomatic pancreatic tumours (<1.5cm) in MEN1 are usually slow growing.

In our patient, we felt a conservative approach is appropriate currently with careful monitoring of growth velocity and activity of the lesion. Optimal timing for surgery, when and if deemed necessary will be decided in our MDT.

P9

Expression of NE markers in non-NETs: a serious diagnostic pitfall. An illustrative case report and review of the literature.

Tu Vinh Luong[1], Roberta Manuguerra[1,2], Jennifer Watkins[1], Ian Clark[1]

[1]Royal Free London NHS Foundation Trust, London, UK, [2]University of Parma, Parma, Italy

Introduction: The RFH is an ENETS Centre of Excellence. Last year the Histopathology Department received 233 referred cases with the diagnosis of neuroendocrine tumour/carcinoma (NET/NEC) for specialist review prior to clinical decision making.

Case Description: We received a referred liver biopsy with the diagnosis of "metastatic carcinoma with neuroendocrine differentiation". The tumour was composed of anastomosing poorly formed glandular/tubular-like structures, set within a dense desmoplastic stroma. Large areas of tumour necrosis were present. Provided immunohistochemistry showed positivity for CK7, CK19 and CD56 and negativity for chromogranin and synaptophysin. The revised diagnosis was of "cholangiolocellular carcinoma", confirmed by imaging findings.

Discussion: CD56 is commonly expressed in NETs, but it is not as specific for neuroendocrine differentiation as chromogranin and synaptophysin, although it is considered as a highly sensitive marker of poorly differentiated neuroendocrine carcinomas. Many times we receive referred cases with the diagnosis of "carcinoma with neuroendocrine differentiation" only because of the expression of CD56.

Our series of misdiagnosed NETs include non-NE epithelial tumours such as: solid pseudopapillary neoplasm of the pancreas, acinar cell pancreatic carcinoma, renal cell carcinoma, post-hormonal therapy poorly differentiated prostate carcinoma, gastrointestinal poorly-differentiated adenocarcinoma/squamous cell carcinoma and head and neck poorly-differentiated carcinoma.

In literature, in addition to our case series, trichilemmal carcinoma and alveolar rhabdomyosarcoma may express non-specific NE markers such as CD56 and NSE, but not synaptophysin and chromogranin.

Conclusion: CD56 is not a specific and reliable neuroendocrine marker. The most important implication is the potential for misclassification of non-NET with NET. Be aware of this pitfall.

P10 & OC3

Serial Assessment of Metastatic Neuroendocrine Tumours: Factors Associated With Progression of Carcinoid Heart Disease & Death

Rebecca Dobson[1,2], Malcolm Burgess[2], Mark Pritchard[1,2], Juan Valle[3], Brian Keevil[4], Joanne Adaway[4], Uschi Hofmann[5], Alan Anthoney[6], Graeme Poston[2], Daniel Cuthbertson[1,2]

[1]University of Liverpool, Liverpool, UK, [2]Merseyside Neuroendocrine Tumour Group, Liverpool, UK, [3]The Christie NHS Foundation Trust, Manchester, UK, [4]University Hospital of South Manchester, Manchester, UK, [5]Huddersfield Royal Infirmary, Huddersfield, UK, [6]St James' University Hospital, Leeds, UK

Introduction: Carcinoid heart disease (CHD) is a complication of metastatic neuroendocrine tumours (NETs). We sought to identify factors associated with CHD progression and death in patients with metastatic NETs.

Methods: Consenting **p**atients underwent prospective serial clinical, biochemical, echocardiographic, and radiological assessment. Patients were classified as CHD progressors (defined as an increase in the degree of tricuspid regurgitation, or an increase in the degree of tricuspid leaflet thickening/immobility), non-progressors or deceased. Multinomial regression was used to assess the univariate association between variables and disease progression.

Results: A total of 133 patients were included (2816 patient years), with a median follow up of 27 months. 13 patients developed CHD or had progression of existing valvular disease. Baseline median levels of both biomarkers were significantly different between groups:

All patients (n=133)							
	CHD + (n=27)			**CHD – (n=106)**			
Biomarker	**Died (n=12)**	**Progressors (n=9)**	**Non-progressors (n=6)**	**Died (n=14)**	**Progressors (n=4)**	**Non-progressors (n=88)**	**P value**
BNP	962	375	125	211	86	75	<0.001
5HIAA	6429	2519	413	353	952	280	0.002

Every 100 nmol/L higher 5HIAA yielded a 6% greater odds of disease progression (OR 1.06, 95% CI: 1.02, 1.11; p=0.006) and 8% greater odds of death (OR 1.08, 95% CI: 1.03, 1.12; p<0.0005). CHD progression occurred more frequently in those with a deterioration in symptoms (69% v 2%, p<0.005).

Conclusion: In patients with metastatic NETs, CHD is a significantly adverse prognostic indicator: associated with poor symptom control, biochemically more severe disease and reduced progression free and overall survival.

P11

Observed Changes in Plasma Chromogranin A and Chromogranin B in Patients with NET undergoing an Octreotide Suppression Test

Lee Armstrong, Teresa Rea, Brian Johnston, David McCance

Belfast HSC Trust, Belfast, UK

In our centre patients with neuroendocrine tumours (NETs), for whom somatostatin analogue therapy has been indicated, undergo an octreotide suppression test (OST). This is performed to assess tolerance and potential biochemical/symptomatic response to long term therapy. During an OST blood samples are taken at 15 and zero minutes before and at 15, 30, 60, 120 and 180 minutes after a bolus injection of 50mcgs octreotide.

We measured chromogranins A and B (CgA, CgB) responses in 15 patients (12 male) mean age 60 years (range 48 - 72).Our reference ranges are <30U/L for CgA and <1.8 nmol/L for CgB. Of the 15 patients 8 had raised basal CgB (range 1.825 - 10.275 nmol/L) and 14 had raised basal CgA (range 43 – 8340 U/L). Various response patterns (best shown graphically) of plasma CgA and CgB concentrations were observed. Four patients had raised basal CgA and CgB which decreased after octreotide. Four patients had raised basal CgA and normal CgB which remained thus after octreotide. The rest showed individual patterns of falls and rises or no response in CgA and/or CgB. Also, the scale of changes in the chromogranins concentrations was greatly variable between patients.

These observations reinforce the variability in nature and biochemical behaviour of NETS. Some secrete both CgA and CgB while some seem to only secrete CgA.

P12

Asymptomatic pancreatic NET and indeterminate genetics- How best to manage?

Raghunath Kadiyala, Agnieszka Falinska, Yong Yong Ling, Preeshila Behary, Raj Tanday, Jeannie Todd

Imperial Centre for Endocrinology, Imperial College Healthcare NHS Trust, London, UK

Case history- A 61 year old lady presented with 2 year history of episodes of blurred vision, shakiness which were originally thought to be seizures. These episodes occurred late afternoon several hours after food intake. There was no significant past medical history or family history of note. During one such episode she was noted to have blood sugar of 1.5 mmol/l and therefore a diagnosis of insulinoma was suspected.

Initial workup revealed symptomatic hypoglycaemia with a blood sugar of 2.2mmol/l and inappropriately elevated c-peptide of 862 pmol/l and insulin of 166 mu/l with negative sulphonyluria screen consistent with an insulinoma. Calcium, pituitary profile and fasting gut hormone levels were normal. Imaging of pancreas (CT scan) showed a hypervascular blush of 1.1 cm in the head of the pancreas and also a further 9mm hypervascular blush in the pancreatic tail. Gallium Dotatate PET CT revealed avid uptake in head and tail of pancreas. EUS confirmed a NET in the head of pancreas, but the tail lesion could not be visualised. Arterial calcium stimulation and hepatic venous sampling showed a single rise in insulin following injection of Gastro duodenal artery from a baseline of 19 mu/l to peak of 245 mu/l and with no rise following injection of the splenic artery. These results are consistent with a single insulinoma in the head/body of pancreas and the pancreatic tail lesion to be non-functioning. Following MDT discussion it was decided that she should undergo resection of the functional lesion only to limit the extent of pancreatic surgery but she will require subsequent surveillance of the tail lesion with cross sectional imaging. She underwent enucleation of lesion in the head of pancreas and histology was consistent with insulinoma with Ki 67 index of <1%. Post-operatively she is well and asymptomatic.

Genetics: Identified a rare base substitution within the 5'UTR of MEN-1 just upstream of the translation site which is of uncertain pathogenecity (c.-6G>A)

Conclusion: Multiple pancreatic NET's are well recognised in patients with MEN-1**.** We present a patient with multiple NET's and rare base mutation the clinical significance of which is unknown. In hindsight, should we have performed resection of two lesions on this lady considering her genetics and potential risk of malignancy?

P13

How to tailor a tail?

Raj Tanday, Raghunath Kadiyala, Agnieszka Falinska, Yong Yong Ling, Preeshila Behary, Jeannie Todd

Imperial Centre for Endocrinology, Imperial College Healthcare NHS Trust, London, UK

We present a case of a 52 year old woman with MEN1.

In her family history her mother had osteoporosis and father died of unknown cancer. She has a ten year history of gastric reflux and whilst being investigated for menorrhagia three years ago was found to have elevated calcium and diagnosed with primary hyperparathyroidism. She underwent a single gland parathyroidectomy initially but the following year had a further 2.5 glands removed. She had genetic testing and was diagnosed with the CO196 deletion in the MEN1 gene.

On referral to our service this year, she was found to have elevated gut hormones (Chromogranin A 65pmol/L, Chromogranin B 84pmol/L, gastrin 189pmol/L off PPI) and elevated prolactin (prolactin 1313mU/L with 40% macroprolactin, TSH 1.98mU/L, fT4 12.1pmol/L, FSH 24.7U/L, LH 19.2U/L, IGF1 12.4nmol/L, random cortisol 219nmol/L, Corrected Ca 2.30mmol/L, PTH 5.5pmol/L.) MRI pituitary this year was normal. MRI pancreas 2012 showed a 2 cm tail lesion – consistent with a neuroendocrine tumour. Subsequent gallium dotatate PET CT this year confirmed that the pancreatic tail lesion was gallium avid and now increased in size to 2.5cm. In addition there were two further areas of increased uptake in D1, D2 and D3 consistent with duodenal neuroendocrine tumours. A recent CT pancreas confirmed a neuroendocrine tumour of 2.5cm. She has been discussed in our neuroendocrinology MDT. We await an EUS to evaluate the duodenal and pancreatic lesions further. Her sister has been advised to have genetic testing.

In summary our patient has MEN1 with surgically treated hyperparathyroidism, normal pituitary function, multiple GI lesions symptomatically managed with a PPI. What should the strategy be for managing the GI lesions? - (a) either a conservative approach with PPI, (b) targeted treatment with distal pancreatectomy to reduce metastatic progression or (c) a more extensive resection with duodenectomy.

P14

The role of primary resection and hepatic resection in the management of metastatic pancreatic Neuroendocrine tumours with irresectable liver metastases

Logan Mills[1], John Ramage[1,2], Andreas Prachalias[1,3], Parthi Srinivasan[1,3], Krishna Menon[1,3], Alberto Quaglia[1,4], Gill Vivian[1], Nigel Heaton[3], Raj Srirajaskanthan[1]

[1]ENETS Centre of Exellence, Institute of Liver Studies, King's College Hospital, London, UK, [2]Department of Gastroenterology, Hampshire Hospitals NHS Trust, Basingstoke, UK, [3]Hepatopancreatobiliary Surgery, Institute of Liver Studies, King's College Hospital, London, UK, [4]Department of Histopathology, Institute of Liver Studies, King's College Hospital, London, UK, [5]Department of Gastroenterology, University Hospital Lewisham, London, UK

Introduction: More than 40% of pancreatic neuroendocrine tumour (PNET) patients have liver metastases (LM) at the time of diagnosis. There is agreement that curative surgery aimed at resection of the primary and metastatic disease offers patients the best outcome. The role of debulking surgery in the context of irresectable LM remains unclear. There is no clear evidence to support resection of the pancreatic primary in the context of irresectable liver metastases. The aim of this study is to investigate the survival benefits of different surgical treatments of irresectable LM.

Methods: Of 111 King's PNET patients, 53 had LM at diagnosis. Patients with sufficient data were divided into 3 cohorts, the remainder were excluded: No Resection (NR) n=27, Pancreatic Resection (PR) n=6 and Pancreatic and Liver Resection (PLR) n=11. Kaplan-Meier survival curves were constructed. Median duration of follow-up was 40.2 months.

Results: Median survival was significantly worse for patients with no resection; NR (23 months) vs. PR (98 months) p=0.047, NR (23 months) vs. PLR (37 months) p=0.008, but there was no significant survival difference between PR and PLR.

Of the 11 patients who received pancreatic and liver resections (PLR), only 5 were intended to completely remove the tumour burden. 6 patients received debulking for irrresectable, bilobar metastases as well as pancreatic resection. Multivariate analysis showed that primary resection (p=0.001) and liver resection (p=0.022) were prognostic variables; resectability of liver metastases was not significant (p=0.118).

Conclusion: Resection of the primary significantly improves survival in the presence of irresectable liver metastases. There may be a role of debulking surgery in patients with irresectable liver metastases, however, the data so far does not appear to suggest a survival benefit over primary resection alone. A larger multicentre study may be able to address the role of debulking liver metastases in PNETs.

P15

Does primary pancreatic tumour resection improve prognosis of patients with pancreatic neuroendocrine tumours

Logan Mills[1], John Ramage[1,2], Andreas Prachalias[1,3], Parthi Srinivasan[1,3], Krishna Menon[1,3], Alberto Quaglia[1,4], Gill Vivian[1], Nigel Heaton[3], Raj Srirajaskanthan[1,5]

[1]ENETS Centre of Exellence, Institute of Liver Studies, King's College Hospital, London, UK, [2]Department of Gastroenterology, Hampshire Hospitals NHS Trust, Basingstoke, UK, [3]Hepatopancreatobiliary Surgery, Institute of Liver Studies, King's College Hospital, London, UK, [4]Department of Histopathology, Institute of Liver Studies, King's College Hospital, London, UK, [5]Department of Gastroenterology, University Hospital Lewisham, London, UK

Introduction: The incidence of pancreatic neuroendocrine tumours (PNETs) has increased in recent years resulting in developments to surgical approaches for PNET patients. The aim of this study is to investigate if there is survival benefit in resecting primary tumour in patients with pancreatic NETs.

Methods: The records of 103 King's PNET patients since 2004 were analysed. At presentation 34 had local disease, 18 had loco-regional disease and 51 had metastatic disease. Kaplan-Meier survival curves were constructed to demonstrate survival of patients undergoing surgery compared with a cohort of 15 patients who were recommended for resection but declined for personal reasons. Multivariate analysis was performed to identify independent prognostic risk factors. The median duration of follow-up was 50.3 months.

Results: All stages of patients undergoing primary pancreatic tumour resection (n=61) had significantly better 5 year survival than those who were offered, but declined surgery (n=15); 94% vs. 41% $p<0.0001$. Multivariate analysis demonstrated that undergoing surgery ($p<0.001$) and age at diagnosis ($p=0.043$) were independent prognostic indicators. Co-morbidity was not an independent prognostic indicator.

Surgical resection margin has important implications for outcome. Of 61 patients that underwent pancreatic resections, 9 experienced recurrence (15%). Of those 1 was stage II, 5 were stage III and 3 were stage IV. Three operations (33%) had R1 or R2 margins. Tumour location within pancreas, laparoscopy vs. laparotomy and GI resection did not significantly correlate with resection margin. 67% of patients with recurrence had nodal metastases at the time of surgery. Overall median survival of PNET patients, irrespective of treatment, was 109 months, with a 5 year survival of 78%.

Conclusion: Primary pancreatic tumour resection significantly improves survival compared to no primary tumour resection. This data demonstrates improved survival of all pancreatic NETs compared to historical SEER data, with an overall 5 year survival of 78%.

P16

Prognostic validity of the WHO 2010 TNM staging and grading criteria for pancreatic neuroendocrine tumours

Logan Mills[1], John Ramage[1,2], Andreas Prachalias[1,3], Parthi Srinivasan[1,3], Krishna Menon[1,3], Alberto Quaglia[1,4], Gill Vivian[1], Nigel Heaton[3], Debashis Sarker[1], Paul Ross[1], Raj Srirajaskanthan[1,5]

[1]ENETS Centre of Exellence, Institute of Liver Studies, King's College Hospital, London, UK, [2]Department of Gastroenterology, Hampshire Hospitals NHS Trust, Basingstoke, UK, [3]Hepatopancreatobiliary Surgery, Institute of Liver Studies, King's College Hospital, London, UK, [4]Department of Histopathology, Institute of Liver Studies, King's College Hospital, London, UK, [5]Department of Gastroenterology, University Hospital Lewisham, London, UK

Introduction: The TNM staging and grading system developed by the WHO is designed to help prognosticate patients and better understand the histological characteristics of tumours. This study aims to retrospectively stage and grade patients with pancreatic neuroendocrine tumours (PNETs) and investigate whether these systems accurately predict prognosis.

Methods: 111 patients with PNETs treated at King's were included in this study. Non-functioning tumours accounted for 97 (87%) of cases; the remainder were functional. Grading was assigned according to the WHO 2010 histopathological criteria. Histological data was available for 80 patients (G1=32, G2=31, G3=17). Mean age at diagnosis 57 (range 23-84). Median duration of follow-up 50.3 months.

Results: Kaplan-Meier survival analysis demonstrated significant median survival differences between all grades. G1(n/a), G2(109 months), G3(37 months); G1vsG2 p=0.036, G1vsG3 p<0.001, G2vsG3 p=0.006.

TNM staging data was obtained for 103 patients; stages IIA and IIB and stages IIIA and IIIB were merged due to low patient numbers. The merged data (stage I=7, stage II=18, stage III=27, stage IV=51) yielded significant survival differences between stage IV and all other stages. 5 year survival I=86%, II=81%, III=89%, IV=54% (stage IV vs. I p=0.021, stage IV vs. II p=0.037, stage IV vs. III p=0.02). Exclusion of 5 patients with tumour unrelated deaths did not alter the result. Overall median survival of PNET patients was 109 months.

The insignificant difference in survival between stages II and III (p=0.69) may be largely due to good surgical outcomes for stage IIIB patients (positive lymph nodes). Of 18 stage IIIB patients, 15 underwent resection including LN excision. 10 operations were curative.

Conclusion: This study demonstrates that tumour grade prognosticates survival. TNM stage IV disease carries significantly worse survival than stages I-III. Aggressive surgical approach to patients with loco-regional disease (stage III), appears to demonstrate excellent outcomes compared with other historical databases.

P17 & OC4

Lymph Node Involvement to Predict Survival in Pulmonary Neuroendocrine Tumours – A Single Centre Experience.

Vanessa Clay[1], Rebecca Stein[3], Erick Piarino[3], Deborah Lam[2], Zena Salih[1], Piotr Krysiak[2], Kandadai Rammohan[2], Wasat Mansoor[1]

[1]The Christie Hospital, Manchester, UK, [2]University Hospital South Manchester, Manchester, UK, [3]The University of Manchester, Manchester, UK

Introduction: Pulmonary carcinoid tumours belong to a spectrum of neuroendocrine neoplasms, they account for only 1-2% of all lung malignancies. This study aimed to examine lymph node (LN) status as a prognostic factor within these well differentiated tumours, specifically; Typical (TC) and Atypical Carcinoid (AC) tumours, presenting to a single centre.

Methods: A retrospective review of 94 patients treated at the Christie Hospital between 2005 and 2013 was carried out. All cases were identified as either TC or AC according to the WHO criteria. Median follow up time was 21 months (1-149 months). The Chi-square test was used for statistical analysis.

Results: There were a total of 73 (77.7%) TC and 21 (22.3%) AC tumours identified.

Significantly more ACs demonstrated LN involvement at the time of diagnosis (66.7%) than TCs (19.2%, p= 0.00008). As such far fewer ACs were suitable for surgical treatment (57.1% vs 83.6% p=0.0104).

Furthermore, Kaplan Meier survival curves demonstrated that LN positive AC patients had a statistically significant survival disadvantage in comparison to LN negative AC patients(p=0.027). In contrast, TC tumours demonstrated no significant survival difference between the LN positive and negative groups (p=0.125).

Conclusion: This study serves to highlight the more aggressive nature of ACs in comparison to TCs. It also suggests that LN status is of paramount importance within the AC group and is a useful prognostic marker. We suggest that the more aggressive nature of AC tumours and the significance of positive LN status support the consideration of adjuvant chemotherapy for these patients.

P18

Retrospective Study of MIBG Therapy for Phaeochromocytoma (PH) and Paraganglioma (PG): The Christie Experience.

Zena Salih[1], Kimberley Fletcher[2], Vanessa Clay[1], Prakash Manoharan[1], Robert Hawkins[1,2], Peter Trainer[1,3], Wasat Mansoor[1]

[1]The Christie Hospital, Manchester, UK, [2]The University of Manchester, Manchester, UK, [3]University Hospital South Manchester, Manchester, UK

Introduction: PH and PG are rare neuroendocrine tumours treated with MIBG therapy. Low prevalence of disease has meant treatment protocols are not standardised and reported results are variable.

Method: We retrospectively studied 7 patients receiving MIBG therapy [M/F: 6/1, median age: 31 yr (17-71)] with metastatic PH (n=4) or PG (n=3) to evaluate efficacy, tolerability and overall survival. Response was assessed using clinical benefit, biochemical markers and radiology.

Results: Median number of metastatic sites was 3 (range: 1-4) including lymph nodes (n=5), lung (n=6), liver (n=2), and bones (n=5). Previous treatments included surgery (n=3), chemotherapy (n=3) and radiotherapy (n=3). 5 of 7 patients were symptomatic. 4/7 had SDHB gene mutations but RET/MEN2 and VHL mutations were not identified in 5 cases tested. 16 cycles of therapy delivered (range: 1-3 per patient). Median MIBG dose was 5000 MBq (range: 3700-7500). 5 of 7 had raised catecholamines before MIBG and 4 responded (2 normalized, 80% clinical response). Six cases had a radiological response (87%, 2 CR, 2 PR, 2 SD and 1 PD). Common side effects were nausea (57%) and lethargy (14%). No patient developed renal dysfunction and 1 developed myelosuppression. 3 patients are alive (3 died and 1 lost to FU). Survival from diagnosis was between 1 to 19 years and between 1 to 11 years from first MIBG therapy. It was not possible to analyze predictors of response or survival.

Conclusion: MIBG therapy is relatively well tolerated and effective. It is possible to achieve benefit even in patients with metastasis.

P19

Hypopituitarism presenting as self diagnosed hypogonadism in carcinoid syndrome

Kristopher Knott[1], Lucy Dumas[1], Naureen Starling[1], Ian Chau[1], Nash Aldin[2], Roger Chinn[2], Daniel Morganstein[2,1]

[1]The Royal Marsden Hospital, London, UK, [2]Chelsea and Westminster Hospital, London, UK

An 80 year old retired civil servant presented with general malaise, weight loss, intermittent flushing and irregular bowel habit. He had a history of left lower lobectomy for a carcinoid cancer ten years previously. CT and MRI demonstrated the presence of several liver lesions, his urinary 5HIAA was raised at 132, chromogranin A over 1000 and chromogranin B was 213. A suspected recurrence of his carcinoid cancer was confirmed with an octreotide scan showing multifocal uptake in the liver. He was commenced on monthly lanreotide injections, on which he remains, 5 years later.

He recently however noted persistent, unexplained fatigue. Reading an article on the “male menopause” in a civil service magazine and feeling he had many of the symptoms, he sought advice from his general practitioner. His testosterone was found to be less than 0.35nmol/L.

Subsequent testing revealed panhypopituitarism and secondary hypothyroidism. A short synacthen test was normal. An MRI scan of his pituitary was performed showing an enhancing pituitary lesion, not typical for an adenoma and more suggestive of a metastasis.

Following correction of his panhypopituitarism and hypothyroidism with testosterone and thyroxine his energy levels and subjective health have improved. He remains under routine clinical follow up.

This is a case of self-diagnosed hypogonadism in carcinoid syndrome possibly due to a carcinoid metasasis. Although rare, we demonstrate here that unexplained symptoms of tiredness may be explained by pituitary metastases in patients with metastatic neuroendocrine tumours and should be investigated with hormone profiling that may reveal unexpected pathology.

P20

Treatment with Lutetium-177- DOTATATE for advanced neuroendocrine tumors

Roberta Elisa Rossi[1,2], Andrew Melville[1], Emmanouil Maragkoudakis[1], Jorge Garcia-Hernandez[1], Mohmaduvesh Mullan[1], Keval Naik[1], Ann-Marie Quigley[3], Shaunak Navalkissoor[3], Martyn Evan Caplin[1], Christos Toumpanakis[1]

[1]Neuroendocrine Tumour Unit, Centre for Gastroenterology, Royal Free Hospital, London, UK, [2]Postgraduate School of Gastroenterology, Universita' degli Studi di Milano, Milan, Italy, [3]Nuclear Medicine Department, Royal Free Hospital, London, UK

Introduction: Peptide receptor radionuclide therapy with Lu-177-DOTATATE is a promising therapy in patients with advanced neuroendocrine tumours (NETs) for symptomatic relief and tumour regression. Aim: To investigate the efficacy and safety of Lu-177-DOTATATE in advanced NETs with progressive disease, despite all previous treatments.

Methods: Patients who received 1to 4 cycles of Lu-177-DOTATATE were identified and retrospectively reviewed. Radiological and symptomatic response were evaluated: radiological assessment according to RECIST; symptomatic assessment: no change, minor response [decrease of 25-50%], major response [decrease > 50%].

Results: 75 patients (40 female, 35 male), median age 63 years were treated overall. 45/75 patients had midgut primary, 10 pancreatic, 6 bronchial, 5 and 9 of other and unknown origin. 74 patients were well-differentiated NETs (G1 40, G2 16). 55% of the patients had previous surgery, 81% somatostatin analogues, 24% chemotherapy, 8% targeted therapy (i.e. everolimus and/or sunitinib), 17.3% Yttrium-90- DOTATATE. 49 patients had ≥2 cycles of Lu-177-DOTATATE. Of these, 38 had restaging Computed Tomography scan after at least 2 cycles: 18% had partial response, 66% stable disease, 16% progressive disease. Among the patients who had ≥2 cycles, 47% had minor symptomatic response, 12% major response, 30% no change, 11% no data. 7% patients had grade 2 and 3 bone marrow toxicity and 3% of the patients had grade 2 renal toxicity.

Conclusions: Lu-177-DOTATATE seems a safe, well tolerated treatment which appears to be effective in controlling symptoms and tumour growth in progressive NETs.

P21

IMPROVED DIAGNOSTIC ACCURACY OF CHROMOGRANIN A DAKO ASSAY FOR GASTRIC CARCINOID TYPE 1

Roberta Elisa Rossi[1,2], Nick Martin[3], Jorge Garcia-Hernandez[1], Dalvinder Mandair[1], Mohmaduvesh Mullan[1], Christos Toumpanakis[1], Martyn Evan Caplin[1]

[1]Neuroendocrine Tumour Unit, Centre of Gastroenterology, Royal Free Hospital, London, UK, [2]Postgraduate School of Gastroenterology, Universita' degli Studi di Milano, Milan, Italy, [3]Department of Clinical Biochemistry, Royal Free Hospital, London, UK

Introduction: Chromogranin A (CgA) is not very accurate for the diagnosis of gastric carcinoid type1 (GC1). Clinical interpretation of CgA results may be affected by the heterogeneity between commonly available CgA assays.

Aim: To compare two different CgA assays, the commercial CgA assay, DAKO (DAKO, Denmark A/S, Glostrup, Denmark) and the Imperial Supra-regional Assay Service radioimmunoassay (SAS Hammersmith Hospital, Imperial College, London) to determine their accuracy in the diagnosis of GC1.

Methods: Patients with a confirmed diagnosis of GC1 and available plasma Chromogranin A (CgA) measurements according to two different assays (Imperial SAS and DAKO) were included and retrospectively reviewed. CgA values were ranked in 4 groups: 1. normal values, 2. increase <2 upper normal limit (ULN), 3.increase between 2-5 ULN 4. Increase >5 ULN.

Results: A total of 25 patients, 16 female and 9 male, median age 58 years (range 26-75) were identified. Median CgA-DAKO were significantly higher than median CgA-Hammersmith (81 IU/l, normal range < 27 IU/l versus 35 pmol/l, normal range < 60 pmol/l, T=38.5, p=0.001). When ranking the data, the results confirmed median CgA-DAKO significantly higher than median CgA-Hammersmith (3 versus 1, T=0, p <0.001). Sensitivity was 76% and 8% for CgA-DAKO and CgA-Hammersmith, respectively.

Conclusions: CgA-DAKO seems to have a better sensitivity than CgA-Hammersmith for the diagnosis of GC1. Further prospective studies are needed to confirm these results.

P22

CHROMOGRANIN A AS A PREDICTOR OF RADIOLOGICAL DISEASE PROGRESSION

Roberta Elisa Rossi[1,2], Jorge Garcia-Hernandez[1], Nick Martin[3], Mohmaduvesh Mullan[1], Tim Meyer[4], Chrissie Thirlwell[4], Jennifer Watkins[5], Martyn Evan Caplin[1], Christos Toumpanakis[1]

[1]Neuroendocrine Tumour Unit, Centre of Gastroenterology, Royal Free Hospital, London, UK, [2]Postgraduate School of Gastroenterology, Universita' degli Studi di Milano, Milan, Italy, [3]Department of Clinical Biochemistry, Royal Free Hospital, London, UK, [4]Cancer Institute, University College London, Huntley Street, London, UK, [5]Histopathology Department, Royal Free Hospital, London, UK

Introduction: Chromogranin A (CgA) is the best established neuroendocrine biomarker.

Aim: To investigate the prognostic value of CgA as a predictor of radiological disease progression in neuroendocrine tumour (NET) patients.

Methods: Patients with metastatic NETs and evidence of radiological progression (RP) according to RECIST 1.1 were identified from a NET database. Plasma CgA were measured 6 and 12 months before RP and at the event of RP. CgA was measured with the Supra-regional-Assay-Service radioimmunoassay (Hammersmith Hospital).

Results: 152 patients were evaluable including midgut NET (91) and pancreatic (61) NET (PNET). Of these, 56 were G1 NETs, 65 G2, 10 G3, 21 of unknown histology. Median CgA for all NET patients 6 months before RP was 213 pmol/L and at 12 months was 166 pmol/L, T=598.5, p=.07. Significant results were found for PNETs [median CgA 6 months before RP was 100 pmol/L and at 12 months was 52 pmol/L, T=52, p=.048], but not for midgut NETs [median CgA 6 months before RP was 389.5 pmol/L and at 12 months was 319 pmol/L, T=191, p=.39]. Midgut and PNETs had significantly higher CgA values at RP than 12 months before [median CgA at RP was 165 pmol/L and at 12 months was 159 pmol/L, T= 394.5, p=.03]. Overall, low-grade tumours had median CgA value at 6 months significantly higher than at 12 months [181 pmol/L versus 149.5 pmol/L, T=70, p=.048].

Conclusions: CgA seems to have predictive value 6 months prior to RP for PNETs and G1 tumours but not for midgut. Further prospective analyses are needed to enable more definitive conclusions.

P23

Responsiveness to chemotherapy (chemo) is independent of primary tumour site in well differentiated gastro-entero-pancreatic (GEP) neuroendocrine tumours (NETs).

Angela Lamarca, Was Mansoor, Richard A Hubner, Juan W Valle

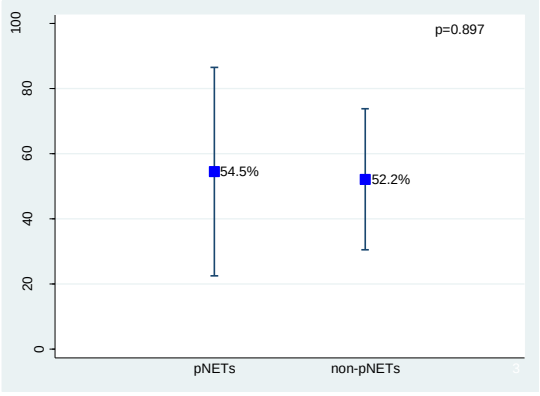
The Christie NHS Foundation Trust, Manchester, UK

Introduction: Chemotherapy is a cornerstone of treatment for patients with advanced well differentiated pancreatic NETs (pNETs); its benefit for well differentiated non-pNETs remains controversial.

Material and methods: We performed a retrospective, single-centre, analysis of patients with well differentiated advanced GEP NET treated with chemo prior to September 2013 aimed at evaluating differences in efficacy between pNETs and non-pNETs (statistical software: Stata v.12).

Results: Twenty-eight patients were identified: median age 61 years (range 28-83); male: 68%; liver metastases: 100%; PS0 21%; PS1 64%; pNET/non-pNET 32%/68% (25% small bowel); median Ki-67 10% (range 1-20); grade (G)1: 11%, G2 86%; there was no correlation between the site of the primary tumour and Ki-67 (p=0.692%). Median time from diagnosis to start of 1st-line chemo was 5.5 months (range 0.3-101.8); chemo schedules (median of 4 cycles (range 1-6)) employed were: streptozocin (STZ)-capecitabine (57%), STZ-capecitabine-cisplatin (14%), carboplatin-etoposide (29%); 32% were treated within a clinical trial; 6 patients also received 2nd-line chemo; 90% of patients have progressed and 46% have died (median follow-up: 24.1 months, range 2.0-102.2). Disease control rate (DCR) for chemo (overall) was 49.9% with no difference between pNETs and non-pNETs (54.5% vs. 52.2%; p=0.897; Figure). The PFS and OS for 1st/2nd-line chemo was 7.1 months (95%CI 2.63-10.19)/5.1 months (95%CI 1.48-not reached (NR)) and 23.5 months (95%CI 15.2-NR)/8.4 months (95%CI 4.67-NR), respectively.

Conclusion: These data suggest that, where indicated, chemotherapy may benefit non-pNET patients as well as pNET patients.



P24

Improving patient selection by predicting response to arterial embolisation of neuroendocrine liver metastases

Abigail Vallance, Colin Wilson, Rob Williams, Ralph Jackson, Petros Perros, Andrew James, Jeremy French, Derek Manas

Freeman Hospital, Newcastle Upon Tyne, UK

Background: Selective hepatic arterial embolisation (HAE) with polyvinyl alcohol particles can provide a biochemical, radiological and clinical improvement in many patients with hepatic gastroenteropancreatic neuroendocrine (GEP-NET) metastases. We aimed to aid patient selection for HAE by establishing variables that may predict a response to treatment or improved survival.

Methods: We reviewed demographics, disease characteristics, treatment response and survival of GEP-NET patients with hepatic metastases undergoing HAE from 2008-12. Response to treatment was evaluated biochemically (reduction in urine 5-HIAA), radiologically (contrast CT) and clinically (symptoms). Univariate and multivariate analyses was used to identify predictors of response and long term survival.

Results: 31 patients underwent 64 procedures (range 1-7). A biochemical, radiological or clinical response was reported in 61%, 62% and 65% respectively. Median survival post procedure was 2.5 years. On univariate and multivariate binary logistic regression the continued presence of the primary tumour negatively affected symptomatic response to HAE (Fisher's test, $p=0.03$). The presence of extrahepatic disease (logrank, $p=0.046$) and the tumour grade (logrank, $p=0.0009$) affected survival. Multivariate Cox regression analysis identified only tumour grade as associated with differential survival (median survival G1/G2 3.4 yrs, G3 10 months; Hazard Ratio 0.13, $p<0.001$).

Conclusions: Patients with primary in situ may experience pain and bowel disturbance related to this primary tumour therefore masking the symptomatic effect of HAE. No other clinical variable predicted a treatment response. HAE can reduce symptoms as well as biochemical and radiological markers of disease in the majority of this complex and heterogeneous cohort of patients.

P25

"Neuroendocrine Surgical follow-up – is there a place for nurse led clinics?"

Lynne McCallum

The Christie NHS Foundation Trust, Manchester, UK

Background: Patients who have received solely surgical intervention/s in the management of their neuroendocrine tumour (NET) are traditionally followed up in a medical oncology clinic. The purpose of this study was to review the number of patients who attend for surgical follow up, the surveillance methods currently in practice and to identify if there was scope to adopt a nurse led review service.

Methods: For a period of 6 months patient details were added to the audit tool by the clinician performing the review. The inclusion criteria were surgical FU patients, with fully resected disease, who have been discussed at the specialist NET MDT and had post-operative imaging. Patients with metastatic disease and whose primary disease was of unknown origin were excluded from this study.

Results: 70 patient details were entered into the audit tool, with 3 distinct disease groups emerging. The groups were: - bowel (*including small bowel, ileum, rectum and colon)* (41%), pancreas (26%) and appendix (11%). There appears to be under reporting for gastric (7%) and lung surgical patients (7%).

Conclusion: There is scope for the development of a nurse led approach to the management of post-surgical follow up. To safely develop a comprehensive nursing service there is need for further work to establish standardised protocols in regards to follow up, working in line with the recommendations of UKINETS and ENETS.

P26

Insulin and glucagon co-secreting pancreatic neuroendocrine tumour (pNET)

Helen Alexander, Naureen Starling, Fieke Froeling, David Cunningham, Daniel Morganstein

Royal Marsden Hospital, London, UK

A 61 year old male presented with anorexia and weight loss. Imaging revealed a liver mass and lymphadenopathy. Biopsy confirmed low grade metastatic pNET. Immunohistochemistry revealed tumour expression of chromogranin, CD56 and synaptophysin but no insulin, glucagon, gastrin or somatostatin expression. However serum glucagon levels were persistently raised with normal glucose levels, suggesting tumour glucagon secretion. Treatment with sunitinib was commenced.

Two years after diagnosis the patient developed deranged liver function tests, and imaging confirmed progression of nodal disease with biliary dilations. At this stage, episodes of hypoglycaemia occurred due to endogenous insulin suggesting the tumour cosecreted insulin and glucagon. Interestingly, he had a five year history of collapses for which no cause had been found, and in retrospect felt they were symptomatically identical to these hypoglycaemic episodes. We hypothesised that the effect of insulin had outweighed the effects of glucagon causing persistent hypoglycaemia, despite diazoxide and glucuocorticoid treatment, perhaps exacerbated by the abnormal liver function leading to reduced glycogen storage.

He was commenced on everolimus, with rapid resolution of hypoglycaemia and some regression of liver lesions. However when the everolimus was interrupted due to pneumonitis, problematic hypoglycaemia recurred.

We have described a rare case of pNET that cosecretes insulin and glucagon. There are published cases of pNETs secreting more than one hormone although no reported cases of insulin and glucagon cosecretion. This report, and the other published cases support the suggestion that pNET tumour cells are derived from precursor cells that have the ability to make multiple hormones.

P27

Venous and arterial thrombosis associated with raised Factor VIII secondary to catecholamine release from phaeochromocytoma.

Thomas Marjot[1], Rebecca Scott[1], Eddy Chua[2], Keith Steer[2]

[1]Imperial College Healthcare NHS Trust, London, UK, [2]North West London Hospitals NHS Trust, London, UK

Case presentation: A 73 year-old lady was admitted for treatment of an ultrasound confirmed left lower limb deep vein thrombosis. Her background included a left upper-quadrant mass identified incidentally on abdominal ultrasound in 2009. Initial computed tomography scanning in 2009 demonstrated a 13.7x12.4x13cm suprarenal mass which had grown to 16.8x15.6x15cm at this admission 3.5yrs later. The patient was a strict Jehovah's Witness who had previously refused any attempt at biopsy or surgical intervention. One 24hr urinary collection in 2009 was found to contain normal levels of catecholamines (CCAs).

During admission she developed an ischaemic left foot despite being anticoagulated, with an INR of 6.88. She subsequently underwent a failed femoral thrombectomy and below-knee amputation. Pre-operatively four consecutive days of urinary CCAs were sent which were reported postoperatively as all yielding markedly elevated levels of noradrenaline, adrenaline and dopamine. ^{123}I- MIBG scanning has since confirmed an adrenal phaeochromocytoma with no evidence of metastasis. During her recovery she developed deranged LFTs and ultrasound showed portal venous thrombosis. A thrombophilia screen was then performed which demonstrated an isolated, raised factor VIII level of 250.5 IU/dL (ref 50-150IU/dL).

Discussion: Studies have shown that factor VIII (FVIII) production is beta-receptor mediated, with plasma levels shown to rise significantly with infusions of adrenaline, noradrenaline and after exercise. Prospective series have also implicated increased FVIII levels in both venous and arterial thrombotic disease. This case is the first to document a profound thrombophilia secondary to isolated raised FVIII in the context of a large and neglected phaeochromocytoma.

P28

Sunitinib and Everolimus in Pancreatic Neuroendocrine Tumors (pNETs), a retrospective UKINETS study

Leila Khoja[1], Tim Meyer[2], Mullan Mohmaduvesh[2], Waters Justin[3], Wadesley Jonathan[4], Yuk Ting Ma[5], Martin Eatock[6], Hiliary Williams[7], Pippa Corrie[8], Sharmila Sothi[12], Daniel Palmer[10], David Farrugia[11], Nicholas Reed[9], Chrissie Thirlwell[2], Juan William Valle[1]

[1]The Christie NHS Foundation Trust, Manchester, UK, [2]Royal Free NHS Foundation Trust, London, UK, [3]Maidstone and Tunbridge Wells NHS Trust, Maidstone, UK, [4]Western Park Hospital, Sheffield, UK, [5]University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK, [6]Northern Ireland Cancer Centre, Belfast City Hospital, Belfast, UK, [7]Velindre Cancer Centre, Cardiff, UK, [8]Cambridge University NHS Foundation Trust, Cambridge, UK, [9]Beatson Oncology Centre, Glasgow, UK, [10]Royal Liverpool Univeristy Hospitals, Liverpool, UK, [11]Gloustershire Hospitals NHS Foundation Trust, Cheltenham, UK, [12]University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK

Two randomized phase III trials in patients with progressive metastatic well-differentiated pNETS reported improved progression free survival (PFS) with sunitinib (Raymond et al NEJM 2011, HR 0.42) or everolimus (Yao et al NEJM 2011, HR 0.35), over placebo. Sunitinib and everolimus were funded through the Cancer Drugs Fund (CDF) in Dec 2010 and Sept 2011. Use of these agents out with trials will inform on benefit in real-world clinical practice.

Methods: We conducted a retrospective study under the auspices of the UK & Ireland Neuroendocrine Tumour Society (UKINETS). Patients were identified through the CDF register and at individual NET centres in England, Wales and Northern Ireland between Dec 2010 - Dec 2012. Clinical data was collected and univariate analysis undertaken for prognostic factors.

Results: 82 patients (51 males, median age 58) were identified. 7 patients received sequential sunitinib then everolimus. Tumour grade was well-differentiated in 72, poorly-differentiated in 3, unknown in 7. Patient characteristics and outcome are shown in Table 1. Median follow up was 7 months. Univariate analysis did not reveal any prognostic factors.

Conclusions: Real-world PFS of sunitinib or everolimus in non-trial more heavily pre-treated pNET patients is lower but approaching published data. Longer follow-up will determine long term benefit and the effect of cross-over between sunitinib and everolimus.

Table 1 (* excluding poorly differentiated tumours).

Characteristic	**Sutent(N=57)**	**Everolimus(N=25)**
Prior treatment	52(91%)	21(84%)
Surgery Curative	19(33%)	7(28%)
Palliative	11(19%)	8(32%)

Somatostatin analogue Previous	7(12%)	1(4%)
Current	14(25%)	8(32%)
Liver directed therapy (TACE/RFA)	5(9%)	3(12%)
Radionucleotide	8(14%)	4(16%)
Chemotherapy/immunotherapy	32(56%)	14(56%)
Reason for cessation Disease progression/ toxicity	30(53%)/7(12%)	4(16%)/10(40%)
Median PFS	8.8	8.9
Median PFS (all patients)	8.8	

P29 & OC5

A randomized, double-blind, placebo-Controlled study of Lanreotide Antiproliferative Response in patients with gastroenteropancreatic NeuroEndocrine Tumors (CLARINET)

Martyn Caplin

Royal Free Hospital, London, UK

Background: The antiproliferative role of somatostatin analogs (SSAs) in GEP-NET patients is still limited, with only one previous prospective trial showing efficacy in patients with midgut tumors and limited liver tumor burden. This is the first large-scale, multinational, phase 3 trial to prospectively evaluate antiproliferative effects of the SSA lanreotide Autogel in a large population with non-functioning GEP-NET, including pancreatic and gastrointestinal tumors.

Methods: CLARINET was a randomized, double-blind, placebo-**C**ontrolled study of **L**anreotide **A**ntiproliferative **R**esponse in patients with GEP-**NET**. In total, 204 patients ≥ 18 yrs, with well or moderately differentiated (Ki67 < 10%) non-functioning GEP- NETs, with no hormone-related symptoms, and who had not received SSAs, interferon, chemoembolization or chemotherapy in the last 6 months, were treated with lanreotide Autogel 120 mg (n=101) or placebo (n=103) every 4 weeks for 96 weeks or until progressive disease (PD) or death. The primary endpoint was progression free survival (PFS; i.e. time to progression using RECIST, or death). Regular CT scans at baseline and at restaging throughout the study were centrally assessed. Secondary endpoints included % of patients with PD or death, and safety. The final analyses in the intent-to-treat and safety populations are presented. The study was sponsored by Ipsen. CT.gov NCT00353496; EudraCT 2005-004904-35.

Results: At enrolment, primary tumor locations were pancreas (45%), midgut (36%), hindgut (7%) and unknown (13%). Most had stable disease (96%) and were treatment-naïve (81%); 22% of patients had Ki67 3%–10% (WHO grade 2), 33% had hepatic tumor load >25%. Two years of treatment with lanreotide showed significantly prolonged PFS over placebo: median PFS was not reached with lanreotide vs 18 months with placebo (hazard ratio 0.47; 95% CI 0.30–0.73; p=0.0002). At end of 2 years of treatment, 62% of lanreotide treated patients vs 22% of placebo treated patients had not progressed or died. Lanreotide showed favourable safety/tolerability consistent with its known safety profile. Treatment-related AEs with lanreotide vs placebo occurred in 50% vs 28% of patients (most frequent event was diarrhea, 26% vs 9%), and few of these were serious events (3% vs 1%). Few AEs led to study withdrawal (3 vs 3 patients).

Conclusions: Lanreotide Autogel 120 mg can substantially prolong PFS for GEP-NET patients. These data offer new and compelling evidence for the antiproliferative effect of lanreotide.
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P30

Dilemmas in management of small and asymptomatic pancreatic neuroendocrine tumours

Agnieszka Falinska, Yong Ling, Preeshila Behary, Raj Tanday, Raghunath Kadiyala, Jeannie Todd

Hammersmith Hospital, Imperial Centre for Endocrinology, London, UK

38 year old female presented to GP with vague abdominal symptoms. She had US abdomen, which suggested possibility of pancreatic lesion. This incidental finding was further investigated with CT abdomen showing single 16mm lesion but also a possible additional 8mm lesion in body of pancreas. Endoscopic US showed two hypoechoic lesions (14x8mm at the head and 14x11mm at the body of pancreas) suggestive of two NETs. However the Ga68 DOTATATE PET CT scan showed only a single area of avid uptake in a lesion at the neck of the pancreas consistent with a NET. She had no radiographic evidence of local invasion or metastases. Her liver function and gut hormones profile were normal. She was well with no significant past medical history apart from back pain and BMI of 43.7 kg/m2. Her case was discussed at MDT and decision to limit surgery to the removal of the gallium avid lesion only was made. She underwent laparoscopic central pancreatectomy. The histology showed well differentiated neuroendocrine tumour with no vascular invasion and limited to pancreas (PT1). It was staining for insulin and had very low Ki67 index (1-2%). Peri-operatively the second lesion was not identified. Currently the patient is 3 months post surgery and is now complaining of symptoms suggestive of hypoglycaemia and is due for 3 day fast, genetic consultation for MEN 1 screen and repeat endoscopic US.

This case highlights the difficulties in managing small and non-functioning PNETs. The decision for surgery can be challenging in asymptomatic patients and surgical risks might outweigh the potential benefits. It also illustrates the challenges with imaging of small PNETs with dis-concordance between radiological imaging and laparoscopic visualisation during surgery. Furthermore it highlights the importance of regular monitoring of functional status.

P31

Current imaging of bronchial neuroendocrine tumours – a pictorial review

Nicola Mulholland, Gill Vivian

Kings College Hospital, London, UK

Aim: To illustrate current imaging appearances of bronchial neuroendocrine tumours.

The incidence of bronchial neuroendocrine tumours is rising, although it remains a rare tumour. This educational pictorial essay will illustrate recognised radiological patterns of typical and atypical carcinoids. CXR and CT features will be displayed as well use of hybrid molecular imaging techniques including SPECT CT and PET CT. The 7th TMN staging system for bronchial NET will be explained.

P32

Evaluation of three commercially available ELISA kits for determination of Chromogranin A

Elsa Grenmyr[1], Lisbeth Witt[1], Liselotte Nilsson[1], Mats Stridsberg[2], Yngve Sommarin[1]

[1]Euro Diagnostica, Malmö, Sweden, [2]Uppsala University Hospital, Uppsala, Sweden

Objective: Chromogranin A (CgA) is generally considered the most useful diagnostic marker for neuroendocrine tumors (NETs). Lately CgA has been proven useful also for treatment and disease monitoring. In this study we evaluated the clinical performance of three commercially available ELISA kits.

Material and Methods: 75 samples were tested for levels of CgA: 43 from patients with NETs and 32 from blood donors. The samples were analyzed using the NEOLISA™ CgA (Euro Diagnostica, Sweden), Chromogranin A (DAKO, Denmark) and ChromoA (Cisbio, France).

Results: At the manufacturer's expected values for healthy individuals compared to patients with NETs, sensitivities and specificities were as follows; NEOLISA 63% and 100%, DAKO 95% and 78%, and ChromoA 67% and 88%, respectively. At specificity stratified to 97%, NEOLISA and DAKO had equal sensitivity, 77%, while the sensitivity of ChromoA was 63%. All assays correlate well with each other, with best correlation seen between NEOLISA and DAKO. ROC plots comparing samples from blood donors and NET patients showed a higher AUC with NEOLISA (0.94) and DAKO (0.96) as compared to ChromoA (0.89).

Conclusions: In our study the NEOLISA CgA and DAKO CgA kits had somewhat better clinical performance than the ChromoA assay. At stratified specificity the results were equal for these both tests. In summary, measured levels correlate well with each other, even though the detection antibodies are of different origin.

P33

Urinary 5-hydroxyindoleacetic acid: correlation with patient symptoms, radiological progression and survival.

Theo Bartholomew[1], Jorge Garcia-Hernandez[1], Roberta Elisa Rossi[1,2], Braude David[1], Jassimran Bansal[1], Mohmaduvesh Mullan[1], Nick Martin[3], Martyn Evan Caplin[1], Christos Toumpanakis[1]

[1]Neuroendocrine Tumour Unit, Centre for Gastroenterology, Royal Free Hospital, London, UK, [2]Postgraduate School of Gastroenterology, Universita' degli Studi di Milano, Milan, Italy, [3]Department of Clinical Biochemistry, Royal Free Hospital, London, UK

Introduction: Urinary 5-hydroxyindoleacetic acid (U-5HIAA) is a useful marker for serotonin-producing neuroendocrine tumours (NETs). U-5HIAA is highly specific for midgut NETs and high levels are also associated with carcinoid heart disease.

Aim: To evaluate the correlation between U-5HIAA and symptoms, percentage of liver involvement, chromogranin A, radiological progression and survival.

Methods: 202 patients with well-differentiated midgut (191) and bronchial (11) NETs were retrospectively reviewed. Radiological data were recorded in all patients. In functioning patients, rate of flushing and bowel movements per day were also recorded. Patients were grouped depending on their 5HIAA level (Group 1: <5x upper normal limit (ULN), 2: 5-10xULN, 3: >10xULN).

Results: There is an association between U-5HIAA and (i) rate of flushing (n=65, p=0.001), (ii) bowel movements per day (n=163, p<0.001) after exclusion of other diarrhoea causes, (iii) percentage of liver involvement (n=166, p<0.001) and (iv) chromogranin A (n=153, p<0.001). U-5HIAA was also raised in 21% of patients with no liver metastases. In a subgroup of patients showing radiological progression, both median and mean levels of U-5HIAA were higher at the time of progression (mean 452.4 to 963.3, median 444 to 616), compared to previous levels. There is a trend towards worse survival in group 2 and 3 patients compared to group 1.

Conclusion: These results further confirm the value of U-5HIAA as a NETs' biomarker, demonstrating a strong correlation between U-5HIAA levels and patients' symptoms, as well as hepatic tumour burden in midgut NETs. More data are needed to identify 5-HIAA prognostic role in survival.

P34

Well differentiated, high grade NENs –a separate entity?

Jonathan O'Leary[1], Dalvinder Mandair[1,2], Tu Vinh Luong[1], Mohmaduvesh Mullan[1], Chrissie Thirlwell[1,2], Tim Meyer[1,2], Martyn Caplin[1], Christos Toumpanakis[1]

[1]Royal Free Hospital, London, UK, [2]Cancer Institute, UCL, London, UK

Background: Neuroendocrine neoplasm's (NENs) are classified histologically using the Ki67 proliferation index. High-grade tumours (Ki67 >20%) are classified as Neuroendocrine Carcinomas (NEC), and regarded as poorly differentiated tumours, with few neuroendocrine features. However high grade NEN's can have well differentiated morphology and may behave differently to NECs.

Patients and Methods: All well differentiated, high grade NENs referred between 2008 and 2013 were identified from histopathology reports. All available clinical data were retrospectively analysed.

Results: 35 patients (23M/12F) with median age at diagnosis 59 (range 14-80) were included. Primary tumours were pancreatic (40%), midgut (14.6%), bronchial (11.4%) and unknown (14.2%).

In 34/35 Ki67>20% and ≤ 50%. Immunohistochemistry showed positivity for chromogranin A (88.6%), synaptophysin (90.6%) and CD56 (88.9%).

Octreoscan / Ga-PET was positive in 83.3% (25/30) with a positive FDG PET 54.5 %(6/11).

25 patients received chemotherapy, as first line option (23/25 platinum based) with objective response (OR) of 52% and mean time to progression of 7.5 months. As second line, Sunitinib used in 6 patients (OR 33%), Everolimus in 3 (OR 33%) and 6 patients received Peptide Receptor Radionuclide Therapy (OR 66.7%) Mean overall survival for all patients was 24.1 months (range 3-199)

Conclusions: The majority of well, differentiated high grade NENs were pancreatic in origin with Ki 67 ≤50%. The sensitivity of Octreoscan/Ga68 PET imaging was greater than that of FDG PET. The objective response to chemotherapy was comparable to previous studies on high grade NENs.

P35

Investigation and Management of Insulinoma; Strategy and Outcome in a Single Centre

Andrew S Powlson[1], Ben Challis[1], Suzanne Curran[1], Asif Jah[2], Raaj Praseedom[2], Emmanuel Huguet[2], Neville Jamieson[2], Andrew Metz[3], Nick Carroll[4], Ashley Shaw[4], Brendan Koo[4], Sue Davies[5], Rebecca Brais[5], David Halsall[6], Mark Gurnell[1], V Krishna Chatterjee[1], Helen L Simpson[1]

[1]Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK, [2]Department of Hepatobiliary Surgery, Addenbrooke's Hospital, Cambridge, UK, [3]Department of Gastroenterology, Addenbrooke's Hospital, Cambridge, UK, [4]Department of Radiology, Addenbrooke's Hospital, Cambridge, UK, [5]Department of Pathology, Addenbrooke's Hospital, Cambridge, UK, [6]Department of Clinical Biochemistry, Addenbrooke's Hospital, Cambridge, UK

24 cases of insulinoma were treated at our centre between 2003 and 2013 (17 female, 7 male, 5 associated with MEN-1). 19 underwent primary investigation here. All presented with symptoms of hypoglycaemia, with a supervised fast demonstrating serum glucose <2.2mmol/L with inappropriately normal/elevated insulin.

16 patients proceeded to surgery, The lesion/s were localised pre-operatively in all cases. 14 had CT as first-line imaging, identifying the lesion in 10/14 cases (sensitivity 71%). EUS demonstrated a lesion in 15/16 cases (94 % sensitivity). Fine needle aspiration biopsy (FNAB) was carried out in addition to EUS in 7 cases, cytology demonstrating grade 1 neuroendocrine tumour. MRI successfully localised 5/7 cases. Coeliac axis angiography was performed in 9/16 (sensitivity 56%). Where this failed to demonstrate a lesion, selective calcium arterial stimulation and venous sampling was successful with 100% sensitivity (5 cases). Specificity was 100% for all modalities. All patients were cured of their symptomatic hypoglycaemia following surgery with no recurrence to date (follow-up range 3 months to 10 years). Histology confirmed all lesions to be insulinoma.

3 patients were not referred for surgery. 2 elderly patients declined further investigation after pancreatic lesion was demonstrated on CT. Conservative management (somatostatin analogues/diet) successfully managed hypoglycaemia. One patient had malignant insulinoma with liver metastases, and underwent hepatic arterial embolisation along with palliative chemotherapy, dying 12 months after diagnosis.

We suggest that a combination of MRI/CT and EUS/FNAB following a biochemical diagnosis of insulinoma accurately identifies lesions, facilitating targeted curative surgery, angiography being reserved for EUS negative patients.

P36

Small intestinal neuroendocrine tumors require multimodal management.

Andrea Frilling[1], Helen Miller[1], Adil Al-Nahhas[1], Andreas Bockisch[3], Anil Vaidya[2], Peter Friend[2]

[1]Imperial College London, London, UK, [2]University Oxford, Oxford, UK, [3]University Hospital Essen, Essen, Germany

Background: Small intestinal neuroendocrine tumors (SI NET) frequently present with locoregional and/or distant metastases. This limits the option of radical surgery with an aim to provide cure and calls for effective non-surgical treatment modalities. The aim of this study was to analyze patients with SI NET regarding their disease stage and their treatment options.

Methods: Data of patients with G1 or G2 SI NET were extracted from data bases prospectively maintained at two tertiary institutions. All patients underwent standard imaging and somatostatin receptor imaging (SRI), in most instances 68Ga DOTA- PET/CT, for tumor staging.

Results: In total 92 patients entered this study. Metastatic disease was documented in 88% (81/92) of patients. SRI detected additional metastatic disease not seen on standard imaging in 75% (60/81). Surgical treatment (e.g. complete resection, debulking and transplantation) was offered to 91% (84/92) of patients during the course of their disease. In one patient with un-resectable stage IV mesenterial metastases of a multifocal primary tumor multivisceral intestinal transplantation after neoadjuvant peptide receptor radionuclide therapy was performed (first case in UK). Of the patients with metastasized tumors, 65/81 (80%) underwent non-surgical treatment options (e.g. RFA, TACE, SIRT, PRRT, targeted drugs) either as the only treatment modality or in combination with surgery.

Conclusions: Somatostatin receptor based imaging is pivotal to staging of SI NET. Effective management of patients with SI NET requires multimodal treatment concepts. Novel approaches have the potential to improve outcome.

P37

A Rare Case of Metastatic Type 1 Gastric Carcinoid

R. Basuroy, A. Higginson, S.J. Mercer, R. Ellis

Portsmouth Hospital NHS Trust, Portsmouth, UK

Introduction: Type 1 Gastric Carcinoids (GCs) develop from enterochromaffin-like (ECL) cells stimulated by hypergastrinaemia that results from achlorydia in chronic atrophic gastritis. We present a rare case of metastatic Type 1 GC.

Case: A 49 year-old lady presented with symptoms of reflux and retrosternal pain that did not improve with PPI therapy. Previous medical history included B12 and iron deficiency with a positive parietal cell antibody. Gastroscopy revealed multiple (>10) 0.3-0.7cm polyps in the body / fundus of the stomach as well as a 1.3cm polyp on the lesser curve. Histology confirmed the larger lesion as a low grade (G1) Type 1 GC with background gastric biopsies demonstrating atrophic gastritis and microcarcinoids deposits. The fasting serum gastrin was elevated (>400 pmol/l). Endoscopic ultrasound identified a small gastric lymph node close the lesser curve with fine needle aspiration confirming carcinoid tumour cells. A CT and Octreotide scan showed no additional disease. A total gastrectomy and full lymphadenectomy was performed. There was invasion into the muscularis propria and 4/27 lymph nodes were involved with staging T2N1M0.

Discussion: The majority (80%) of Type 1 GCs are low grade (G1). Invasion beyond the submucosa is said to occur in only 25% of cases and metastases in less than 5%. Lesions >1cm should be assessed by EUS prior to endoscopic resection. This case is unusual for Type 1 GCs as there was invasion into the muscularis propria as well as metastatic nodal disease. Type 1 GC is a recurring disease due to persisting hypergastrinaemia arising from the antral G cells. Patients with Type 1 GCs require surveillance endoscopy of any gastric remnant for both GCs and adenocarcinoma.

P38

A rare case of colo-colonic intussusception caused by a caecal NET

R. Basuroy, J.K. Ramage, N. Mulholland, G. Vivian, S. Dias-Cano, R. Srirajaskanthan

ENETS Centre of Excellence Neuroendocrine Tumour Unity, Institute of Liver studies, King's College Hospital, London, UK

Introduction: Intussusception is a rare cause of bowel obstruction in adults that invariably results from a structural abnormality. NETs have previously only been described causing small bowel or ileocaecal intussusception. We describe a case of colo-colonic intussusception caused by a caecal NET.

Case: A 61 year-old man presented with a week's history of abdominal symptoms consistent with sub-acute bowel obstruction. CT imaging revealed a caecal mass causing anterograde colo-colonic intussusception through to the splenic flexure. In addition, bilobar liver lesions were identified. The patient underwent an emergency right hemicolectomy with primary anastomosis. Histology confirmed a 3.5cm G2 NET of the caecum (Ki67- 3%, 3 mitoses/10 HPF) invading the muscularis propria through to the peritoneum and 8 out of 25 lymph nodes involved. There was mucosal infarction secondary to the intussusception. Staging was pT4N2M1 according to WHO (2010) criteria. A postoperative Octreotide scan showed evidence of octreotide avid liver lesions. The patient has stable disease on a somatostatin analogue.

Discussion: Colonic intussusceptions almost always present with abdominal pain and up to 50% will have abdominal distension and a palpable mass. A colonic NET presenting with anterograde colo-colonic intussusception has not previously been described. The majority of colonic intussusceptions are caused by adenocarcinomas. Colonic NETs represent 4-8% of all NETs with an incidence of 0.2 per 100 000. Abdominal CT is the most useful tool for identifying an intussusception and the underlying cause. Undiagnosed causes of colonic intussusception should be treated as malignancies with surgical oncological en-bloc resections.

P39

PLASMA CHROMOGRANIN B: DOES IT HAVE A ROLE IN MANAGEMENT OF NEUROENDOCRINE TUMOURS?

David Braude[1], Roberta Elisa Rossi[1,2], Jorge Garcia-Hernandez[1], Theo Bartholomew[1], Mohmaduvesh Mullan[1], Martyn Evan Caplin[1], Christos Toumpanakis[1]

[1]Neuroendocrine Tumour Unit, Centre of Gastroenterology, Royal Free Hospital, London, UK, [2]Postgraduate School of Gastroenterology, Universita' degli Studi di Milano, Milan, Italy

Introduction: Chromogranin-B (CgB) is expressed in most neuroendocrine tumours (NETs), yet little is understood about its clinical utility as a biomarker.

Aim: To investigate the role of CgB in follow-up of NET patients.

Methods: 161 patients (121 midgut, 40 pancreatic) with elevated plasma CgB levels were retrospectively reviewed. The correlations between CgB (normal <150pmol/L) and tumour burden and histological grade, as well as its predictive value for radiological progression, were investigated.

Results: In 144 patients, both CgB & Chromogranin-A (CgA) were raised (115 midgut, 29 pancreatic), whilst 17 patients showed an increase of CgB (6 midgut, 11 pancreatic) only. Of the latter, three had advanced VIPomas. CgB was found to be significantly associated with hepatic tumour burden in pancreatic NETs ($p=0.09$), but not in midguts ($p=0.632$). In 51 progressive midgut NETs, 56 events of radiological progression (RP) were recorded during the study period. Median CgB in these patients, 12 months before RP, was 134 pmol/L and 169 ($T=121$, $p=0.013$) 6 months before RP, suggesting that CgB might predict RP. Median CgB at the event of RP (190) was also higher than CgB values 12 months before (134) and 6 months before RP (169)[$T=33$, $p<0.001$ and $T=118.5$, $p=0.04$, respectively]. For those patients, median CgA at 12 (221 pmol/L) and 6 months (527) prior to RP also showed a significant predictive value ($T=61$, $p=0.001$).

Conclusion: CgB seems to correlate with hepatic tumour burden in pancreatic NETs and could serve as a complementary biomarker to CgA for prediction of RP in midgut NETs.

P40

Rectal neuroendocrine tumours: A single-centre retrospective analysis of 60 patients

Keval Naik[1], Roberta Elisa Rossi[1,2], Jorge Garcia-Hernandez[1], Mohmaduvesh Mullan[1], Dalvinder Mandair[1], Christos Toumpanakis[1], Martyn Evan Caplin[1]

[1]Neuroendocrine Tumour Unit, Centre for Gastroenterology, London, UK, [2]Postgraduate School of Gastroenterology, Universita' degli Studi di Milano, Milan, Italy

Introduction: Rectal neuroendocrine tumours (NETs) are increasing in incidence, with more found incidentally on routine or surveillance colonoscopy.

Aim: To retrospectively analyse a cohort of rectal NET to characterise their diagnostic features and clinical behaviour.

Methods: Patients with a confirmed diagnosis of rectal NET were identified from our database and retrospectively analysed.

Results: 60 patients were evaluated (M/F ratio 1.6:1), median age 55 years (range 23-78). Most common presenting symptom was rectal bleeding (48%). 48% (n=29) of patients had tumour size <1cm, 12% (n=7) 1-2cm, 37% (n=22) >2cm, and in 3% size was unknown. Tumour size <1cm, 97% were G1, 3% G2; 1-2cm:14% G1, 72% G2 14% G3; >2cm: 23% G2 73% G3, 24 patients had metastases at presentation, 5 developed metastases during follow-up (of these 29 patients 86% liver, 40% bone, 10% lung) and all were tumour size >1cm. Of 29 patients with metastases, 24 had somatostatin receptor imaging with 62% avid uptake. Of 29 patients with metastases, 59% had systemic chemotherapy, 52% somatostatin analogues, 34% peptide-receptor-radionuclide-therapy. Overall during median follow-up of 20 months (range 9.5– 46.5), 100% of patients with primary tumour <1cm are currently alive, 86% tumour size 1-2cm and only 25% with tumour size >2cm. Primary tumour size >2cm have a significantly poorer outcome compared to the other two groups ($p<0.001$).

Conclusion: Tumours >2cm are of higher grade, associated with poor prognosis and require systemic therapy. Prospective studies are needed especially to determine the metastatic risk of lesions 1-2 cm.

P41

Combination of Molecular imaging for assessment of Neuroendocrine Tumours with heterogeneous cell population

Amy Barker[1], Roberta Elisa Rossi[1,2], Tu-Vinh Luong[3], Shaunak Navalkissoor[4], Martyn Evan Caplin[1], Christos Toumpanakis[1]

[1]Neuroendocrine Tumour Unit, Centre of Gastroenterology, Royal Free Hospital, London, UK, [2]Postgraduate School of Gastroenterology, Universita' degli Studi di Milano, Milan, Italy, [3]Histopathology Department, Royal Free Hospital, London, UK, [4]Nuclear Medicine Department, Royal Free Hospital, London, UK

Introduction: Neuroendocrine tumors (NETs) represent a heterogeneous group of neoplasms. The choice of the appropriate molecular imaging study for assessment of disease extent depends mainly on tumour grade.

Aim: To assess the value of combination of molecular imaging when a heterogeneous cell population is suspected or established.

Methods: Patients with two different-grade NET lesions existing simultaneously were identified. Tumour histology and molecular imaging including Fluorodeoxyglucose Positron Emission Tomography (FDG PET) and Gallium-68 octreotate PET (Ga-68 DOTATATE) were reviewed.

Results: Three patients (2 males, 1 female) were included. Patient 1 with metastatic midgut NET had a rapidly progressing left ovarian lesion. FDG PET showed uptake only in left ovary, whilst Ga-68 DOTATATE showed uptake in that lesion and also in the other known patient's NET lesions. Histology showed a G1 NET (Ki67 2%) mixed with a poorly-differentiated G3 (Ki67 30%). Patient 2 had a mixed appearance of G1 and G2 cells (Ki67 <2% and 20%), in his resected rectal NET. FDG-PET showed uptake in para-rectal lymph nodes, which were Ga-68 DOTATATE negative. Patient 3 presented with an orbital NET, which was the only site of uptake in Ga-68 DOTATATE. The patient's primary bronchial tumour and metastatic disease were revealed by FDG-PET which showed no orbital uptake. Histology of bronchial and orbital lesions showed different grades (G2, Ki67 10% and G1, Ki67 <2% respectively).

Conclusion: In cases of heterogeneous NET population, a combination of molecular imaging could contribute to accurate assessment of tumour load and may have implication to patients' management.

P42

Comparison of radiolabeled somatostatin analogue and (131) I-MIBG treatment for the management of patients with metastatic/progressive pheochromocytomas and paragangliomas.

Konstantinos Nastos[1], Vincent Cheung[1], Christos Toumpanakis[1], Shaunak Navalkissoor[2], Martyn Caplin[1], Bernard Khoo[3]

[1]Neuroendocrine Tumor Unit, Royal Free Hospital, London, UK, [2]Department of Nuclear Medicine, Royal Free Hospital, London, UK, [3]Department of Endocrinology, Royal Free Hospital, London, UK

Introduction: Radionuclide therapy has been used to treat patients with progressive/metastatic paragangliomas(PGGs) and pheochromocytomas(PCCs). To date, there is no study comparing (131)I-MIBG treatment and radiolabeled somatostatin analogue(RSA) treatment in the management of patients with progressive PCCs and PGGs. The aim of the present study is to compare the effectiveness of these modalities in treating progressive/metastatic PCCs and PGGs.

Methods: Patients with progressive/metastatic PGGs and PCCs that were subjected to radionuclide treatment in our department were retrieved from our department's database for the period 1980-2013. Patient demographics, and tumor characteristics were recorded. Overall survival(OS), progression free survival(PFS), event free survival(EFS) and response to treatment were calculated. Renal and hematological toxicity of treatments was documented.

Results: Twenty two patients with progressive/metastatic PGGs or PCCs were referred for radionuclide therapy with either (131)I-MIBG, or RSA treatment. A total of 30 treatments were administered (17 treatments with (131)I-MIBG, and 13 with RSA). Patients treated with RSA had increased PFS and response to treatment compared to (131)I-MIBG treated patients ($p<0.05$). However, difference in OS was marginally non significant ($p=0.09$). There was no difference in major toxicities between groups. When comparing only patients with PGGs, OS, PFS, EFS and response to treatment were significantly higher in the RSA treatment group ($p<0.01$).

Conclusion: RSA treatment seems to be a more effective than (131)I-MIBG therapy in the management of patients with progressive/malignant PGGs and PCCS. This difference seems to be more prominent in patients with PGGs.

P43

A ten year experience of the use of ^{68}Gallium-DOTATATE PET/CT in the localisation of insulinoma.

Sheba Jarvis[1], Richard Carroll[1], Karim Meeran[1], Imene Zerizer[2], Adil Al-Nahhas[2], Jeannie Todd[1]

[1]Imperial Centre for Endocrinology,Imperial College Healthcare NHS Trust,, London, UK, [2]Department of Nuclear Medicine, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK

Background: The diagnosis of insulinoma involves recognition of consistent symptoms, biochemical documentation of hyperinsulinaemic hypoglycaemia often achieved through a 72-hour supervised fast. The sensitivity of radiological modalities including CT, MRI, endoscopic US and Octreotide scintigraphy can be variable and may delay diagnosis. ^{68}Gallium-DOTA-D-Phe^{1},Tyr^{3}-octreotate (^{68}Ga-DOTATATE) is a novel PET/CT tracer, which has shown superiority to other radionuclide somatostatin receptor analogues in neuroendocrine tumours partly due to 100-fold higher affinity of ^{68}Ga-DOTATATE to type 2 somatostatin receptors compared to Octreotide. Previous studies have reported the use of other 68Ga-DOTA-conjugate peptides PET/CT in insulinoma.

Aims and Methods: We aimed to analyse the performance of ^{68}Gallium-DOTATATE PET/CT in the detection of insulinoma over a 10-year period (between 2004-2013) using retrospective data analysis of patient cases. Symptomatic hypoglycaemia (defined as blood glucose <2.2 mmol/L) was documented either on a random venous glucose or during a 72 hour fast. Concomitant inappropriate hyperinsulinaemia (>3 mU/L) and C-peptidaemia (>300 pmol/L), confirmed endogenous hyperinsulinaemia, in the absence of sulphonylurea compounds. All had normal prolonged oral glucose tolerance tests.

Results: Data was reviewed from 16 patients (aged between 31-80 years) 15 patients had histologically confirmed insulinoma (staining positive for insulin, CD56 and synaptophysin). All had ^{68}Gallium-DOTATATE PET/CT scans to preoperatively localize the tumour. We found that 14 out of 16 patients (88%) had gallium avid lesions ranging between 7-41 SUV_{max} units. The two patients in whom ^{68}Gallium-DOTATATE PET/CT scans were negative had histologically confirmed insulinoma at surgical resection. There were no complications during the administration of the compound, or adverse events.

Conclusions: Despite technical advances, insulinomas are frequently a difficult tumour to localize and patients require multiple cross-sectional imaging and angiographic procedures pre-operatively to confirm functionality. We conclude that ^{68}Ga-DOTATATE PET/CT should be the functional imaging technique of choice in localizing insulinoma, and lessens the need for venous sampling.

P44 & OC6

Metastatic Phaeochromocytoma/ Paraganglioma is predominantly associated with inherited mutations in the SDH complex

Bahram Jafar-Mohammadi[1], Louise Izatt[2], Klaus-Martin Schulte[3], Paul Carroll[4], Barbara McGowan[4], Jack Powrie[4], Benjamin Whitelaw[1], Salvador Diaz-Cano[5], Simon J B Aylwin[1]

[1]Department of Endocrinology, King's College Hospital, London, UK, [2]Department of Clinical Genetics, Guy's and St Thomas's Hospital, London, UK, [3]Department of Endocrine Surgery, King's College Hospital, London, UK, [4]Department of Endocrinology, Guy's and St Thomas's Hospital, London, UK, [5]Department of Histopathology, King's College Hospital, London, UK

Phaeochromocytomas (PCC) and Paraganglioma (PGL) are neural crest tumours arising from the chromaffin producing cells of the adrenal medulla or sympathetic/parasympathetic system respectively. Recently, in part due to advances in high throughput sequencing, our understanding of the genetic predisposition to these tumours has greatly increased. To date, thirteen genes have been implicated in the pathogenesis of these conditions (ten available for testing at our centre). We aimed to determine the frequency that metastatic PCC/PGL was associated with mutations in known susceptibility genes.

The genetic profile of all individuals diagnosed with metastatic PCC and PGL in our centre was ascertained and compared to individuals with PCC/PGL without evidence of metastasis. 82 individuals with a diagnosis of PCC or PGL fulfilled the criteria for genetic testing in the past 5 years. This included 16 individuals with metastatic disease. Among the patients with confirmed metastatic disease 13/16 (81%) had a genetic mutation identified in *SDHB*, *SDHA* or *SDHD* predisposing to PCC and PGL. However, among those patients with no metastatic disease identified to date, only 42% (29/69) had a genetic mutation identified (p=0.001). Among the subjects with metastatic PCC, 11/13 had mutations (85%) in *SDHB.*

Our results imply that the identification of a mutation in the known PCC/PGL susceptibility genes confers an increased metastatic potential and also subjects with metastatic disease are most likely to harbour mutations in *SDHB*. Subjects with metastatic PGL/PCC are highly likely to have a genetic predisposition. In addition, identification of those individuals with PGL/PCC with a genetic mutation should be considered at high risk for harbouring tumours with metastatic malignant potential.

P45

Tale of a broken heart: Takostsubo Cardiomyopathy in a Neuroendocrine patient

Saira Khalique, Tim Meyer

Royal Free Hospital, London, UK

Takostsubo cardiomyopathy, first reported in Japan, describes a transient systolic dysfunction of the left ventricle. It is associated with physical or emotional stress triggers in post-menopausal women.

A 50 year old female, previously well, presented with right upper quadrant pain and a one year history of diarrhoea up to 20 times daily, A CT showed a pancreatic head lesion and multiple lesions within the liver. Biopsy confirmed an Intermediate grade neuroendocrine tumour of the pancreas with liver metastases Ki67 7%, (1 mitosis per 10 HPF). An octreotide scan showed liver uptake and she started Sandostatin. Due to persistent symptoms after three months, she was initiated on FCiST chemotherapy (5-Fluorouracil, Cisplatin and Streptozocin). Within 24 hours of administration of the first dose, she had severe vomiting and was admitted to hospital. She developed chest pain, had a raised troponin level and an ECG showed ST elevation. A coronary angiogram showed unobstructed arteries. MRI and echocardiogram demonstrated a dilated left ventricle with severely impaired systolic function with an ejection fraction of 31.7%. She was commenced on Aspirin, Bisoprolol and Ramipril and after 6 weeks her ejection fraction was 58%. Ten weeks after chemotherapy had been discontinued; she was commenced on Everolimus, and to date, has maintained disease control. She has not had any further episodes of cardiac failure. Repeat echocardiogram nine months later showed her normal ejection fraction to be maintained.

This case adds to the growing number of cases related to chemotherapy induced cardiomyopathy, mainly with 5-Fluorouracil, Capecitabine and Sunitinib.

P46

An early multi-modal cyto-reductive treatment strategy is associated with prolonged survival in a cohort of patients with metastatic neuro-endocrine tumours

Vinodh Vijayakumaran, Harriet Connor, Thomas Armstrong, Arjun Takhar, Neil Pearce

University Hospitals Southampton NHS Trust, Southampton, UK

Since 2003 we have adopted a policy of early, aggressive cyto-reductive intervention where possible for all patients with neuroendocrine liver metastases (NELM). We reviewed all patients with NELM to identify the impact of this strategy on long term survival rate, compared with other published data.

Methods: 346 patient records on the UHST NET database were analysed; 142 patients who had been diagnosed with NELM from 2003 to 2013 were identified and their treatment (resection, ablation, medical) and outcomes were assessed. All primary sites, patterns of metastases and tumour grades were included.

Results: Of the 142 patients, 53% were males and 47% were females. The median age was 64. 29 patients not suitable for intervention received conservative management; 114 patients underwent either single or multi-modality treatment. Of these patients; 43% had single treatment and 57% underwent multi-modal treatment.

The primary site of NET was identified; 82% had either a midgut or pancreatic origin. We used GEP-NETs grading system to assess tumour grades; 57% of the patients who received treatment had a grade 1, 38% had grade 2 tumour and 5% had grade 3 tumour.

The overall 5 year survival rate for the entire cohort was 60%. Patients who were treated conservatively had a survival rate of 42% and patients who received multi-modal treatment had a survival rate of 79% compared to single modal treatment group which was 62%.

A cohort of patients with NELM showed prolonged survival with a policy of early cyto-reductive treatment strategy, compared to other reported cohort series.

P47

^{68}Ga-DOTATATE PET in localising Neuroendocrine Tumours- could this be the state-of-the-art diagnostic test?

Jian Wu[1], Andreas Prachalias[2], Raj Srirajaskanthan[2,3], Roy Sherwood[2], Nicola Mulholland[2], John Ramage[1,2]

[1]Basingstoke and North Hampshire Hospital, Basingstoke, UK, [2]King's College Hospital, London, UK, [3]University Hospital Lewisham, London, UK

^{68}Ga-DOTATATE PET is an established tool for localising primary tumour in metastatic neuroendocrine tumours (NETs) and in the diagnosis of additional NET metastases not seen on cross-sectional imaging. There is little published regarding its role in detecting occult primary sites in suspected NET.

A series of patients with primary gastrinoma/insulinoma seen only on DOTATATE imaging are presented.

A 61 year-old male presented with dyspepsia, diarrhoea and multiple spontaneous jejunal perforations. Fasting gastrin and chromogranin A were elevated (>700 pmol/L and 106 pmol/L respectively). An Octreoscan showed a possible abnormal area in the pancreatic body not corroborated by CT, MRI, PET-FDG and EUS. DOTATATE revealed a soft tissue density in the pancreatic head. Post-Whipples, histology demonstrated NET tumour in peri-pancreatic lymph nodes and gastrin levels normalised.

A 64 year-old female presented with an upper gastrointestinal bleed from extensive duodenal ulceration. Fasting gastrin level was elevated (>400 pmol/L). DOTATATE identified a focus within the gastrinoma triangle. Resection confirmed a 15mm nodule of peri-pancreatic tumour with histological evidence of endocrine differentiation.

A 77 year-old male presented with abdominal pain and spontaneous duodenal perforation. Biochemistry showed hypoglycaemia (0.2mmol/L) and an inappropriately elevated insulin level (14.3 mU/L) and c-peptide (1063 pmol/L). Gastrin was also raised (55 pmol/L). CT and MRI were normal. A small lesion in the tail of pancreas was visualised on DOTATATE and surgery is planned.

These cases highlight the potential diagnostic use of DOTATATE PET in suspected but not yet localised primary cases of gastrinoma/insulinoma where cross-sectional imaging is normal.

These cases highlight..

Sensitivity and specificity…

Suggests consideration for further use…

Emerging data shows its role In detection of recurrent tumour

P48

MGMT expression in Paraganglioma and Phaeochromocytoma

Sama Hassan[1], Nahal Masrour[1], Raghunath Kadiyala[1], Fausto Palazzo[1], Bob Brown[1], Roberto Dina[1], Bernard Khoo[2], Tricia Tan[1]

[1]Imperial College, London, UK, [2]UCL Medical School, London, UK

Phaeochromocytomas (PCC) and Paragangliomas (PGLs) are rare neuroendocrine tumours develop from chromaffin cells of the sympathetic and parasympathetic paraganglia. Both can occur in familial and sporadic forms with incidence of one in 300,000/year and malignancy rate of 3-36%. Surgical resection of the tumours is the primary treatment; radiolabelled ^{131}I-MIBG can be useful therapy, however this is rarely curative. Chemotherapy regimens like cyclophosphamide, vincristine and decarbazine (CVD) have been used but their effect remain unsatisfactory. The enzyme O^6-methylguanine DNA methyl transferase (MGMT) is a key defense of cancer cells against the action of DNA alkylating anticancer agents such as Temozolomide. MGMT expression is thought to be controlled by promoter methylation of CpG residues where hypermethylation suppresses MGMT expression. MGMT promoter methylation status has been shown to be prognostic in gliomas, and to influence their response to Temozolomide chemotherapy. As Temozolomide has been proposed as a potential therapy for metastatic PCC and PGL, we decided to investigate the level of MGMT promoter methylation in PCC and PGL by pyrosequencing. We assessed 21 formalin fixed paraffin embedded tumour specimens both from sporadic and familial cases for MGMT promoter methylation. We evaluated MGMT protein expression by immunohistochemistry to identify the association between IHC results and MGMT methylation. Pyrosequencing analysis showed low levels of MGMT methylation in tumours. IHC evaluation of the same cases showed varying levels of MGMT protein expression. The comparison between pyrosequencing and IHC showed no correlation between the two methods. The pilot data from this study therefore indicate that the MGMT promoter is generally hypomethylated. No relationship could be discerned between promoter methylation and MGMT expression which may suggest that MGMT expression in these tumours is not influenced by promoter methylation.

Notes

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Managed by:

Conference Secretariat
BioScientifica Ltd

Euro House
22 Apex Court
Woodlands
Bradley Stoke
Bristol, BS32 4JT, UK

Contact: Rebecca Davies
Tel: +44-(0)1454 642770
Fax: +44-(0)1454 642222
Email: conferences@bioscientifica.com
Website: www.ukinets.org