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Basic Science – mTOR and Other Pathways, Signalling, Receptors

A1

Dual High Throughput Proteomic and Transcriptomic Screen for Predictive Biomarkers of Everolimus Sensitivity in Pancreatic NET

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Introduction: mTOR inhibitor Everolimus is approved for the treatment of well-differentiated PNET. The heterogeneity of the response rate and the potential toxicity warrant predictive biomarkers. **Aim(s):** Define through a dual high throughput proteomic and transcriptomic approach predictive biomarkers of Everolimus sensitivity. **Materials and Methods:** Fifteen well-differentiated PNET tumors were minced in 300 uM slices and cultured for 48 h with no drug, Everolimus or BEZ235. Caspase 3 levels assessed by immunohistochemistry at 48 h were used to define sensitive and resistant tumors. Transcriptomic profiles were determined and key oncogenic proteins were quantified by reverse phase protein array (RPPA). **Results:** Nine tumors were defined as resistant to mTOR inhibitors. RPPA showed that resistant tumors had a higher level of the activated phosphorylated forms of mTOR, p70S6K and S6 but not 4EBP1. Phosphorylated form of p38, b-catenin and NF-kB p65 were also increased in resistant tumors. Transcriptomic signatures of hypoxia and glycolysis were enriched in resistant tumors together with signatures linked to chromatin remodeling. **Conclusion:** In this model, resistant tumors harbor non-canonical activation of the mTOR pathway together with hypoxia and specific metabolic (glycolytic) gene signatures. Chromatin remodeling signatures suggest that DAXX/ATRX status may impact mTOR inhibitors sensitivity. This warrants further metabolomic investigations and validation in a cohort of patient treated with mTOR inhibitors. **Keywords:** PNET, Everolimus, Predictive biomarkers.

A2

Immunohistochemical Expression of Estrogen and Progesterone Receptors in Neuroendocrine Tumors

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Introduction: Expression of progesterone (PR) and estrogen receptor (ER) in some neuroendocrine tumors (NET) raises the possibility of hormonal regulation in these tumors, but those prevalence and clinical implication are unknown. **Aim(s):** To determine presence and prognostic value of ER and PR in NET. **Materials and Methods:** Immunohistochemical expression of ER and PR were retrospectively examined in NET treated in a single institution between 2007 and 2015 and correlated with clinicopathological features and survival. **Results:** We analyzed 96 cases. Gastroenteropancreatic tract was the most common site of involvement (76%) with 20.8% and 18.8% showing positive ER and PR staining, respectively. All primary sites presented expression of hormonal receptors, except colon and rectum. ER positivity was significantly associated with functional syndrome ($p = 0.005$) and absence of tumor necrosis ($p = 0.03$); PR positivity was associated with non-metastatic disease ($p = 0.02$) and primary site ($p = 0.04$), with 50% of pancreatic NET having PR expression. No association was demonstrated with tumor grade, but there was a low number of G3 NET in this study (12%). The overall 5-year survival rate of ER positive tumors was 86.5% and 74.4% for ER negative NET ($p = 0.77$) and 94% and 72.4% for PR positive and negative NET respectively ($p = 0.20$). **Conclusion:** In this study NET with favorable prognostic features had higher ER and PR expression. This could potentially help in risk stratification and provide a target for novel treatment strategies. **Keywords:** Progesterone, Estrogen, Carcinoid.

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A3

Slit-Robo Signaling Links to Ras Activity to Suppress Metastasis and Is Associated with Time-to-Progression in Pancreatic Neuroendocrine Tumors

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Introduction: mRNA signatures of distinct metastatic phenotypes of pancreatic NETs (pNETs) exhibit differences in several components of the Slit-Robo axon guidance system. **Aim(s):** We aimed at delineating the role of Slit-Robo signaling for tumor progression in pNETs. **Materials and Methods:** Expression of Slit2 and Robo1 on human pNET tissues was determined by IHC and qPCR. Migration and colony formation as well as metastasis in mice were evaluated as read-outs. **Results:** Slit2 mRNA expression was reduced in pNET tissues as compared to healthy pancreas. Robo1 immunoreactivity localized to epithelial tumor cells of pNETs, and reduction of Robo1 mRNA levels correlated to shorter time-to-progression in pNET patients. Experimentally, restored Slit2 expression in BON cells inhibited proliferation, migration and colony formation. Conversely, disruption of Slit2-Robo signaling via Robo1 knockdown or sequestration of endogenous Slit2 in QGP cells by a soluble Robo1 receptor stimulated directed migration and colony formation. Mechanistically, Slit2-Robo1 signaling stimulated Ras activity and delayed cell cycle progression, consistent with a growth suppressive function of Ras in endocrine cells. Finally, incidence of lymphatic metastases and lymphangiogenesis were reduced in orthotopic BON tumors with restored Slit2 expression. **Conclusion:** Our data assign to Slit2-Robo1 a novel function as metastasis suppressor. Loss of Slit2-Robo1 signaling may contribute to a metastatic phenotype of pNETs. **Keywords:** Slit2, Robo1, Pancreatic, NET, pNET, Metastasis, Mouse model.

A4

Cross-Talk between EGFR and IGF1R Influences the Response to RTK Inhibitors in Bronchopulmonary (BP)-NET Cell Lines

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Introduction: BP-NETs represent ~30% of all neuroendocrine tumors. BP-NET treatment is challenging due to onset of resistance to chemo and targeted therapies. EGFR and IGF1R had been associated with tumor onset and progression in several neoplasia. **Aim(s):** To investigate the role of EGFR and IGF1R and their possible cross-talk in BP-NET cells. **Materials and Methods:** Receptors expression was evaluated by Western blot in 2 BP-NET cell lines (NCI-H720, NCI-H727 cells). Cell viability and apoptosis were measured by ATPlite assay and Caspase3/7 assay, respectively. IGF1R and EGFR heterodimer formation was evaluated by immunoprecipitation (IP). **Results:** Both cell lines express IGF1R while only NCI-H727 cells express EGFR detectable levels. Cells were treated with EGF and IGF1: both induced cell viability. As expected, Linsitinib (IGFR inhibitor) was able to reduce cell viability and increase apoptosis activation in both cell lines. Erlotinib (EGFR inhibitor) was able to reduce cell viability and increase apoptosis activation in both cell lines, even in NCI-H720 cells in which EGFR was not detectable. To explain why Erlotinib exerts its effects on NCI-H720 cells we performed IP using IGF1R antibody, and found that IGF1R forms heterodimers with EGFR, possibly explaining the effects of Erlotinib on these cells. **Conclusion:** Our data demonstrate an interaction between EGFR and IGF1R that could affect response to therapy. The relationship between EGFR and IGFR should be further analyzed and considered as possible new target for BP-NET therapy. **Keywords:** BP-NET RTK.

A5

Are eIFs Ingredients for Neuroendocrine Tumorigenesis?

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Introduction: Neuroendocrine tumors (NETs) develop in almost any organ, therefore they are a very heterogeneous group of tumors. One of the major activities in every cell is the translation of mRNA to the corresponding protein, which plays an important role in cancer development. Crucial for this translation process are eukaryotic initiation factors (eIFs), which are themselves regulated by the mammalian target of Rapamycin (mTOR)-pathway. Mutation or deregulated expression of eIFs influences cell growth and proliferation, contributing to carcinogenesis. The incidence of NETs has increased fivefold over the last three decades. **Aim(s):** We aimed at investigating the contribution of eIFs to NETs. **Materials and Methods:** NETs and their metastases from 3 individuals were analyzed on protein expression level for eIFs and mTOR members by Western Blot. Additionally we have investigated various eIF subunits in gastroenteropancreatic NETs and neuroendocrine carcinomas by immunohistochemistry. Normal adjacent tissue served as control. **Results:** Indeed, eIFs and members of the mTOR pathway were differentially expressed in NETs, and were changed in NET cell lines pointing to a possible mechanistic link between NETs and mTOR. **Conclusion:** Our data indicate a contribution of eIFs and mTOR signaling to the development and progression of NETs. A better understanding of the molecu-

lar mechanisms leading to neuroendocrine tumorigenesis is crucial for establishing novel and tailored treatment strategies for NET patients. **Keywords:** NETs, mTOR, Eukaryotic translation initiation.

A6

Differential Somatostatin and CXCR4 Chemokine Receptor Expression in Primary Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NEN) and Their Metastases

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Introduction: Somatostatin receptors (SSTR) are known for their overexpression in well-differentiated GEP-NEN, where they serve as molecular targets for different imaging and treatment modalities. The chemokine receptor CXCR4, in contrast, is present mainly in highly proliferative and advanced tumors. **Aim(s):** Evaluation of the SSTR, CXCR4 and Ki-67 expression in primary tumors (PT) (n = 50) and metastases (MTS) (n = 76) of GEP-NEN from 3 different places of origin (small intestine, pancreas, colon/rectum). **Materials and Methods:** The SSTR and CXCR4 expression was determined by means of immunohistochemistry and rated by means of the Immunoreactive Score (0-12 points). **Results:** No noticeable differences were noticed between PT and MTS. Between the different places of origin, dissimilarities were mainly seen for the SSTR2A expression. Here, PT of the small intestine had the highest mean expression (IRS: 10.3), followed by pancreatic (IRS: 8.5) and colorectal neoplasms (IRS: 5.5). The Ki-67 index, in contrast, was the lowest in PT of the small intestine (5.4%), whereas PT of colorectal origin displayed the highest values (24.6%). Within the MTS, those of pancreatic origin showed the highest mean SSTR2A expression (IRS: 9.5), followed by metastases of the small intestine (8.5) and the colon/rectum (IRS: 6.8). **Conclusion:** GEP-NEN exhibit distinct differences in the SSTR and Ki-67 expression intensity depending on their place of origin, whereas relevant differences between PT and MTS were not detected. **Keywords:** Somatostatin receptor, Chemokine receptor, SSTR.

A7

Efficacy of Everolimus and Somatostatin Analogs as Single Agents or in Combination in Human Pancreatic Neuroendocrine Tumors Primary Cultures

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Introduction: Among the therapeutic options available for the treatment of neuroendocrine tumors, one targeted therapy, everolimus (RAD) has been approved for advanced progressive pancreatic neuroendocrine tumors (pNETs). It improve progression free survival but is not curative. Alterations of the PI3K/Akt/mTOR pathway in pNETs have given the rational for the use of this signaling pathway inhibitors. **Aim(s):** The objective of the study was to evaluate efficacy of RAD alone or in combination with somatostatin analogs in human pNETs. **Materials and Methods:** Measure of cell viability, chromogranin A (CgA) secretion, caspase and Akt activities in 20 human pNETs in primary culture. **Results:** RAD decreases viable cell number and CgA secretion respectively in 78% and 67% of pNETs (with respective median of 45% and 57%). Combined treatments with RAD and octreotide or pasireotide do not improved inhibition of CgA secretion and partially reduce inhibition of cell viability observed in the presence of RAD alone. Analogs-dependent Caspase activities are abolished in combined treatments. Furthermore, whereas RAD repression of S6K activity is still observed in combined treatments, the analogs do not reduce the activated level of Akt induced by RAD. **Conclusion:** Combined treatments of pNETs in primary culture with Rad and somatostatin analogs do not improved inhibition of cell viability and CgA secretion observed with RAD single treatment. **Keywords:** pNETs primary culture, Everolimus, Somatostatin analogues, Cell viability, Chromogranin a secretion, Akt activity.

A8

Selective Inhibition of PI3Kalpha (BYL719) – Promising Therapeutic Option for Neuroendocrine Tumors?

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Introduction: Neuroendocrine tumors are heterogeneous, often functional malignancies and their therapeutic options are limited. As the PI3 kinase signaling is in GEP-NENs, selective PI3Kalpha inhibitors may be more potent than panPI3K inhibitors. **Aim(s):** Therefore, we assessed the effects of BYL719 in different NEN cell lines (pancreatic and lung NET) compared to the established mTORC1 inhibitor everolimus. **Materials and Methods:** We treated the cell lines BON, QGP-1, NCI-H727 with increasing concentrations of the inhibitor BYL-719, compared to everolimus and DMSO. We performed WST-1 assay in order to determine efficacy and growth inhibition. The induction of apoptosis was shown by caspase 3/7 activation and cell cycle was analyzed by FACS. We determined changes in the signaling network by phospho-specific western blot analysis. **Results:** BYL-719 showed dose-dependent, reversible, anti-proliferative effects in all tested cell lines. Unless the potency was much lower than the potency of everolimus, the maximum effects were more beneficial. Treatment with BYL719 led to cell cycle arrest and decrease of cell viability through marked inhibition of PI3K/AKT and mTORC1-signaling. **Conclusion:** PI3Kalpha-Inhibition is an interesting new therapeutic approach in neuroendocrine tumor disease that should be evaluated in further preclinical trials. **Keywords:** PI3Kalpha, BYl719, Neuroendocrine tumor cell lines.

A9

A New Immunohistochemistry Prognostic Score (IPS) Based on MGMT, NDRG-1 and PHLDA-3 for Recurrence and Survival in Resected Pancreatic Neuroendocrine Tumors (PanNET)

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Introduction: In PanNET tumors contradictory data about the prognostic role of MGMT (O6-methylguanine DNA methyltransferase) has been published. NDRG-1 (N-myc downstream-regulated gen-1) and PHLDA-3 (Pleckstrin homology-like domain family A member 3) immunohistochemistry (IHC) expressions have been evaluated in several solid malignant tumors, but their roles in PanNET remain unknown. **Aim(s):** We aimed to evaluate the prognostic significance of NDRG-1, MGMT and PHLDA-3 by IHC and methylation analysis in resected pancreatic neuroendocrine tumors. **Materials and Methods:** Ninety-two patients with resected primary PanNET and follow-up >24 months were included in this study. An immunohistochemistry prognostic score (IPS) was developed based on MGMT, NDRG-1 and PHLDA-3 IHC expression to predict disease free survival (DFS) and overall survival (OS). The discriminatory ability of multivariate models combining the IPS and important clinical variables was assessed with Harrel's c-index (HCI). **Results:** In multivariate analyses, ki-67 (HR: 2.45; 95% CI: 1.20, 5.01; p = 0.01) and IPS (HR: 2.68; 95% CI: 1.60, 4.49; p = 0.00018) were independent prognostic factors for DFS, while age (HR: 7.67; 95% CI: 2.14, 27.45; p = 0.0017) and IPS (HR: 2.67; 95% CI: 1.11, 6.41; p = 0.03) were independent prognostic factors for OS. HCI for the multivariate DFS and OS models were 0.796 and 0.788, respectivel. **Conclusion:** Our IPS is a useful prognostic biomarker for recurrence and survival in patients following resection for PanNET. **Keywords:** Pancreatic neuroendocrine tumor, MGMT, NDRG-1, PHLDA-3.

A10

Targeting Tumor Metabolism in NETs: A Novel Mechanism of Action of the Somatostatin Analog Lanreotide

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Introduction: One of the hallmarks of cancer is reprogramming of energy metabolism, characterized by a shift to aerobic glycolysis. This metabolic switch provides cancer cells appropriate conditions required for enhanced proliferation and survival. The effects of somatostatin on tumor metabolism had not been determined yet.

Aim(s): Study the effects of lanreotide on the metabolic activity of NETs cells. **Materials and Methods:** BON-1 and NCI-H727 cells were used. Levels of metabolites were determined using 1H-NMR spectrometry. Hexokinase (HK) 2 activity was tested using HK enzymatic assay. Proteins expression and phosphorylation were tested using Western blot. Viability was tested using colony formation assay. **Results:** The AKT pathway promotes, while the master energy sensor AMP-activated kinase (AMPK) alters, metabolism of cancer cells. Lanreotide inhibited the AKT pathway but activated AMPK, resulting in inhibition of the downstream effector acetyl CoA carboxylase (ACC). Lanreotide treatment reduced mRNA levels of the key glycolytic regulatory enzymes lactate dehydrogenase and HK2 and inhibited enzymatic activity of HK2. Finally, the effects on viability and metabolites levels were examined. Lanreotide decreased colony formation of both cells and decreased lactate concentration in the media, indicating reduced glycolysis. **Conclusion:** These data indicate reversal of the metabolic switch as a novel mechanism of action of lanreotide and may pave the way to a rational design of somatostatin analogs-based combinations. **Keywords:** Metabolism, Glucose.

Basic Science – Genetics, Epigenetics, miRNAs

B1

Whole Exome Sequencing of Three Families with Small Intestine Neuroendocrine Tumors

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Introduction: Small intestine neuroendocrine tumors (siNETs) are the most prevalent small intestine neoplasms. However, familial siNETs are rarely described. **Aim(s):** Three families with multiple siNET-affected family members were studied to identify disease-causing genes. Family studies in this rare cancer could help identify novel genes implicated in siNET tumorigenesis. **Materials and Methods:** We performed whole exome sequencing on germline DNA of 3 affected siblings and 1 non-affected sibling in family A, on the affected mother-son pair in family B and on two affected and four non-affected members in family C. Using a custom variant filtering strategy for autosomal dominant and recessive mutations, possibly protein-damaging stoploss, stopgain and non-synonymous SNVs and frameshift indels were filtered. **Results:** The above-mentioned filtering strategies identified 5 homozygous and 251 heterozygous SNVs in family A and 3 homozygous and 347 heterozygous SNVs in family B. Both WES datasets were put together and analyzed further. Among the 16 genes that contained mutations in both families, 4 genes shared the same variant. Variant analysis of family three is still pending. **Conclusion:** Interesting SNVs and indels have been identified in all families studied. Further variant filtering using predictions programs to rank the pathogenicity of the identified candidate genes for familial siNET could help to refine the results. Furthermore, we are eager to expand our familial siNET cohort through collaborations. **Keywords:** Familial sinet, Whole exome, Candidate gene.

B2

Splicing Dysregulation Impacts on Neuroendocrine Tumors: Evidence from Altered Spliceosoma Components and Somatostatin and Ghrelin Systems

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Introduction: Splicing is an emerging cancer hallmark influencing multiple tumor cell (dys)functions. We have shown that aberrantly spliced variants of somatostatin receptor subtype 5 (sst5TMD4) and of the pleiotropic neuropeptide ghrelin (in1ghrelin) are linked to poor prognosis in gastroenteropancreatic neuroendocrine tumors (GEPNETs) and may enhance their aggressiveness features. **Aim(s):** We hypothesized that alterations in the splicing machinery can contribute to generate these abnormal variants, and offer novel intervention points in GEPNETs. **Materials and Methods:** To ascertain this question, an array of selected components of the major (n = 13) and minor spliceosome (n = 4), and associated splicing factors (n = 28) was devised, and their levels of expression were evaluated using a Fluidigm methodology, in a series of 20 pancreatic NETs samples (47% G1, 47% G2 and 6% G3) and control-adjacent non-tumoral tissues. **Results:** Results revealed that expression of a number of splicing factors and spliceosoma components was altered in tumor tissue vs. non-tumoral adjacent tissue. Of note, relevant splicing factors (Celf4, NOVA1, SKIP/Prp45, RAVER1) and spliceosoma components (PRP8) not associated previously to NETs were heavily overexpressed in tumor tissue, and some of these changes correlated with tumor features (invasion) and clinical parameters (relapse). **Conclusion:** Thus, splicing machinery is clearly altered in GEPNETs, which can underlie aberrant splicing mechanisms, and may provide novel diagnostic biomarkers and therapeutic tools. **Keywords:** Splicing.

B3

The MEN2B Due to de Novo Mutation M918T at Algiers

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Introduction: The MEN2B, or Gorlin syndrome is a very rare disorder where there are a medullary cancer of thyroide associated with pheochromocytoma and other clinical signs such as a ganglion – neuromatose or a Marfan syndrome. The MEN2B belongs MEN2 are rare hereditary disease, transmitted as an autosomal dominant mutations linked to the RET proto-oncogene. **Aim(s):** In a case of MEN2B whose diagnosis is clinical and biological, the genotypic analysis is required and is based on the detection of mutations in exons 15 or 16 of the RET gene. **Materials and Methods:** Three patients belonging to three different families diagnosed MEN2B 1 woman aged 23 years and 2 young men aged 19 and 22 years are benefit of genetic analysis. The genetic study to focus on the relatives. DNA extraction was done by the method to salts. Genetic study involved exons 15 and 16, by amplification by PCR followed by sequencing on ABI 3130 Applied Biosystems. **Results:** We found in the three patients, the same M918T mutation which is localized in exon 16 in heterozygous form. This mutation was not found in other family members. **Conclusion:** The discovery of the M918T germline mutation in these three MEN2B index cases confirms the diagnosis. This mutation at codon 918 of exon 16 is highly specific (95%) of the MEN2B. Seing that the genetic testing of related has not found the mutation in other family members, we can conclude that this mutation is de novo, as found in the literature. **Keywords:** MEN2B, de novo mutation, Genotypic analysis.

B4

Multiregion Analysis Reveal Evolutionary Patterns and a Chromosomal Instability Signature in Pancreatic Neuroendocrine Tumours

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Introduction: Pancreatic neuroendocrine tumors (PNETs) are potentially lethal diseases that show variable degrees of proliferation and invasiveness. Although genetic subgroups have been suggested to give prognostic information the impact of clonal evolution to the development and outcome of PNETs remains unexplored. **Aim(s):** To elucidate the aberrations in PNET genomes and their role in tumourigenesis and metastatic spread. **Materials and Methods:** An integrative analysis of mutational spectra and copy number variations in 169 PNET samples from 94 patients. **Results:** Recurrent mutations in MEN1 (n = 35) and ATRX/DAXX (n = 17) were detected and classified as early disease drivers. Tumors with mutated ATRX/DAXX had increased chromosomal instability early in tumorigenesis. Multiregional analyses revealed subclonal mutations in TP53 (n = 3) and PTEN (n = 3). Preliminary data suggest that PTEN inactivation could be associated with increased tumor cell proliferation. **Conclusion:** This work provides insight into the mutational timing during PNET development and revealed a potential basis for disease progression through PTEN and/or TP53 inactivation. Our findings highlighted ATRX/DAXX mutation in PNET and subsequent chromosomal instability. These data could ultimately define potential druggable targets as well as prognostic and predictive biomarkers. **Keywords:** Cancer evolution, Molecular genetics, Neuroendocrine tumor.

B5

Well Differentiated Pancreatic Neuroendocrine Tumors (WDPNET) G3: Does the Ki67 Really Do It All?

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Introduction: WDPNET G3, although not recognized by the 2010 WHO classification are far from exceptional. They also represent a great therapeutic challenge especially since their molecular drivers are unknown. **Aim(s):** Compare the transcriptomic profiles of aggressive WDPNET with those of less proliferative WDPNET and of poorly differentiated neuroendocrine carcinomas (NEC) to identify driver oncogenic pathways. **Materials and Methods:** Two pathologists determined differentiation and hand counted the ki67 of 29 PNET. Transcriptomic profiles were obtained with Affymetrix HTA 2.0 chips. Among the 26 WDPNET, 7 tumors had a Ki67 below 5%, 5 between 5–15% and 14 between 17–39%. 3 NEC had a Ki67 between 47–95%. **Results:** Besides increased proliferation gene signatures, aggressive WDPNET harbored enriched gene signatures classically found in NEC such as E2F, MYC and increased glucose metabolism. These signatures were further enriched in the NEC group. Unsupervised analysis showed that aggressive WDPNET actually formed 2 clusters: 10/14 clustered with NEC and 4, without NEC-like signatures, clustered with Ki67 <15% PNET. Ki67 distribution was similar in these 2 aggressive WDPNET groups. **Conclusion:** Aggressive WDPNET are heterogeneous. Some harbor NEC-like transcriptomic signatures while other, even with a Ki67 >20%, show low proliferating NET-like profile. This warrants further validation on a larger cohort to address how it affects survival and response to treatment. **Keywords:** G3 PNET, Transcriptomic profiles, NEC.

B6

mTOR Controls an Epigenetic Program Leading to Autophagy and Cell Growth Control

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Introduction: Makroautophagy represents an evolutionary highly conserved process involved in the clearance of proteins and organelles. The induction of this central cellular process is tightly connected with programs regulating cell growth control. While the cytoplasmic machinery that orchestrates autophagy is relatively well understood the key epigenetic events that initiate autophagy-related cell growth programs remain largely unknown. **Aim(s):** In this study we aim to understood epigenetic mechanisms controlling autophagy-related cell growth programs in neuroendocrine cancer cells. **Materials and Methods:** Using neuroendocrine cancer cells we studied cell growth, cell cycle, cell cycle-related protein expression and chromatin modifications following pharmacological inhibition or RNA interference (RNAi)-mediated suppression of mTOR and G9a. **Results:** Herein we describe that mTOR inhibition diminished cell proliferation by regulation of the methyltransferase G9a. Mechanistically, we found that mTOR inhibition altered G9a function resulted in re-expression of the CDK inhibitor p27Kip1, leading to G1 cell cycle arrest. Significantly, we show that G9a associated with the p27Kip1 promoter and maintained H3K9me2, which is diminished following mTOR inhibition in a JNK dependent manner. Moreover, increased p27Kip1 expression leads to a reduced cyclin A expression. **Conclusion:** mTOR controls an autophagy-related epigenetic program that suppresses p27Kip1 expression in a G9a dependent manner. **Keywords:** Autophagy, G9a, p27Kip1, mTOR, Epigenetic growth control.

B7

Epigenetic Remodeling Upon DAXX and ATRX Loss in Pancreatic Neuro-Endocrine Tumors (pNETs)

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Introduction: DAXX and or ATRX loss occur in 40% of sporadic pNETs. DAXX and ATRX participate in the cell epigenetic status maintenance. Epigenetic changes influence gene expression, function of telomeres and genomic stability. We hypothesize that DAXX/ATRX loss drives tumor progression in pNET through epigenetic changes affecting genomic stability. **Aim(s):** To investigate the epigenetic changes occurring upon DAXX and ATRX loss. **Materials and Methods:** LINE1 and global DNA methylation levels were assessed respectively in 24 and 105 human pNETs by pyrosequencing and IHC (Immuno Histo Chemistry) and correlated with DAXX/ATRX status, ALT (Alternative Lengthening Telomeres) activation and CIN (Chromosomal Instability). H3K4me3 levels were evaluated by IHC in 105 pNET samples. DNA methylation status as well as H3K4me3 and CIN were measured in vitro upon DAXX knock-down in pNET cell lines. **Results:** We observed that DAXX/ATRX negative and CIN+ tumors show lower level of DNA methylation compared to DAXX/ATRX positive ones ($p < 0.05$) and that LINE1 is hypo-methylated in CIN+ tumors ($p < 0.05$). Additionally, H3K4me3 is reduced in DAXX/ATRX positive tumors and ALT negative ones. In vitro, upon DAXX knock-down, we observed an increase in micro-nuclei formation as well as G1 arrest which may indicate a higher genomic instability. **Conclusion:** Our data show that DAXX/ATRX loss impairs DNA methylation and histone modification. These epigenetic changes are associated with CIN and ALT activation and thereby lead to tumor progression. **Keywords:** DAXX/ATRX, Epigenetic, CIN.

B8

Even Malignant Appendiceal Neuroendocrine Tumors Exhibit No Recurrent Chromosomal Alterations

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Introduction: Neuroendocrine tumors (NETs) of the midgut are located in the ileum (iNET), caecum or appendix (aNET). Despite of the similar origin, NETs of the ileum and the appendix behave remarkably different. iNETs show high malignant potential, which manifests with early lymph node or liver metastases. Genetically, the loss of chromosome 18 (Ch18) in 60–74% of cases is the most frequent alteration in iNETs. aNETs are often incidental findings, rarely show metastases, and no chromosomal alterations are known. **Aim(s):** We addressed the question whether aNETs harbor chromosomal aberrations which are possibly related to malignant behavior. **Materials and Methods:** We analyzed chromosomal copy number (CN) variations in 7 nodal positive and 8 nodal negative formalin-fixed paraffin-embedded aNETs using the OncoScan assay (Affymetrix). Fluorescence in-situ Hybridization (FISH) with a Ch18-centromer probe was carried out on tissue microarrays containing 45 aNETs. **Results:** OncoScan assay revealed non-recurrent large (>10 Mb) CN gains on Ch1, 3, 5, and 16 and large losses on Ch2, 4, 6, and 11 in aNETs. Tumor-related genes as ROBO1, RB1, PTEN, RET, and SMAD6 were affected by these alterations in single cases. FISH exhibited loss of Ch18 in 4% (2/45) of aNETs. **Conclusion:** aNETs

are chromosomally highly stable neoplasms, irrespective of their biological behavior. In contrast to iNETs, aNETs show low rates of Ch18 losses that may partly explain the differences in the malignant potential and highlights the different pathogenesis of these two midgut NETs. **Keywords:** NET.

B9

The Role of p27 in Pheochromocytoma Development

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Introduction: The Cdkn1b gene, encoding p27, is a tumor susceptibility gene for multiple endocrine neoplasia syndromes in rats (MENX) and humans (MEN4) with development of pheochromocytoma (PCC), respectively. Recently, it was reported that p27 indirectly regulates gene transcription by associating with transcription factors (TF) and inhibiting gene transcription at specific promoters. **Aim(s):** We hypothesized that defective p27 may promote tumor formation in adrenomedullary cells because of aberrant gene expression regulation. **Materials and Methods:** We used adrenomedullary tissue from WT rats (with normal p27 levels) or normal adrenomedullary cells of human individuals and performed chromatin immunoprecipitation-sequencing (ChIP-Seq). **Results:** We could successfully pull down DNA sequences with an anti-p27 antibody, thereby suggesting that p27, together with unknown TF or co-factors, can bind the chromatin in adrenomedullary cells. NGS determined DNA sites bound by p27-containing complexes. These sequences were mapped on the rat/human genome and the Genomatix© software identified downstream genes and the most enriched TF binding sites among these sequences. The p27-dependent regulation of the expression of selected target genes will be verified by modulating p27 levels in PCC cell lines and in adrenal medulla and PCC of MENX-affected rats (with loss of functional p27). **Conclusion:** The observation will give insight into pathomechanisms associated with reduced p27 function specifically in neuroendocrine cells. **Keywords:** Pheochromocytoma, p27, ChIP-Seq.

B10

Association between miRNAs and HDACs in Pancreatic Neuroendocrine Tumors

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Introduction: Epigenetic factors are essentially involved in carcinogenesis, tumor promotion and chemo resistance with their major key players of miRNAs and histone deacetylases (HDACs). As shown by own theoretical databank analysis, the crosstalk between miRNAs and HDACs are relevant in different human chronic diseases and cancerogenic pathways. **Aim(s):** The aim of our study was the investigation of a well-defined subset of 'pro-proliferative' miRNAs, which are related to expression of HDACs and clinical parameters in pancreatic neuroendocrine tumors (pNETs). **Materials and Methods:** We investigated the expression levels of miR132-3p, miR145-5p, miR183-5p, miR34a-5p and miR449a in 57 pNETs resected between 1997 and 2015. These findings were linked to the immunhistochemical expression pattern of members of the four HDAC classes on human tissue microarrays. All pNET cases were clinically and pathologically characterized according to published guidelines. **Results:** Correlation analysis revealed a significant association of miRNAs with most of the HDACs. Additionally, a linkage between the miRNAs and clinic-pathological parameters like grading and nodal infiltration could be statistically established. **Conclusion:** Overall, we demonstrated that specific miRNAs could be linked to HDAC expression in pNETs. These first data could help, to improve our knowledge of the complex interactions of these epigenetic drivers in pNETs for further therapeutic approaches. **Keywords:** Epigenetics, miRNA, Histone deacetylases, Pancreatic neuroendocrine tumor.

B11

A Novel Hereditary Pancreatic Neuroendocrine Tumor Syndrome Associated with Biallelic Inactivation of the Glucagon Receptor

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Introduction: Hereditary pancreatic neuroendocrine tumors (PanNETs) are associated with 4 known autosomal dominant syndromes including MEN1, vHL disease, NF1, and TS. Glucagon receptor (GCGR) inactivation in human (Mahvash disease) has been associated with asymptomatic hyperglucagonemia, α-cell hyperplasia, and PanNET, and may represent a new hereditary syndrome. **Aim(s):** We identified an index case with suspected Mahvash disease (MD) and collected information from 44 family members in 4 generations and genotyped the GCGR in 10 family members. **Materials and Methods:** The mutant GCGR transcriptions in were evaluated by mRNA/cDNA sequencing. **Results:** At least 3 individuals with suspected MD in this family presented with PanNET. We identified two heterozygous inactivating mutations of GCGR in germline and somatic DNA: 1) c187 G-to-A missense mutation in exon 4 culminated in pD63N; 2) c-1 position of the intron-exon border of exon 4 (IVS3-1G>T) with a stop codon. We confirmed that the two mutations occurred on separate alleles which were inherited from heterozygous carriers via an autosomal recessive mode. The heterozygous carriers did not have apparent syndromes; compound heterozygous inactivation of GCGR was associated with MD with the triad of asymptomatic hyperglucagonemia, diffuse α-cell hyperplasia, and PanNET. **Conclusion:** We have established the genetic basis for the fifth hereditary PanNET syndrome which is associated with biallelic inactivating mutations of GCGR via autosomal recessive inheritance with 100% penetrance. **Keywords:** Hereditary PanNET.

B12

Genes Involved in Angiogenesis and mTOR Are Frequently Found Mutated in Asian Patients with Pancreatic Neuroendocrine Tumors

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Introduction: There are limited data and inconsistent findings of genetic alteration in pancreatic neuroendocrine tumors (pNET). **Aim(s):** We sequenced genes known to be associated with pNET and analyzed their impact on clinical outcomes in a Taiwanese cohort. **Materials and Methods:** Tissue samples from 40 Taiwanese patients with sporadic pNETs were sequenced using a customized sequencing panel that analyzed 43 genes known to be potentially associated with pNET. Genetic mutations and clinical outcomes were analyzed for potential association. **Results:** With a median follow-up of 5.9 (range, 0.3–18.4) years, 33 patients (82.5%) were alive. The median number of mutations per patient was 3 (range 0–16). The most frequently found mutations were ATRX (28%), MEN1 (28%), ASCL1(28%), TP53 (20%), mTOR (20%), ARID1A (20%) and VHL (20%). The mutation frequencies of the MENI pathway (including MENI/PSIP1/ARID1A), mTOR pathway (including mTOR/PIK3CA/AKT1/PTEN/TS1/TS2/ATM), DAXX/ATRX, and angiogenesis pathway (including VHL/ANGPT1/ANGPT2/HIF1A) genes were 48%, 48%, 38%, and 45%, respectively. ATRX mutation was associated with WHO grade I pNET (vs. grade II or grade III, $p = 0.043$), and so were genes involved in angiogenesis pathway ($p = 0.002$). **Conclusion:** Our study showed that genetic profiles in Asian pNET patients were distinct from Caucasian. Asian pNET patients had more frequent mutations in mTOR and angiogenesis pathway genes. This could partially explain a better outcome with targeted therapy among Asian pNET patients. **Keywords:** Pancreatic NETs, Gene mutation, mTOR.

B13

Characterization and Rescue of a Pathogenic D63N Mutant Human Glucagon Receptor That Causes a Pancreatic Neuroendocrine Tumor Syndrome (Mahvash Disease)

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Introduction: We have previously demonstrated that inactivating glucagon receptor (GCGR) mutations cause a novel hereditary human disease of hyperglucagonemia, pancreatic α cell hyperplasia, and pancreatic neuroendocrine tumor (Mahvash disease). We recently identified a novel missense GCGR mutation, D63N, in a family with Mahvash disease. **Aim(s):** To characterize and rescue the D63N mutant GCGR. **Materials and Methods:** An EGFP-tagged D63N (D63N-EGFP) was expressed in HEK 293 cells. **Results:** D63N-EGFP exhibited abnormal, predominantly endoplasmic reticulum (ER) localization. Glucagon-stimulated cAMP production by D63N was much less at higher concentrations than that by a previously-described P86S mutant GCGR. Multiple osmotic chaperones, low temperature, and 3 lipophilic GCGR antagonists did not significantly change the D63N localization. ER stressor thapsigargin, but not curcumin, significantly trafficked D63N to plasma membrane. On western blot, D63N-EGFP migrated mainly as an 80-kD band while WT GCGR-EGFP as a 100-kD band. Thapsigargin treatment resulted in decrease of the 80-kD D63N-EGFP and increase of the 100-kD form. Pretreatment with thapsigarin resulted in significantly more cAMP upon stimulation by glucagon. **Conclusion:** The D63N mutant GCGR is functionally inactive mostly due to abnormal trafficking but D63N can be rescued and correctly trafficked to the plasma membrane by a chaperone, which suggests pharmacological chaperones may be useful in patients with Mahvash disease. **Keywords:** Mutant glucagon receptor, Chaperone, Mahvash disease.

Basic Science – In vitro Models, Tumor Growth, CTCs

C1

A Novel in vitro Model of a Highly Proliferative Pancreatic Neuroendocrine Neoplasia

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Introduction: Transformation of well-differentiated neuroendocrine tumors into highly proliferative neuroendocrine neoplasms is a rare, but clinical relevant phenomenon. So far, it is unclear whether these tumors should be treated in analogy to neuroendocrine tumors or as bona fide neuroendocrine carcinoma. **Aim(s):** To develope a new in vitro model to study treatment responses in tumor cells. **Materials and Methods:** We here report the establishment of a pair of neuroendocrine cell lines from the primary site and and from a liver metastasis of a patient with a neuroendocrine neoplasm. The patient was initially diagnosed with a G2 pancreatic neuroendocrine tumor. After several lines of treatment the tumor eventually transformed into a G3 (Ki-67 60%) neuroendocrine neoplasm. **Results:** The new cell lines ('NT-18P' and 'NT18-LM') express chromogranin A and synaptophysin as markers of neuroendocrine differentiation. They also express the neuroendocrine differentiation factors NeuroD, Isl-1 and Pax-6, while having no expression of Ngn3, Pax-4 and PDX-1. SSTR 1 and 2 expression is higher compared to BON and QGP cells. Upon treatment the cells were resistant towards streptozotocin, 5-FU and temozolomid, but responded to treatment with everolimus and cisplatin. **Conclusion:** In summary, we have established a new pair of neuroendocrine cell lines from an in vivo transformed pancreatic neuroendocrine neoplasm sharing features of neuroendocrine tumors and carcinoma. Besides platin-based therapies, targeting the mTOR pathway might benefit these patients. **Keywords:** Cell line.

C2

Regulation of Neuroendocrine Differentiation by Growth Factor Induced Proliferation in a Well-Differentiated Pancreatic Neuroendocrine Tumor Cell Line

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Introduction: The regulation of neuroendocrine differentiation in NET tumor cells is poorly understood. Clinical experience suggests a correlation between proliferation and neuroendocrine dedifferentiation. **Aim(s):** To study neuroendocrine differentiation in slow and fast growing neuroendocrine tumor cells. **Materials and Methods:** We analyzed mRNA expression of NET markers and transcription factors (TFs) in BON, QGP and NT-3 cells, a recently established NET cell line. **Results:** NT-3 cells express CgA, Syn, VMAT1/2, TPH-1 and DDC. In contrast BON cells lack expression of VMAT2 and DDC, while QGP cells lack expression of VMAT1/2 and have only weak CgA expression. Analysis of TFs revealed a strong expression of PDX-1, Ngn3, NeuroD, Isl-1, Pax4 and Pax6 in NT-3 cells, while BON cells expressed NeuroD and Pax4 and QGP cells expressed Isl-1 and Pax6. Growth factor (GF) stimulation increased Ki-67 index of NT-3 cells from 2% to 14%, while proliferation of BON and QGP cells remained unchanged at high level (above 80%). The expression of CgA, Syn, TPH-1 and DDC decreased 3- to 20-fold upon GF stimulation in NT-3 cells. Correspondingly, the expression of neuroendocrine TFs decreased as well. In contrast, BON and QGP cells showed only minor changes in NET marker expression upon GF treatment. **Conclusion:** Neuroendocrine differentiation is related to proliferation and the expression of neuroendocrine-specific TFs. Re-enforcing neuroendocrine TF expression in tumors might prove to induce differentiation and limit proliferation. **Keywords:** Cell line, Differentiation.

C3

Detection of SSTR2 and 5 Expression on Circulating Tumour Cells in Neuroendocrine Tumours

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Introduction: Neuroendocrine tumours (NET) overexpress somatostatin receptors (SSTR) which can be targeted for therapy with somatostatin analogues (SSA) or radionuclide treatment. **Aim(s):** To develop an assay to detect SSTR2 and 5 expression on CTCs in NET patients. **Materials and Methods:** MCF7 cells

were transfected with plasmid DNA carrying human SSTR2 or 5 and spiked into donor blood for testing using the CellSearch platform. Optimum antibody concentrations and exposure times were determined. Flow cytometry was used to assess whether marker detection was affected by presence of SSA. For clinical evaluation, 7.5 mls patient blood was analysed by CellSearch and SSTR2/5 immunohistochemistry (IHC) was performed on matched FFPE samples. **Results:** Flow cytometry demonstrated that detection of SSTR was unaffected by presence of SSA up to a maximum concentration of 100 ug/ml. 31 NET patients were recruited: grade; G1 (34%), G2 (52%) G3 (13%), primary site; midgut (58%), pancreatic (39%). 87% had SSTR positive tumours on functional imaging and 62% were receiving SSA at time of collection. CTCs were detected in 21/31 patients (68%) of which 33% had evidence of SSTR2 (n = 5) or SSTR5 (n = 2) staining. SSTR expression on CTCs was detectable in patients where IHC for the corresponding receptor was negative. **Conclusion:** SSTR2 and 5 are detectable on CTCs from NET patients, but expression is heterogeneous. The clinical relevance of SSTR expression on CTCs is being prospectively evaluated using this assay in the phase IV CALMNET trial (NCT02075606). **Keywords:** CTC, SSTR.

C4

Cannabinoids as Inhibitor of Tumour Growth and Invasiveness in Small Intestine Neuroendocrine Cancer

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Introduction: Tumour cell invasion and proliferation is a key factor for the prognosis and progression of cancer. A recent study revealed that cannabinoids can inhibit tumour invasion and proliferation in breast cancer through the down-regulation of ID-1, an inhibitor of helix-turn-helix transcription factors. **Aim(s):** ID1 is highly expressed in the small intestine neuroendocrine tumour cell line P-STS. We therefore hypothesize that cannabinoids can also inhibit proliferation and invasion of P-STS via the down-regulation of ID-1. **Materials and Methods:** P-STS cells were treated with the CB-receptor agonist WIN-55,212. Subsequently, the ID1 expression was observed and proliferation, viability, apoptosis and mitosis were assessed. The tumour cells were xenografted onto a chicken chorioallantoic membrane (CAM) and the tissue was further stained immunohistochemically for Ki67 and a TUNEL-Assay was performed. Angiogenesis was assessed with CAM-Assays. **Results:** PSTS-cells showed significantly reduced cell proliferation and viability and increased apoptosis. Treated P-STS cells had a significantly reduced fraction of cells in mitosis. Whereas the fraction of apoptotic cells was increased. Angiogenesis was inhibited as well by WIN-55. Treatment with WIN-55,212 led to a downregulation of ID-1 mRNA and to a reduced frequency of solid tumour formation. **Conclusion:** The results of this work should demonstrate cannabinoids to be a viable and non-toxic therapeutic approach for the treatment of SI-NETs. **Keywords:** SI-NET, ID1, Cannabinoid.

C5

Establishment and Characterization of Three GEP-NEC Cell Lines for in vitro and in vivo Studies

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Introduction: To date chemotherapeutic concepts applying cisplatin/etoposide for the treatment of highly aggressive GEP-NEC do not provide convincing results. Thus, there is an urgent need for NEC cell line models that provide a reliable experimental system in identifying novel therapeutic targets. **Aim(s):** Three NEC cell lines were established from a liver metastasis, a lymph node metastasis and an inguinal metastasis from patients with large cell NEC arising from the gastroesophageal junction, colon and anal canal, respectively. **Materials and Methods:** Neuroendocrine markers were analyzed by using RT-PCR and immunohistochemistry. Authenticity of the cell lines was verified by DNA fingerprinting and array CGH. In vivo tumorigenicity was evaluated in a mouse model and sensitivity against chemotherapeutic agents was assessed in vitro. **Results:** Cell lines exhibited morphological and molecular features of NEC, such as the expression of typical neuroendocrine markers. In vitro and in vivo experiments demonstrated that NEC cell lines retained their malignant properties. Cell lines exhibited highly similar genetic alterations when compared to the primary tumor and metastases, respectively. Whereas NEC-DUE1 and -DUE2 were resistant to chemotherapeutic drugs such as cisplatin and oxaliplatin, a high sensitivity to 5-FU was observed for the NEC-DUE1 cell line. **Conclusion:** We established 3 GEP-NEC cell lines. These cell lines might serve as a helpful tool for further research on NEC tumor biology and in identifying novel druggable targets. **Keywords:** GEP-NEC.

C6

Chemoprevention with a Long Acting Somatostatin Analogue in a Multiple Endocrine Neoplasia Type 1 (MEN1) Knockout Mouse Model Does Delay the Progression of Pancreatic Neuroendocrine Neoplasms (pNENs)

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Introduction: Long acting somatostatin analogues (LAR) are an essential part of the treatment of neuroendocrine tumours. **Aim(s):** The aim of this study was to evaluated the chemopreventive effects of a long acting somatostatin analogue on the development of pancreatic neuroendocrine neoplasms (pNENs) in a MEN1 Knockout mouse model. **Materials and Methods:** MEN1 knockout mice were treated with monthly subcutaneous injections of the somatostatin analogue Lanreotid (Somatuline Autogel ©;Ipsen Pharma) or a placebo, starting at day 35. Mice were killed after a determined period (after 6, 9, 12, 15 and 18 months, each group contained 5 mice) and size of pNENs were measured due histological analysis and compared to the control group. **Results:** The median tumor-size of pNENs was statistically significant different after 9 (control group vs. LAR-group; 706.476 μm^2 vs. 195.271 μm^2 $p = 0.0012$), 12 (control group vs. LAR-group 822.022 vs. 255.482; $p \leq 0.001$), 15 (control group vs. LAR-group 1.192.568 vs. 273.533 $p \leq 0.001$) and after 18 months (control group vs. LAR-group 1.328.299 vs. 864.587 $p \leq 0.001$). **Conclusion:** LAR may be an effective chemopreventiv approach to delay the progression of MEN1 associated PNENs. After our preclinical results we would strongly recommend to evaluate the effects of LAR in a prospective clinical trial. **Conflict of Interest:** The tested LAR (Lanreotid, Somatuline Autogel) was provided by Ipsen PHARMA, Ipsen PHARMA invited Lopez C and Albers MB to ENETS 2016, Barcelona. **Keywords:** Chemoprevention, Neuroendocrine neoplasms, Somatostatin analogue.

C7

Inhibition of Intestinal Neuroendocrine Tumor by a New Marker of Normal Neuroendocrine Cells

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Introduction: Although gastrointestinal neuroendocrine tumors are increasing worldwidely, few treatment options could be chosen. **Aim(s):** By comparative proteome, we discovered a new protein Xpec was expressed only in normal intestinal tissue, but not in intestinal neuroendocrine tumor (INET), this study will illustrate the role of Xpec in INET. **Materials and Methods:** Xpec were detected in 30 INET tissues and their adjacent normal controls with immunostain. Subcellular collocation of Xpec with chromogranin A (CGA) or neuron-specific enolase (NSE), markers of gastrointestinal neuroendocrine cells, were determined by immunofluroscence stain. Cell proliferation, cell cycle, expression of related molecules were observed after Lentiviral overexpression or RNAi of Xpec in INET cells, NCI-H716 (low Xpec) or Colo320 (high Xpec). Further, Xpec lentivirus was used to treat INET xenografts in nude mice. **Results:** Xpec was only expressed in all normal tissues but no INET tissues. In normal intestinal mucosa, Xpec was co-expressed with CGA or NSE. Overexpressed Xpec inhibited the growth and cell cycle of INET cells, and up-regulated NSE and Wnt5a, but down-regulated Cyclin D1 and CGA, a potential therapeutic target of GEP-NETs. Those molecules were regulated oppositely when Xpec knocked-down. However, Wnt1, Wnt3 and β-catenin were no changed. Moreover, Xpec could significantly suppress INET in vivo. **Conclusion:** Xpec shows to be a new marker of normal intestinal neuroendocrine cells, and inhibits INET growth through non-canonical Wnt pathway. **Keywords:** GEP-NETs, Wnt, Marker.

C8

Antitumor Activity of Desmopressin (dDAVP) and the New Analog [V4Q5]dDAVP in Human Small Cell Lung Cancer

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Introduction: Lung cancer is the main cause of cancer death. Non small cell lung cancer (NSCLC) cause about 85% of cases and small cell lung cancer (SCLC) represents 15%. Therapy resistance is commonly related with a transformation from adenocarcinoma to SCLC. SCLC shows neuroendocrine (NE) features and exhibits aggressive behavior. In vitro production of vasopressin (AVP) was reported in SCLC. The AVP V1 receptors are associated with mitogenic signaling pathways, while AVP V2 receptor (V2r) is related with an opposite effect. DDAVP is a synthetic analog of AVP that acts as a selective agonist for V2r. DDAVP displays cytostatic and antimetastatic properties in breast and colorectal cancer. In our laboratory a new analog, [V4Q5]dDAVP, showed improved cytostatic activity. **Aim(s):** In this study we evaluated the antitumor ability of the analogs mediated by V2r on a human SCLC cell line. **Materials and Methods:** We used NCI-H82. V2r expression and NE markers were confirmed by immunofluorescence and qRT-PCR. Cytostatic activity of the analogs was studied with MTS assay. V2r was depleted using siRNA. The tumor progression was evaluated with a mouse xenograft model. **Results:** In this model [V4Q5]dDAVP showed a higher cytostatic effect than dDAVP. The silencing of V2r significantly attenuated the inhibitory effects of [V4Q5]dDAVP on cell proliferation. Analogs also inhibited 40% subcutaneous tumor growth. **Conclusion:** These results show for the first time the antitumor properties of AVP analogs mediated by V2r on a tumor cell line of SCLC. **Keywords:** V2r, Antitumor, NE.

C9

Medullary Thyroid Carcinoma Cell Lines – An Update

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Introduction: Medullary Thyroid Carcinoma (MTC) originates from calcitonin-producing neuroendocrine C-cells of the thyroid gland. Mutations in the RET-proto-oncogene are associated with both sporadic and familial MTC. As MTC are poorly responsive to chemo- and radiation-therapy, surgery is the only curative treatment at the moment. The cytogenetics of MTC have been sparsely investigated because the cells are very difficult to cultivate. In the last three decades our research group has established 10 continues cell lines derived from primary tumor and lymph node metastasis of patients with either sporadic or hereditary MTC. **Aim(s):** In this study, we provide an overview of our MTC cell lines and compare them to the firstly established TT cell line. **Materials and Methods:** Immunocytochemistry and RT-PCR was used for the characterization of the cells. In vivo xenograft studies were performed to study the tumorigenicity of the cell lines. **Results:** The expression of characteristic neuroendocrine markers (e.g. calcitonin, chromogranin A, ...) and the expression pattern of metalloproteases show a diversity within our MTC cell lines. However, all 10 cell lines formed macroscopically visible tumors on chicken chorioallantoic membrane and became well vascularized. In SCID mice tumor nodules proved the tumorigenicity of the cell lines. **Conclusion:** We conclude, that our cell lines exhibit diverse features and make them suitable tools to study MTC biology and to develop new therapeutics. **Keywords:** MTC continuous cell line, Characterisation, Xenografts.

C10

Osteotropism of NETs: Role of the SDF1/CXCR4 Axis in Regulating EMT

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Introduction: NETs metastasize to the bone in up to 20% of patients. The SDF1/CXCR4 axis is a key determinant of osteotropism, and we showed that NETs overexpressing CXCR4 are more likely to develop bone metastases. **Aim(s):** To explore the biologic mechanisms underlying CXCR4-driven NET bone metastases. **Materials and Methods:** BON1, QGP1, CM, H727 and CNDT2.5 cells were evaluated in their CXCR4 expression by flow cytometry. Migration and invasion towards the bone or SDF1-conditioned medium were assessed by functional assays. Transcription and expression levels of EMT-related genes were assessed by RT-PCR and immunocytochemistry before and after SDF1 treatment. Secretion of SDF1 was studied by ELISA. Confocal microscopy and WB were used to investigate the subcellular distribution of CXCR4. **Results:** Expression of CXCR4 varied amongst NET cells (BON1: 35%; CM: 10%; others: 25–30%). BON1 cells showed an intrinsic osteotropism ($p < 0.0001$), whereas no migration towards the SDF1-conditioned medium was observed. After pretreatment with SDF1, migration and invasion of CM and QGP1 cells significantly increased ($p < 0.01$), and a cadherin switch and TGF-β1 overexpression was detected ($p < 0.03$). BON1 cells secreted SDF1, and showed a overexpression of EMT-related genes along with a mesenchymal cellular shape. After SDF1 stimulation, CXCR4 migrated to the nuclei of BON1, CM and H727 cells, where its nuclear levels increased up to 240%. **Conclusion:** Osteotropism of NETs may be fostered by CXCR4 and its nuclear translocation may play a role in this process. **Keywords:** EMT, CXCR4.

C11

Clinical Utility of EpCAM-Positive Circulating Tumor Cells in Neuroendocrine Neoplasms Using the CellSearch Platform

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Introduction: Circulating tumor cells are captured to predict the prognosis of patients in many types of cancers, but reports are rare on clinical utility and tumor cell shedding in neuroendocrine neoplasms (NENs). **Aim(s):** To capture EpCAM-positive circulating tumor cells in NENs using the CellSearch platform. **Materials and Methods:** From Sep 2014 to Jul 2015, 11 patients with NENs were recruited consecutively in our center. All the peripheral venous blood samples were received after the resection. **Results:** The mean age was 51.82 (range 32–67). 54.5% were males. Ten patients were pancreatic NENs (30%G1, 70%G2) and 4 of them had liver metastases. One patient was small intestine NENs (G2) with LM. The median size of the primary tumor was 3 cm, and the median Ki-67 index was 5.0. CTCs were detected (≥1 CTC/7.5 ml blood sample) in 54.5% of patients, the mean count was 2 CTCs (median 1). For all pNENs, the positive rate of CTCs was 50%. The median CTC count of pNENs with LM and pNENs without LM were 1 and 0.5, respectively. For one siNEN with LM, the count was 1 CTC. **Conclusion:** Circulating tumor cells are detectable in NENs using CellSearch platform even after the surgical removal of tumor burden, clinical utility is warranted in a larger cohort of patients due to biological significance of CTCs heterogeneity in NENs. **Keywords:** NEN, CTC, CellSearch.

Epidemiology/Natural History/ Prognosis – Registries, Nationwide and Regional Surveys

D1

Merkel Cell Carcinoma – Epidemiology Data from the Czech National Cancer Registry

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Introduction: Merkel cell carcinoma (MCC) is rare and aggressive neuroendocrine tumor. The incidence is increasing worldwide, most probably due to population aging (mostly in the Western Europe), higher rates of sun exposure, immunosuppression and other not well defined epigenetic changes. **Aim(s):** To analyse retrospectively situation of MCC in the Czech republic. Based on analysis results to plan further centralised care and international cooperation. **Materials and Methods:** It is a retrospective analysis of epidemiology data collected from the Czech National Cancer Registry (CNCR) during 19 years period (1994–2012). Incidence, age distribution, gender ratio, localisation of MCC, extent of disease, type of treatment and absolute mortality rate is analysed. **Results:** 283 cases of MCC has been registered in the CNCR. It represents 0.04% of the all malignancies diagnosed in the same period. The estimated annual incidence is 1.44 : 1 milliion and there is a clear evidence of increasing trend (from 0.19 : 1 million in 1994 to 2.28 : 1 million in 2012). M : F ratio is 1:1.88. Age peak was in erderly patients (over 70 years). The most frequent localisation was face (30%) and extremities (44%). 53.4% MCC were diagnosed with localised disease and 9% with initial metastatic spread. 183 patients (64.,7%) died of disease. **Conclusion:** Our collected data corresponded with literature data except female predominance. Epidemiologic analyses and centralised care are mandatory for further management of MCC. **Keywords:** Merkel cell carcinoma, Register, Epidemiology.

D2

The Symptoms Experienced by Small Bowel and Pancreatic NET Patients Prior to Diagnosis Do Not Meet the Criteria for a Functional Diarrhoea (IBS-D) Diagnosis

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Introduction: Patients with neuroendocrine tumours (NETs) complain of symptoms that may be mistaken for irritable bowel syndrome (IBS). There is no clear data if these symptoms overlap with those of IBS or if differentiating symptoms co-exist. **Aim(s):** To identify if NET patients' pre-diagnosis symptoms meet the criteria for a diagnosis of functional diarrhoea (IBS-D). **Materials and Methods:** An anonymised online questionnaire of NET patients was developed via SurveyMonkey that incorporated a screen for IBS–D (Rome III criteria). **Results:** There were 229 complete responses (303 responses, 205 female). Top primary sites were 99 small-bowel (sb), 64 pancreas (p). 69% of sbNET and 42% of pNET patients were over 50 years old at the time of developing their 1st symptom. The mean 1st symptom duration was 60 months for sbNETs and 39 months for pNETs. The mean reported weight change was –4.1 kg for sbNETs and –0.4 kg for pNETs patients with 60% and 45% respectively reporting greater than 4.5 kg weight loss. When pain was not considered, 24% and 15% of sbNET and pNET patients respectively meet part of the criteria for IBS-D for loose bowel symptoms and duration. However, only 4–5% of sb and pNET patients met the full criteria for IBS-D. 32% of sbNET and 17% of pNET patients reported that their GP or hospital specialist considered IBS as a diagnosis. **Conclusion:** NET patients do not fulfil the criteria of IBS-D despite this being considered by healthcare practitioners. Pain, weight loss and age >50 are concerning factors. **Keywords:** IBS, NET, Functional diarrhoea.

D3

Does Faecal Occult Blood Testing Help Identify Ileo-Colonic NETs in the UK Bowel Cancer Screening Programme (BCSP)?

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Introduction: There has been an increase in the incidence of ileo-colonic NETs in recent years, partly from endoscopy. There is no published data on the incidence of NETs diagnosed in the UK 'double' screen BCSP of initial Faecal Occult Blood stool test (FOBt) and, if abnormal, colonoscopy. The incidence (per 100k) of colorectal cancer (CRC) in FOBt abnormal UK BCSP colonoscopy is 55 times that

of the population incidence (10k vs. 184). **Aim(s):** To identify NETs diagnosed and recorded at UK BCSP colonoscopy between 2005–14. **Materials and Methods:** Data requests were made to UK BCSP for details of screened populations. Three NET related BCSP database queries were run and incidence (per 100k) was compared with those from the SEER database. **Results:** 13 million people completed FOBt screening with 260k abnormal FOBt and 217k colonoscopies. 146 NETs were identified with an incidence of 67 (per 100k). The incidence of NETs by site was 29 rectal, 18 other colonic, 1 appendiceal, and 11 small intestine. Ratios of BCSP to SEER incidences was 29 overall NET, 32 rectal, 45 other colonic, 5 appendiceal, and 12 small intestine. **Conclusion:** The incidence of NETs at UK BCSP colonoscopy following an abnormal FOBt is markedly higher than the SEER population incidence. The effect is greatest for rectal and other colonic NETs although less than that seen with CRC (55x). The incidence of UK BCSP rectal NETs vs. published colonoscopy-only BCSP (50-70 per 100k) suggests endoscopic screening is more helpful than FOBt. **Keywords:** Bowel cancer screening, Ileo-colonic, NETs, Rectal.

D4

Delays in Diagnosing Neuroendocrine Tumours by Secondary Care Specialities

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Introduction: Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) are considered to be a diagnostic challenge, many patients presenting with metastatic disease to a number of specialities in secondary care. **Aim(s):** To evaluate time taken to diagnose NETs and to explore the specialities and pathways involved in making diagnoses. **Materials and Methods:** Retrospective analyses were conducted on records from patients visiting NET clinics and from the NET MDT in South East Wales. Data on presenting symptoms, specialities involved in addition to tumour characteristics were collected. **Results:** 51 patients with histologically confirmed GEP-NETs were included, 46 having complete data. Mean time of diagnosis from symptom onset was 20.3 months. Final diagnosis was made by General Surgery (22%), Gastroenterology (22%), Colorectal Surgery (20%), Upper GI Surgery (13%), HPB surgery (9%) and other (14%). Most common presenting symptoms were abdominal pain (72%) and diarrhea (36%). 23% of cases were diagnosed as an acute emergency and 11% incidentally. Patients saw a mean of 1.48 (range 0–5) specialities. 12/38 (32%) patients were discharged from secondary care once prior to being re-referred for final diagnosis, 5/38 (13%) discharged twice. **Conclusion:** Diagnosis involves more than one speciality. Previous discharge to primary care necessitates re-referral and delays diagnosis. The majority of cases are diagnosed by gastroenterological specialities indicating the need to raise awareness of NETs in those specialities for timely diagnosis. **Keywords:** Diagnosis, Gastroenterology, Symptoms.

D5

Neuroendocrine Cancer Patient Experience Survey

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Introduction: Annually a national patient cancer survey (NCPES) is performed to assess perceived patient care. It was noted that in the previous cancer experience surveys patients with NET had not been invited to participate. The NET Patient Foundation (NETPF) commissioned Quality Health to undertake this survey in patients with a known diagnosis of neuroendocrine cancer. The patients were identified via NET centres of excellence around England. **Aim(s):** To assess perceived level of patient care in 8 areas:initial diagnosis and referral, communication, information, treatment, CNS, support and overall NHS care. **Materials and Methods:** Study population were adults with a confirmed diagnosis of neuroendocrine cancer between August 2011 to July 2014. The questionnaire was adapted from the NCPES 2014 questionnaire and underwent a process of cognitive testing. Send out undertaken between January to September 2015. The send out followed the same methodology as the CPES. **Results:** 7 trusts submitted data which amounted to a sample size of 1849. The overall response rate was 56%. A total of 996 questionnaires returned. **Conclusion:** The patient population for the responses is biased due to the centres approached, which is a concern since patient access to information and therapy choices may be more limited in non-specialist centres. There appears to be simple changes in terms of improved patient information that may improve patient experience of the NET cancer services. **Keywords:** Diagnosis and referral, Communication, Information, Explanation, Treatment, CNS, Support.

D6

Clinicopathologic Features, Management and Outcome of Neuroendocrine Tumors (NETs) in MEN1: The Verona Multidisciplinary PlaNET Group

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Introduction: Gastroenteropancreatic endocrine tumors (GEP-NETs) are a frequent manifestation of MEN1. They represent an important prognostic factor in these patients. There is still a debate on

their management, mainly on surgical strategy, due to their multicentricity and high recurrence rate. **Aim(s):** To assess clinicopathologic features, management and outcome of MEN1 patients with GEP-NETs. **Materials and Methods:** Data on a cohort of MEN1 patients referring to the multidisciplinary group PlaNET of the University of Verona between 1990 and August 2015 were retrospectively analyzed. **Results:** MEN1 was diagnosed in 75 patients, of whom 61 presented pNET during the study. In 32 patients (42.7%) GEP-NET was the manifestation which lead to the diagnosis of MEN1 and primary hyperparathyroidism (PHPT) was already present at the time of diagnosis in 84.4% (59.2%, asymptomatic). Among 61 GEP-NETs, 32 (19 NF, 8 ZES, 5 insulinomas) underwent surgery with radical intent. After a median 3-yr follow up 63% NF, 12.5% ZES and 60% insulinomas were disease free. 11/14 (78.6%) NF p-NETs ≤2 cm not operated were stable after a median 4-yr follow-up. **Conclusion:** GEP-NETs were the manifestation that lead to diagnosis of MEN1 in about 40% of cases. Thus MEN1 should be looked for in all patients presented with GEP-NETs. Surgery can be effective in most NF-GEP-NETs and insulinomas, but only in a minority of ZES. Patients with pNETs ≤2 cm can be treated conservatively, if periodically followed with appropriate imaging. **Keywords:** MEN1, GEP-NET, Management.

D7

Clinicopathologic Features, Treatments and Survival of Patients with Ectopic Cushing's Syndrome from Neuroendocrine Tumors: Data from an Italian Multicenter Study

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Introduction: Literature on ectopic Cushing syndrome (ECS) and NET is scarce. **Aim(s):** This is the first Italian multicenter study on clinicopathologic features, treatment and survival of ECS-NET patients. **Materials and Methods:** Retrospective analysis of data on ECS-NET from 17 centers, obtained by a questionnaire. **Results:** 110 patients, 58.2% females, mean ± SD age at diagnosis 49.5 ± 15.9 yr. Clinical presentation: hypertension 89.1%, diabetes mellitus 65.5%, proximal myopathy 70.9%, weight loss 29.1%, skin fragility 54.5%, hypercoagulability 30%, osteoporosis 48.2%, psychiatric disease 34.5%. NET prevalence: 40.9% bronchial carcinoids (BC), 22.7% occult, 15.5% pancreatic pNET, 6.4% pheochromocytomas, 5.5% thymic carcinoids (TC), 3.6% SCLC, other (5.4%). pNET tumor diameter was larger than BC ($p = 0.002$). Distant metastases were more prevalent in pNET, SCLC and TC than in BC and occult. Curative surgery was performed in 56.7% (76.5% of BC, 11% of pNET). Adrenalectomy in 28.2%. Steroidogenesis inhibitors were used in 94.9%, SA in 54.5%. 5 yr OS was higher in BC vs. pNET and occult ($p = 0.009$), in G1 vs. G2-G3($p = 0.007$), in patients with S-U cortisol and ACTH <5ULN, without ipokaliemia ($p < 0.002$) and metastases ($p = 0.019$) with NET surgery ($p < 0.01$) and adrenalectomy. **Conclusion:** BC are the main ECS-NET with high curative surgical rate and best survival. 23%are occult with poorer prognosis than BC. Type of NET, grading, distant metastases, severity of hypercortisolism are main prognostic factors. A multimodal treatment, including surgery and adrenalectomy, can prolong survival. **Keywords:** Ectopic acth.

D8

Neuroendocrine Tumors in Russia: NET Observational Registry Data

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Introduction/Aim(s): To assess prevalence, incidence and regional trends in the diagnosis, practical clinical management and outcome measures of NETs in Russia. **Materials and Methods:** Data were collected at 57 sites. Enrollment began in Sep-12. Data were collected every 6 months for 2 yrs and was completed on 31-Jul-14. **Results:** In total, 337pts were enrolled. Median age at diagnosis was 54 yrs (range:18–88 yrs); 69% were female. ECOG score was 0-1 in 90%pts. Mean duration of NET history was approx 2 yrs (23 ± 36 months), and the mean interval between first disease symptoms to an established NET diagnosis was 10 ± 22 months. Prior to enrollment, most pts were treated by an oncologist (52%) or by a general practitioner (48%). At enrollment, 82% had symptoms: most commonly pain (52%), fatigue (23%), weight loss (20%), diarrhea (15%). The GI tract was the most common primary site (62%), second was lung and thymus (19%pts each). Among the GI tumors, pancreatic were the most prevalent (21%); followed by large (17%) and small (14%) intestinal tumors. Metastasis to regional lymph nodes were diagnosed in 31%pts, with distant metastasis in 46%. Mitotic index

was determined in only 11%pts, Ki-67 index in 56%, synaptophysin in 38%, CgA in 37%. The most common therapy was surgery (71%), and pharmacotherapy (56%) with somatostatin analogues 35%), platinum compounds (29%), podophyllotoxin derivatives (21%) and interferon (13%) being most common. Mean overall survival was 19±0.4 mths. **Conclusion:** The registry provides important information about NET in Russia. **Keywords:** Registry.

D9

Multidisciplinary Management and Patient Flow in Neuroendocrine Tumors (NET): Consensus of a Tertiary Hospital

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Introduction: Currently, there has been an improvement in diagnostic procedures and treatments of NET. Therefore, an effective teamwork is needed to choose the best approach for patients. **Aim(s):** To design a clinical guideline. **Materials and Methods:** HUCA is a tertiary care center in Spain that serves about 40 new patients with NET each year from a population over one million. The multidisciplinary team meets monthly to discuss all new cases and consider other treatment options for those previously diagnosed. The committee is made up of different specialists: endocrinologist, pathologist, gastroenterologist, nuclear medicine, radiologist, surgeon and medical oncologist. Patient flow was designed from the previous clinical guidelines adapting them to our center and resources (Italian one was the reference guideline, Grimandi F. Endocrinol Invest 2014). **Results:** In a practical way, patients were subdivided in those presenting to hospital with an incidental finding of pancreatic or liver masses on a radiological examination, patients with unspecific gastrointestinal symptoms or those with symptoms suggestive of functioning tumor. For each of 4 patients prototypes, consecutive procedures, responsible specialists and the most appropriate treatment were collected in a flowchart (4 flowcharts will be presented graphically at ENET 2016 conference). **Conclusion:** Our multidisciplinary team has developed a consensus clinical guideline applicable in clinical practice to achieve the better care for patients with NET. **Keywords:** Mutidisciplinary team, Guideline, NET.

D10

Epidemiology, Pathological Features and Clinical Outcome of Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NENs): Results from the National Neuroendocrine Cancer Registry of Spain (R-GETNE)

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Introduction: The Spanish National Neuroendocrine Cancer Registry is a hospital-based registry of GEP-NENs coordinated by the scientific multidisciplinary Spanish society GETNE, that covers 57 academic and community sites representing all regions of Spain. **Aim(s):** We present the updated report of the registry. **Materials and Methods:** Data was provided online and assessed for internal consistency by external independent reviewers. **Results:** The study cohort comprised 2487 patients diagnosed since 2000. The median age was 59 years and 54% were men. MEN was diagnosed in 3%. 7% were incidental diagnosis. IHC staining for chromogranin and synaptophysin was done in 72% and 63%, being positive in 67% and 61%, respectively. Tumor was detected in: CT (74%), octreotide scintigraphy (64%), endoscopy (48%) and ultrasound (38%). Serum chromogranin A or urinary 5-HIIA were determined in 38% and 34% and were increased in 24% and 14% of tested patients, respectively. The most common primary tumor locations were: small bowel (37%), pancreas (40%), unknown primary (9%) and colorectal (9%). Stage at diagnosis was: I (18%), II (7%), III (7%) and IV (27%). 40% were grade 1 and 9%, grade 3. Median OS was 7,6 years (95% CI, 5,7–12,5) for stage IV, 10,3 y (95% CI, 8,6-NA) for stage III, and not reached for stage I-II. OS by Ki67 and primary tumor location will be presented at the ENETs conference. **Conclusion:** This national database reveals relevant information regarding epidemiology and clinical outcome of GEP-NENs in Spain. **Keywords:** Neuroendocrine tumor, Registry, Spain, Survival.

D11

A Nation-Wide Retrospective Epidemiological Study of Gastroenteropancreatic Neuroendocrine Neoplasms in China

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Introduction: Representative data on the gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) in Chinese patients is rare. **Aim(s):** This study aims to create a GEP-NENs profile of Chinese patients. **Materials and Methods:** Hospitals at tertiary level in each seven geographic region in China were selected. All inpatient GEP-NEN patients with confirmed pathology were included and their information was collected based on the designed case report form. The primary GEP-NEN sites were measured; the epidemiological and clinical information of each tumor site were compared. **Results:** The most common primary sites for GEP-NEN were the pancreas (31.5%) and rectum (29.6%), followed by the body (15.4%) and cardia (11.6%) of stomach. Small intestinal and colonic NENs took up a relatively small proportion, at 5.6% and 3.0% respectively. Pancreatic and rectal NENs, rather than gastric cardiac and gastric body NENs, tended to be found in younger, female, urban residents with higher education levels ($P < 0.05$) and were also diagnosed at earlier stage and lower grade ($P < 0.001$). Surgery remained the primary treatment method in all groups. Chemotherapy was more commonly used in the gastric NENs. Biotherapy was only performed frequently on pancreatic NEN patients. **Conclusion:** The pancreatic and rectal NEN patients comprised majorities in all Chinese GEP-NEN patients, and their stage and grade at diagnosis were lower than NENs from stomach and other sites. **Keywords:** Gastroenteropancreatic neuroendocrine neoplasm, Multi-center, Retrospective study, Epidemiology.

D12

NETs in Russian Cancer Center Hospital Registry

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Introduction: Studies show an increasing number of pts diagnosed with NETs within the study period 1990–2015. **Aim(s):** To evaluate the different types of NETs based on medical records and follow up the status of those pts. **Materials and Methods:** Retrospective analysis of data. **Results:** Seven hundred and fifty two pts with NETs were in the study. The most common primary sites were: GEP-NETs – 292 pts, BNETs-230, small intestine – 66, bowel – 53. Primary tumors were not determined in 5.6%. Distribution of the disease is following: 28.2%-localized, 14.9%-locally advanced, 56.9%-metastatic, no data – 23.5%. Grade was defined only for 246 pts. Five year survival for pancreatic NETs – 72.3%, BNETs – 88.3%, gastric NETs – 56.1%, small intestine NETs 67.0%, bowel NETs – 61.4%, not determined NETs – 56.5%. There were no mts in 74.1% in pts with local stage. We analyzed 420 records with head and neck NETs. Age at diagnosis was 40-47 years for male and 50-52 for female. There are 78pts with aesthesioneuroblastoma, located in 41 cases in nose cavity, 30 cases in ethmoid sinus, and 7 cases in nasopharynx. Time from the first symptoms to the start of treatment was from 1 to 125 month. Five year OS-55%, 10 year – 44.6%. more than 20 years – 5.6%. 5 year disease free survival (DFS) was 72.2%, 10 years – 56.9%, 20 years – 56.3%. Median DFS was not reached. **Conclusion:** Number GEP-NETs pts in our center for the study period is among the highest. **Keywords:** NETs, Overall survival, Grade.

D13

Metastatic Neuro Endocrine Tumors: Epidemiological Characteristics, Management and Prognostics Factors. Results from an Inter-Regional Network in France between Upper and Lower Normandy

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Introduction: Metastatic neuro-endocrine tumors (MNETs) are rare and their management are complex. To standardize therapeutic strategies in France, a national network of clinicians (RENATEN) has been created, composed of 17 expert centres. **Aim(s):** To describe characteristics, management and prognostic factors of MNETs in one expert centre. **Materials and Methods:** Between 2012 and 2014, patients with histologically proven MNET discussed in Normandy's

inter-regional meetings of RENATEN network were retrospectively included. Data were actualized until January 2015. **Results:** 179 patients were included. Mean diagnosis age was 60 years; clinical performance status (PS) was 0-1 for 85% of patients; median follow-up period was 45,3 months; 33 patients died. Most frequent primary sites were small bowel (36%), pancreas (28%) and unknown (13,4%). The WHO 2010 classification was available for 96% of patients. Respective rates of G1, G2 and G3 were 42%, 29% and 25%. 57,5% of patients underwent surgery. 102 patients were treated with palliative purpose: somatostatin analogues (71,5%), chemotherapy (50%) (of whom 36% with FOLFOX regimen), and intra hepatic chemo-embolization (28%). Five year overall survival (OS) was 77%. Multivariate analysis showed that PS ($p < 0.001$) and WHO 2010 classification grade ($p = 0.006$) were independents predictors of OS. **Conclusion:** RENATEN network helped to have a better knowledge of MNET treated in Normandy. Availability rate of WHO 2010 classification was high. **Keywords:** Metastatic neuro-endocrine tumors, Epidemiological characteristics.

D14

Metastatic Disease in Gastroenteropancreatic Neuroendocrine Cancer: Incidence, Treatment and Survival

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Introduction: Data on patients with metastatic disease from GEP-NETs are rare. **Aim(s):** To provide detailed population-based data on incidence, patterns of metastases, treatment and prognosis of patients with metastatic GEP-NETs. **Materials and Methods:** Data from all patients diagnosed during 2007-2013 with a metastasized GEP-NET were retrieved from the Netherlands Cancer Registry. **Results:** In total, 1,231 patients with a GEP-NET (30% of all GEP-NETs) presented with synchronous metastases. European age-standardized incidence rates of metastasized GEP-NETs increased during the study period from 0.6 to 1.0 per 100,000 persons/year. Patients with appendiceal NETs exhibited the lowest proportion of metastases (n = 33; 3%); left colon the highest (n = 72; 67%). Liver metastases were most frequent (n = 961; 78%) and most patients only had one site of metastases (n = 770, 63%). Overall survival was highest in small intestinal NETs and poorest in esophagus NETs (2-year survival rates 80% vs. 7%, respectively). Survival was highest after resection of the primary tumor (n = 378, 30%) or treatment with somatostatin (n = 284, 23%) (2-year survival rates 69% and 79%, respectively). **Conclusion:** Patients with GEP-NET often present with metastases at time of diagnosis. Primary tumor site is not only the single most important prognostic factor, but also predictive for the pattern of metastatic spread. **Keywords:** Metastases, Carcinoid, Gastroenteropancreatic neuroendocrine tumors, GEP-NETs, NETs, Frequency, Treatment, Prognosis, Survival.

D15

Chilean Neuroendocrine Tumours Hospital Registry: Initial Data of a Latin-America Perspective

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Introduction: Neuroendocrine tumours (NET) have increasing area of clinical and scientific research. The NET registry of the Pontificia Universidad Católica de Chile (PUC) is the first chilean database which systematically collects data on patients with neuroendocrine tumours. **Aim(s):** Monitoring the overall number of patients with TNE who have been treated, with assessment of safety and effectiveness of treatment. **Materials and Methods:** Non-interventional, retrospective and prospective observational study (between January 1995 to October 2015) of demographic data, clinical features and survival rate of patient with diagnosis of NET at the PUC. Data are collected as anonymous records with encrypted personal data of patients. **Results:** We identified 106 NET with 57.5% men. Median age was 52.6 years, 84.9% of patients had PS < 2. The most common primary sites were the small intestine (40.6%), pancreas (20.7%) and colorectal (8.5%). Average of chromogranine A was 1286, distant disease 68%, metastases in 76.3% in the liver. Grade 2 disease in 27% and Ki-67 3–20% in 47%. Surgery was used in 62.3%; medical therapy with chemotherapy in 21.7%, peptide receptor radionuclide therapy in 21,7% and somatostatin analogues in 27,4%. Five years overall survival was 60. **Conclusion:** A Latin–American perspective of Chilean NET was obtained, with a favorable prognosis despite to debut with metastases in 68%, representing a challenge in treatment in Grade 2 disease. **Keywords:** Neuroendocrine tumors, Hospital registry, Latin-america perspective, Overall survival.

D16

Extra-Pulmonary Neuroendocrine Carcinomas: A National Population Based Study

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Introduction: Extra pulmonary neuroendocrine carcinomas (EPNEC) are rare tumours, this implies lack of knowledge on the burden. **Aim(s):** With this study we aim to analyse the incidence, relative survival (RS) and treatment for EPNEC patients in the Netherlands. **Materials and Methods:** Patients diagnosed with EPNEC and NEC with unknown primary (UP) were included from the Netherlands can-

cer registry between 2008-2012. Correctness checks on this data were conducted by linkage to the archived pathology report. Incidence was analysed using the European Standardized Rate (ESR). For treatment we assigned patients to the hospital that set the treatment plan. RS was calculated using the Ederer II method. **Results:** 1544 NEC cases were included, 1045 EPNEC and 499 UP. For EPNEC the incidence was 1.0 per 100,000ESR, resulting in 209 cases annually. The mean age was 68 year. A female to male ratio of 1:1.6 was observed. Most frequent EPNEC localisation was the bladder. Overall 5 year RS was 20.5%;38.2% for local disease (n = 435), and 7.6% in distant disease (n = 601). Patients treated in university hospitals had a significant higher 1 year RS than in non-university hospitals (64% vs. 50%). No significant differences were found for the longer term survival. For UP patients (n = 499) 5 year RS was 5.8%. **Conclusion:** In the Netherlands 209 EPNEC cases were found annually with a 5 year RS of 20.5%. Based on literature we estimate this to be 226 taking into account the proportion of UP. We observed better outcome at 1 year in EPNEC patients treated in university hospitals. **Keywords:** EPNEC.

D17

Exploring the Rising Incidence of Gastroenteropancreatic Neuroendocrine Tumors According to the Data from Regional Cancer Registry: A Population-Based Analysis of Epidemiology

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Introduction: The incidence of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) is reported to arise worldwide. Similar tendency is observed in Bulgaria during the recent 6 years. **Aim(s):** Our objective was studying the epidemiological characteristics of the diagnosed GEP-NETs for a period of 6 years tumors according to database from Regional Cancer Registry in Pleven, Bulgaria and assessing the influence of the early detection of GEP-NETs over their rising incidence. **Materials and Methods:** A population-based retrospective study for GEP-NETs according to data from Regional Cancer Registry in Pleven, Bulgaria from 2010 to November 2015. The main outcomes include epidemiological information for sex, age, date of death, pathological characteristics, localization, degree of differentiation, TNM-classification and conducted surgical treatment. **Results:** Thirty-eight cases of GEP-NETs are registered for the studied period. Their frequency has increased from 10.5% for 2010 to 23.7% for 2015. They are more frequent in woman than in man. 47.4% of the patients are in Stage 4 in the moment of diagnosing. Seven cases of GEP-NETs were G2 by the degree of differentiation. **Conclusion:** According to our results, the incidence of GEP-NETs, registered at Regional Cancer Registry in Pleven, Bulgaria has increased from 10.5% to 23.7% for the studied period, which confirms the world tendency. The increased frequency is closely related to the better diagnosis and better cooperation between pathologists and surgeons. **Keywords:** GEP-NETs, Incidence, Regional cancer registry.

D18

Neuroendocrine Tumors of the Appendix Are Probably Harmless Neoplasms

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Introduction: Appendiceal neuroendocrine tumors (aNETs) have a 5-year survival rate between 74% and 95% according to recent data from Cancer Registry of Norway and the United States, respectively. However, in the daily clinical practice one almost never encounters patients suffering from aNETs with distant metastasis or dying of the disease. **Aim(s):** In order to resolve this contradiction, we performed a systematic search in PubMed. **Materials and Methods:** Systematic search was carried out using key words 'appendix or appendiceal', 'carcinoid or neuroendocrine tumors', 'survival' and 'registry or register'. We accessed the row data from Surveillance, Epidemiology and End Results Program (SEER) and received recent data from Cancer Registry of Norway (CRN). **Results:** 26 papers reporting 976 patients with appendiceal NETs were identified. 3 disease related cases of death have been recorded which accounted for a mortality rate of 0.31%. Analysis of the data from SEER revealed 95% and 89% survival rate of aNETs for 5 and 40 years, respectively. CRN registered a 5-year survival rate of 80.1% for aNETs. **Conclusion:** Published institutional series of aNETs revealed an almost negligible mortality rate of 0.31%. Data from large cancer registries demonstrate strikingly higher mortality rates. However, these cases have not been documented in the medical literature. The reason for this discrepancy could be partly due to low accuracy of disease coding and imprecise data on causes of death. aNETs are probably less aggressive neoplasms than previously thought. **Keywords:** NET.

D19

Multicenter Retrospective Analysis of Clinical and Pathological Features of Gallbladder and Extrahepatic Biliary Duct Neuroendocrine Neoplasm

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Introduction: Primary neuroendocrine neoplasm of the gallbladder (GB) and extrahepatic biliary duct (EHBD) were considered as rare malignant tumors. **Aim(s):** This study was to explore the clinical and pathological characteristics and prognostic features of GB and EHBD NEN. **Materials and Methods:** 18 GB-NEN and 2 EHBD-NEN were enrolled from February 2001 to April 2015. **Results:** Of GB-NEN, there were 8 male and 10 female. Both 2 EHBD-NEN

were male. The median age was 55.05 ± 12.10 years (26-72). 20 cases were nonfunctional, representing as jaundice, cholecystitis, and abdominal or back pain. The median sizes of the GB-NEN and EHBD-NEN were 2.25 ± 0.35 cm and 4.21 ± 2.72 cm. Our entity included 3 G1, 1 G2 and 16 G3; 4 NET, 10 NEC and 6 MANEC. Pathologic IHC showed CgA(+)70%(14/20), NSE(+)87.5%(7/8), Syn(+)82.4%(14/17), CD56(+)85.7%(12/14). At diagnosis, 10(50%) had a localized disease,3 (15%) had regional advanced tumor, and 7(35%) had liver metastasis. Surgery was adopted in 17 cases, 4 cases accepted chemotherapy after surgery. Up to December 2015, 16 cases completed follow-up data survival analysis, with a median survival time of 46.3 months (95% CI 29.33–63.28). The 1-, 2- and 3-year survival rates were 78.1%, 67.6% and 50.2%.3 unresectable GB-NECs accepted multidisciplinary treatment with OS over 36.8 months. **Conclusion:** Most of tumors in out entity were high-level NEC and MANEC with aggressive biological behaviors. Surgery was the mainstay for GB and EHBD NEN. Multidisciplinary treatment could increased the survival. **Keywords:** Gallbladder, Extrahepatic biliary duct, Neuroendocrine tumor.

Epidemiology/Natural History/ Prognosis – Prognosis

E1

Prognosis and Treatment Outcomes of Patients with Mixed Adenoneuroendocrine Carcinoma (MANEC)

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Introduction: Mixed adenoneuroendocrine carcinomas (MANEC) are rare tumors, commonly treated in analogy to adenocarcinomas (AC) or neuroendocrine carcinomas (NEC) without systematic data regarding response to therapy. **Aim(s):** To analyze the treatment outcomes of MANEC patients. **Materials and Methods:** Retrospective analysis of all patients with MANEC at our center between 12/2011 and 09/2015. **Results:** In the total of 32 patients identified, overall survival (OS) from diagnosis was 21.0 months. 26 patients in a localized stage underwent surgery, median recurrence-free survival (RFS) was 11.2 months. In multimodally treated patients (including chemotherapy and/or radiotherapy) vs. patients receiving surgery alone RFS and OS were significantly prolonged with 14.9 vs. 7.0 months (p = 0.0024) and 44.5 vs. 18.0 months (p = 0.0073) respectively. 17 patients received palliative first-line chemotherapy for metastatic disease. Partial response (PR) was observed in 41.2% and stable disease (SD) in 17.6% of cases. Median progression-free survival (PFS) and OS was 3.9 and 9.4 months respectively without any significant difference between platinum and etoposide, or oxaliplatin and 5-FU based regimens. 8 patients received a second-line therapy without any documented PR or SD as best response. **Conclusion:** Prognosis of localized MANEC seems to be improved by multimodal treatment. In first-line therapy of metastatic MANEC both regimens for AC and NEC seem equally effective. Our data show no benefit of second-line therapy. **Keywords:** MANEC, Mixed adenoneuroendocrine carcinoma.

E2

Neuroendocrine Tumors of the Biliary Tract: A Retrospective, Observational Multicenter Study

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Introduction: Neuroendocrine tumors of the biliary tract (BTNETs) constitute a heterogeneous group of neoplasms. Because of their rarity, the clinical behavior is unclear. **Aim(s):** To elucidate the characteristics of BTNETs patients. **Materials and Methods:** From 9 single institution database we collected biological and clinical features of BTNETs patients (pts). Between 1996 and 2015, gallbladder, all region of bile duct and ampulla of Vater neuroendocrine tumors were considered. According to WHO 2010 classification, a centrally revision of the pathological staining was performed. **Results:** A total of 50 pts were enrolled (68% male, median age 64 years). Tumors were symptomatic in 58% of pts. Common symptoms were abdominal pain (30.0%) and jaundice (10%). Primary sites were Ampulla of Vater (40%), gallbladder (22%), extra-hepatic duct (12%), intra-hepatic duct (6%), and others biliary tracts (20%). Seventy-four percent were radically resected. Based on WHO 2010 classification 47% had NET G1, 12% NET G2, 31% NEC G3 and 10% mixed adenoneuroendocrine carcinoma (MANEC). No one pts received adjuvant treatment. First line somatostatin analogue was administered in 24% of pts and chemotherapy in 34% of pts. After 21 events, median overall survival was significant longer in NET G1/G2 than NEC G3/MANEC (19.8 vs. 2.3 years, HR 3.1, 95% CI 1.16–8.39, p = 0.0.18. **Conclusion:** All the currently known spectrum of neuroendocrine tumors can arise in the biliary tract. As for the other organs WHO 2010 classification can predict the outcome of pts. **Keywords:** Biliary tract NET.

E3

Access to Care and Outcomes for Neuroendocrine Tumors: Does Socio-Economic Status Matter? A Population-Based Analysis

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Introduction: Neuroendocrine Tumors (NET) lack standardized care. Differences in socioeconomic status (SES) worsen the impact of non-standardized care. **Aim(s):** We examined the impact of SES on NET peri-diagnostic care patterns and outcomes. **Materials and Methods:** All adults with NET identified from a cancer registry (1994-2009) were divided into low (1st-2nd income quintiles) and high SES (3rd-5th). We compared peri-diagnostic healthcare utilization (–60 days to +6 months), metastatic recurrence, and overall survival (OS). **Results:** Of 4966 NET patients, 38.3% had low SES. Neither primary NET sites ($p = 0.15$) nor metastatic presentation differed ($p = 0.31$). Patients with low SES had higher mean number of physician visits (20.1 ± 19.9 vs. 18.1 ± 16.5; $p = 0.001$) and imaging studies (56 ± 50 vs. 52 ± 44; $p = 0.009$) prior to diagnosis. Primary tumor resection ($p = 0.14$), hepatectomy ($p = 0.45$), systemic therapy ($p = 0.38$), and liver embolization ($p = 0.13$) did not differ with SES. Recurrence was more likely with low SES (41.1% vs. 37.6%; $p = 0.01$). 10-year OS was inferior with low SES (47.1% vs. 52.2%; $p < 0.01$). Low SES was independently associated with worse OS (HR 1.16; 95% CI: 1.06–1.26). **Conclusion:** Low SES was associated with need for more physician visits and imaging to reach NET diagnosis, but not with more common advanced stage presentation or impact on patterns of therapy. Long-term outcomes were inferior for low SES patients. This data provides further insight for future directives in enhancing healthcare delivery. **Keywords:** Socio-economic status, Outcomes.

E4

Development and Validation of Nomogram in Predicting Individualized Postoperative Survival for Nonfunctional Pancreatic Neuroendocrine Tumors: A Multicenter Retrospective Study

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Introduction: NA. **Aim(s):** To establish a nomogram to provide individualized predictions of nonfunctional pancreatic neuroendocrine tumors (NF-PNETs) patients treated with surgery. **Materials and Methods:** The retrospective multi-institutional study consisted of consecutive 204 postoperative NF-PNETs from Zhongshan and Changhai Hospital during 1999 to 2012. A nomogram to predict the OS with variables selected in multivariate Cox regression was constructed. The validation of nomogram was determined by C-index, calibration curve and decision curve analyses, comparing with existing prognostic stratification systems. **Results:** Ki-67, mitotic count, preoperative stage (local, regional, distant), differentiation (well, moderate, poor), ENETS and AJCC TNM, tumor size, lymphnode metastases, necrosis, neighbouring organs invasion, encapsulation, large vessel invasion, perineural invasion, abdominal distension, anorexia and weight loss were correlated with OS ($P < 0.05$). Only Ki-67, preoperative stage, differentiation, encapsulation were selected as independent factors incorporating into nomogram. The nomogram showed optimal calibration with C-index of 0.90 (95% CI: 0.86–0.94). The nomogram demonstrated superior discrimination compared to ENETS TNM and AJCC TNM criteria. In decision curve, the nomogram demonstrated higher net benefit and relativity gains compared with other stratification systems. **Conclusion:** The proposed nomogram orchestrates accurate prediction and discrimination of postoperative NF-PNETs offer a reference basis to stratification. **Keywords:** Nomogram NF-PNETs.

E5

Gastric Neuroendocrine Tumors-Experience in a Chinese General Hospital

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Introduction: Gastric neuroendocrine tumors (GNET) were categories to three subtypes. **Aim(s):** Retrospective study of patients with GNET admitted in our hospital between 2005 and 2014 to dem-

onstrate the clinicopathologic features. **Materials and Methods:** Demographic factors, WHO classification, staging, therapy and survival (Kaplan-Meirer method) were analyzed. **Results:** Forty patients, 23M and 17F, aged between 40 and 85 years (average 59.5 years). Twenty-two patients (55%) with type I, 2 (5%) with type II, and 16(40%) with type III. Regarding location, 12.5% (5/40) were antrum, 72.5% (29/40) were corpus, and 5% (2/40) were fundus,10%(4/40) were cardia. They were classified (WHO 2010) as NET G1, G2 and G3 (or named elevated proliferation NET), respectively, 47.5% (19/40), 35% (14/40) and 17.5% (7/40) of patients. 55% had stage (ENETS. AJCC/UICC) I, 35% stage II, 7.5% stage III, and 2.5% stage IV. Out of 40 GNET, 25 were treated with endoscopy submucosa dissection (ESD). Fifteen (37.5%) patients were operated. Overall 5-year survival was 93% (median 23.5 months), depending mainly on WHO classification, and presence of liver metastases. OS of radically operated GNET patients was 100%. **Conclusion:** In our series, type III GNET incidence is higher than it in Caucasian cohort. ESD was an effective method to treat type III pts in stage I. **Keywords:** Gastric, Neuroendocrine tumor, Endoscopic submucosa dissection, Prognosis, Liver metastases.

E6

Clinicopathological Features and Prognostic Factors of Colorectal Neuroendocrine Neoplasms in China

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Introduction: Limited research is available regarding colorectal neuroendocrine neoplasms (NENs), especially in China. **Aim(s):** To perform an epidemiological and prognosis research of colorectal NENs in China. **Materials and Methods:** A total of 68 patients with colorectal NENs were studied retrospectively. Clinical characteristics and prognosis between were compared. The Cox regression models were used to evaluate the capacity of various factors to predict the outcome. **Results:** Of the 68 colorectal NENs patients, 43 (63.2%) had rectal NENs, and 25 (36.8%) had colonic NENs. Compared with rectal NENs, colonic NENs more frequently exhibited larger tumor siz and distant metastasis. Colonic NENs had a worse prognosis, with 5-year overall survival rates of 66.7% vs. 88.1% compared with rectal NENs. Neuroendocrine tumors (NET), neuroendocrine carcinomas (NEC) and mixed adenoendocrine carcinomas (MANEC) were noted in 61.8%, 23.5% and 14.7% of patients, respectively. Multivariate analyses revealed that tumor location was not an independent prognostic factor ($P = 0.081$), but tumor size ($P = 0.037$) and tumor classification ($P = 0.012$) were independent prognostic factors. **Conclusion:** Tumor size and tumor classification were associated with the prognosis. However, tumor location was not an independent factor. The worse outcome of colonic NENs observed in clinical practice might be due to the larger tumor size caused by the delayed diagnosis. **Keywords:** Colorectal neuroendocrine neoplasms, Clinical characteristics, Prognosis, Tumor location, Early detection.

E7

A Univariate Analysis of Factors Influencing Survival in Advanced Pancreatic Neuroendocrine Tumors

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Introduction: Pancreatic neuroendocrine tumors (pNET) are rare and display clinical heterogeneity. **Aim(s):** We propose a clinical risk stratification tool for well differentiated, metastatic pNET. **Materials and Methods:** Retrospective study using clinical, pathological and laboratory variables for univariate analyses in a consecutive multicenter cohort (N = 312) with pathologically confirmed, sporadic, well differentiated (grade 1 or 2), metastatic (Stage IV) pNET diagnosed between 1993 and 2010 with a minimum follow-up of 5 years. Data are presented as the mean with standard deviation (SD) and/or 95% confidence interval (CI). Overall survival was calculated using the Kaplan-Meier method with log-rank testing for potentially prognostic factors. **Results:** Patients (N = 312), ≥70 year-old (11%), male (58%), ECOG PS0-1 (66%) with non-functional (67%) and predominantly grade 2 (65%) tumors. Hepatic metastases were present in 83% (69% bilobar), extrahepatic metastases in 64%. Overall Survival (OS) was 6.6 Years (5.8180–8.1316). On univariate analysis ECOG PS >1 ($p = 0.00$), grade 2 ($p = 0.00$), bilobar hepatic metastases ($p = 0.031$), elevation of Chromogranin A (CgA) (56%, $p = 0.015$), Alkaline Phospatase (AP) (24%, $p = 0.000$) and Lactatdehydrogenase (LDH) (18%, $p = 0.042$) were associated with worse prognosis. **Conclusion:** Univariate analysis of the abovementioned variables showed a statistically significant correlation with prognosis in the study population. The integration of these variables could provide a prognostic score for this subgroup of pNET. **Keywords:** pNET, Prognosis.

E8

The Impact of PD-L1 Expression in Patients with Metastatic GEP-NETs

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Introduction: Programmed death-ligand 1 (PD-L1), which is expressed on many cancer cells, interacts with PD1 expressed on the surface of T cells, inhibiting the T cells and blocking the antitumor immune response. **Aim(s):** We investigated the impact of PD-L1 expression in 32 patients with metastatic GEP-NET. **Materials and Methods:** The expression of PD-L1 was evaluated using an anti-PD-

L1 immunohistochemistry (IHC) antibody optimized for staining of formalin-fixed paraffin-embedded (FFPE) tissue samples. **Results:** Primary sites were 24 foregut-derived GEP-NETs, including stomach (n = 1), duodenum (n = 2), biliary tract (n = 7), and pancreas (n = 14), and 8 hindgut-derived GEP-NETs of the distal colon and rectum. Among the 32 patients with metastatic GEP-NET analyzed in this study, 7 (21.9%) had expression of PD-L1 in tumor tissues. Expression of PD-L1 was significantly associated with high-grade WHO classification (grade 3) ($p = 0.008$) but not with gender, primary site, and number of metastatic sites ($p > 0.05$). The status of PD-L1 expression was statistically associated with progression-free survival (PFS) for first-line systemic treatment ($p = 0.047$). Moreover, the status of PD-L1 expression could significantly predict overall survival ($p = 0.037$). **Conclusion:** The expression of PD-L1 was associated with higher WHO tumor grade (grade 3) in metastatic GEP-NETs. PD-L1 expression had both predictive and prognostic value for survival of patients with metastatic GEP-NETs. **Keywords:** PD-L1, GEP-NETs.

E9

Neuroendocrine Neoplasm of the Colon and Rectum, Pathological and Clinical Characteristics, Based on pTNM WHO 2010 Classification

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Introduction: Large bowel neuroendocrine neoplasms (NENs). **Aim(s):** To assess the clinico-pathological characteristics of colon NEN including rectal carcinoids, based on pTNM, WHO 2010. **Materials and Methods:** A retrospective study 179 patients with confirmed large bowel NEN. **Results:** Mean age 55.7 yrs. Female to male ratio 1.45:1. The localization of large bowel NEN: caecum 40; 22%, colon 17; 19%, sigmoid 23; 13% and rectum 99; 55%. Based on pTNM, WHO 2010 classification: NETG1 89; 50%, G2 32; 18%, NECG3 44; 25% and MANEC 14; 8%. Local spread CSI-IIIA noted in 91 subjects (51%). CS IIIB seen in 40 (22%) and CS IV 48 pts (27%). Initial liver involvement in 38 pts 21%. Mean Ki-67 in NETG1 = 1.1%, G2 = 6.3%, NECG3 = 61.1%, MANEC 62.9%. Additional analyses considering localization of primary & degree of differentiation identified: G1 caecal, colon, sigmoid & rectum 28%, 5%, 22%, 72%, G2: 28%, 12%, 9%, 17%, NECG3: 33%, 53%, 57%, 9%; MANEC: 13%, 24%, 13%, 2%. Carcinoid syndrome seen in 6 (all caecal tumours, 3% of all pts). Mean size of primary 28.7 mm, for ceacal 50.7; colon 51.6, sigmoid 38.1 & rectum 13.8 mm. Median OS (whole cohort) was 130M. In selected groups: NETG1=n.r, G2 = 80M, NECG3 = 19M and MANEC = 26M. Median OS in CS IV was 40M. OS including localization: caecal 132M, colon 39M, sigmoid 71M and rectum 130M. **Conclusion:** Primary large bowel NENs favors rectum & caecum, followed by sigmoid & colon with bad prognosis. Histology NEC or MANEC associated with worse prognosis. Patients with initial CS IV also had unfavorable prognosis. **Keywords:** Colon NENs, pTNM WHO 2010.

E10

Prospective Validation of Prognostic Score in High-Grade Gastrointestinal Neuroendocrine Carcinomas (GI-NECs)

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Introduction: Prognostic markers for risk-stratification of GI-NECs are lacking. **Aim(s):** We aimed to validate our prognostic score for GI-NECs (liver metastases, alkaline phosphatase, lactate dehydrogenase, ECOG performance status (PS) and Ki67; Lamarca et al, ASCO 2015). **Materials and Methods:** We prospectively identified all consecutive patients (pts) diagnosed with GI-NECs seen at The Christie (July'14-Nov'15). Our previously designed score was applied. Cox regression and Kaplan Meier were used for survival analysis. **Results:** Twenty-four pts were identified; 22 eligible. Median follow-up time was 4.6 months; 13 pts (59%) had died at time of analysis. Median age: 68.2 years, 73% male, 77% metastatic. Median Ki67: 80% (26–100); PS 0/1 59%; 68% received chemotherapy. Estimated median overall survival (OS) was 10.1 months (95% CI 3.5-not reached [nr]). Our score classified pts in four groups with incremental risk of death: group A (0-1 points (p); 5 pts (25%); median OS 53.6 months (95% CI nr-nr)), B (2 p; 9 pts (45%); median OS 15.7 months (95% CI 3.5-nr)), C (3 p; 3 pts (15%); median OS 3.5 months (95% CI 2.3-nr)) and D (4-6 p; 3 pts (15%); median OS 2.8 months (95% CI 1.9-nr)). On multivariable analysis (adjusted for sodium and stage), the score was an independent prognostic factor for OS (HR 4.5, 95% CI 1.9–10.9; p 0.001). **Conclusion:** These preliminary prospective data validate the capability of our score for prognosticating survival in pts with GI NECs; external validation is ongoing. **Keywords:** NEC, Score, Overall survival, High grade, Prognostic.

E11

Long-Term Outcomes of Colorectal Neuroendocrine Tumors: A Sub Group Analysis of 29 G3 Cases According to the 2010 WHO Classification

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Introduction: Colorectal neuroendocrine tumors (NETs) are a group of heterogenous neoplasm. **Aim(s):** This study was designed to address the clinicopathological features and long-term survival of patients with colorectal NETs according to the 2010 WHO classification. **Materials and Methods:** A total of 88 patients with colorectal NETs were identified from January 2010 to June 2015 at Peking University Cancer Hospital database. Clinicopathological features and long-term outcomes were evaluated. **Results:** For 88 patients identified, 43 (48.9%) were male and 45 (51.1%) were female. The median age was 55.2 years. 38 patients were classified as G1, 21 as G2 and 29 as G3. Tumor size was 7.1 ± 10.5 mm for G1, 18.7 ± 13.4 mm for G2 and 38.8 ± 19.8 mm for G3. After a median follow-up of 27.6 months. The median OS were not reached for G1 and G2 tumors.

For G3 tumors the lower and the middle third of the rectum was the most common tumor site (48.5%). Radical surgery, palliative surgery were performed for 13 (44.8%) and 8 (27.5%) patients, 8 patients (27.5%) did not take any surgery because of advanced stage. The median survival time was only 12.2 months (95% CI, 7.8–16.5). Either radical or palliative surgery did not improve the outcome. **Conclusion:** In patients with colorectal NETs grade was the most significant prognostic factor. For G3 colorectal NEC the outcome was dismal and did not show any difference even radical surgery was performed. **Keywords:** Colorectal neuroendocrine tumors, WHO classification, Long-term outcome.

E12

CEA Level, Radical Surgery and CD56 Expression Are Prognostic Factors for Patients with Locoregional Gastrin-Independent GNET

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Introduction: Gastrin-independent gastric neuroendocrine tumors (GNETs) are highly malignant. Radical resections and lymphadenectomy are considered to be the only possible curative treatment for these tumors. However, the prognosis of gastrin-independent GNETs is not well defined. **Aim(s):** In this study, we identified prognostic factors of locoregional gastrin-independent GNETs. **Materials and Methods:** All patients diagnosed with locoregional gastrin-independent GNETs between 2000 and 2014 were included in this retrospective study. Clinical characteristics, blood tests, pathological characteristics, treatments, and follow-up data of the patients were collected and analyzed. **Results:** Of the 66 patients diagnosed with locoregional gastrin-independent GNETs, 57 (86.4%) received radical resections, 7 (10.6%) with palliative resection, 1 (1.5%) with gastrojejunostomy, and 1 (1.5%) with exploration surgeries. The median survival time for these patients was 19.0 months (IQR, 11.0–38.0). The 1-, 3-, and 5-year survival rates were 72%, 34%, and 28%, respectively. Multivariate analysis indicated that CEA (carcino-embryonic antigen) level (P = 0.04), radical resection (P = 0.04), and positive CD56 expression (P = 0.016) were significant prognostic factors on overall survival rate. **Conclusion:** Gastrin-independent GNETs had poor prognosis. Serum CEA level, radical surgery, and CD56 expression are markers to evaluate the survival of patients with locoregional gastrin-independent GNETs. **Keywords:** Gastrin-independent GNET, Prognosis, CEA, Surgery, CD56 expression.

E13

Prognosis of Stage IV Sporadic Pancreatic Neuroendocrine Tumors (pNET): Tumor Slope Is Prognostic Together with Tumor Burden and Grade

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Introduction: Currently, no prognostic stratification exists in stage IV pNET patients. **Aim(s):** To provide prognostic stratification of stage IV pNETs by analyzing 1) prognostic parameters at the time of stage IV diagnosis 2) Per RECIST tumor slope over 3-6 months prior therapy. **Materials and Methods:** Multicenter retrospective study. Inclusion criteria were: 1) Confirmed pNET naive of therapy 2) Measurable stage IV disease 3) sporadic tumor. Primary endpoint was OS. Two multivariate analyses were performed: model 1 'at the time of stage IV diagnosis'; model 2 'after the characterization of tumor slope'. **Results:** We included 208 patients (median follow-up 45 months). Parameters independently associated with OS were: model 1: T4 (P = 0.04, HR = 1.9, 95% CI = 1.04–3.7), metastatic tumor load (2 sites P = 0.004, HR = 2.6, 95% CI = 1.3–5.1; >2 sites P ≤ 0.0001, HR = 9.1, 95% CI = 3.3–24.8), >70% liver replacement (P ≤ 0.0001,

HR = 5.8, 95% CI = 2.5–13.0), Ki67 and/or mitotic index >10 (P = 0.01, HR = 2.8, 95% CI = 1.2–6.5); model 2: T4 (P = 0.04, HR = 1.9, 95% CI = 1.01–3.7), metastatic tumor load (2 sites P = 0.006, HR = 2.7, 95% CI = 1.3–5.5; >2 sites P ≤ 0.0001, HR = 8.6, 95% CI = 3.2–23.7), >70% liver replacement (P ≤ 0.0002, HR = 4.9, 95% CI = 2.1–11.5), Ki67 and/or mitotic index >10 (P = 0.03, HR = 2.5, 95% CI = 1.1–5.7), and spontaneous disease progression (P = 0.001, HR = 4.0, 95% CI = 1.7–9.2). **Conclusion:** Tumor burden and grade were found to best stratify the prognosis at diagnosis. At the time of first follow up, tumor slope improved the prognostic stratification. **Keywords:** Stage IV, Pancreatic neuroendocrine tumor, Prognosis, Survival.

E14

Peritoneal Carcinomatosis in Digestive Neuroendocrine Neoplasms: Complications and Response to Therapy

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Introduction: Peritoneal carcinomatosis (PC) is present in 10–30% of digestive neuroendocrine neoplasms (DNENs), affecting prognosis and quality of life with recurrent abdominal pain and bowel obstruction. **Aim(s):** To describe in a consecutive series of DNENs with PC the evolution of PC and correlation to therapy. **Materials and Methods:** Retrospective analysis of pts with sporadic DNENs diagnosed in 1993-2014 with at least 12-month follow-up after PC diagnosis. **Results:** 67 pts (82.1% small bowel, SbNENs) were analyzed, with a 2%-median ki67 (1%–20%). 50.7% had liver metastases at PC diagnosis, 23.9% extra-hepatic disease. PC was present at diagnosis in 53.7% of cases, median time to detection was 46 months (0–168); PC diagnosis occurred intra-operatively in 46.3% of pts. Symptoms related to bowel subocclusion occurred in 17 pts (25.4%) (7 needing surgery): 4 had received prior PRRT and 8 pts were on somatostatin analogs (SSAs); risk factors for bowel obstruction were PC nodules >6 mm in size (OR 9.00) and diffuse PC (OR 5.47), P < 0.05. **Conclusion:** Bowel obstruction symptoms occurred in 25% of our population, especially with diffuse large nodules-PC; the potential risk this clinical presentation in somatostatin-treated PC (SSAs+PRRT) pts needs to be further investigated. A larger population is needed to confirm these data. **Keywords:** Peritoneal carcinomatosis, Neuroendocrine, Bowel obstruction.

E15

Assessment of the Growth Rate of Paragangliomas Related to SDHx Gene Mutations Using Computed Tomography

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Introduction: SDHx mutations are associated with a lifelong risk of multifocal paragangliomas (PGL), so patients need regular follow-up examinations. **Aim(s):** The aim of the study was to estimate the growth rate of PGL and analyze of its depending on the location base on computed tomography (CT) images. **Materials and Methods:** 27 patients with SDHx mutations (21 SDHD,6 SDHB,19 index case) who had at least two CT examinations were included to the study. We analyzed 58 PGL (23 abdominal, 1 pheochromocytoma, 9 thoracic, 25 head and neck). A mean percentage volume (in ml) increase within a month and the volume doubling time were estimated. The patients treated by radio-, chemio-, radionuclear therapy were excluded from the analysis. The PGL were divided depending on their localization into: head, neck (HN), thoracic (TH), abdomen, pelvis (AP). **Results:** The time of follow-up ranged from 10.0 to 74.0 months (median 38.0). The mean volume growth rate of the total 58 paragangliomas was 1.3%/month (95% CI 0.71; 1.88), the volume doubling time was 4.5 years (95% CI 3.1; 8.2). The mean volume growth rate of HNP, TH and AP were respectively 0.95% (95% CI 0.13; 1,77), 0.97% (95% CI –0.21; 2.15), 1.64% (95% CI 0.56; 2.72) per month, (p > 0.6). The volume doubling time was 73.3 for HNP, 71.8 for TH, 42.6 months for AP PGL. **Conclusion:** PGL related to SDHx mutations are slow growing tumors. The fastest growth has been observed in extraadrenal PGL located in the AP, but without statistical difference compering to other localizations. **Keywords:** SDHx mutation, Paraganglioma.

E16

Neuroendocrine Pancreatic Tumors Secreting Calcitonin

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Introduction: Neuroendocrine Pancreatic Tumors (NPT) secreting calcitonin are rare. **Aim(s):** We reviewed our experience in NPT from January 1999 to December 2012 to identify clinical presentation and prognosis of NPT secreting calcitonin. **Materials and Methods:** Among all the patients presenting with a NPT, we enrolled who had an increased serum calcitonin level (n.v.0–10 ng/L). Follow up to December 2014. **Results:** Among 182 cases of NPT observed, ten had hyper-calcitoninemia (5.5%). 6 M/4 F, averaging 58.8 years

(range 38–72). One tumor was functioning (hypoglicaemia). Most frequent symptoms were epigastric pain (7/10), weight loss (6/10). Nobody showed diarrhea. The primary tumor was single, mean size 6.6 cm, (range 3–15) and in 7/10 cases in the body-tail of the pancreas. Six patients presented with liver metastases. Mean value of serum calcitonin was 1358 ng/L (median 141 ng/L, range 37–9540). Calcitonin immunostaining was proven in 7/10 tumors. Three were G2 and four G3 tumors. Seven patients had the primary tumor resected: 4 distal pancreatectomy (3 extended to other organs), 2 pancreaticoduodenectomy, and one tumor excision. Three cases died within six months for progression, and 3 others died 54–118 months after diagnosis. Four patients are alive from 82 to 156 months (one with disease). Calcitonin returned to normal range even after R2 resections or cytotoxic or ablative procedures. **Conclusion:** Calcitonin secreting NPT are very rare. Treatment may result in long-term survival despite advanced disease at diagnosis. **Keywords:** Calcitonin.

E17

Evaluation of the Concordance between the Stage of the Disease and Ki-67 Proliferation Index in Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

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Aim(s): To demonstrate the degree of concordance between TNM staging used in the determination of the prognosis of GEP-NET patients and Ki-67 proliferation index value used in the grading of these tumors and investigate the most reliable prognostic parameter among them. **Materials and Methods:** The patients with GEP-NET who were diagnosed or followed up in Erciyes University were retrospectively examined and demographic and histopathological characteristics and survival times were recorded. **Results:** 141 patients were enrolled. Mean age 53 and male/female ratio 0.95. Primary sites were stomach (33%), pancreas (27%), colorectal (16%), small intestine (13%) and appendix (11%). The GEP-NET of the patients was in Grade (G) 1 (n:103), G2 (n:24) and G3 (n:14), Stage (S) 1 (n:66), S2 (n:14), S3 (n:12) and S4 (n:49). Ki-67 increased in parallel with the stage of the disease ($p < 0.001$). As Ki-67 increased at a rate of 1%, survival rates decreased 1.027 times ($p = 0.01$). Patients in the G2 and G3 had a 6.6 and 12.3 times lesser chance of survival when compared with G1 patients, respectively. Survival rates of S4 patients were 5.6 times lower relative to S1-S2 patients. At univariate analysis, age, grade, and stage were found to be parametres effective on overall survival. At multivariate analysis, survival rates decreased inversely with increased age and grade. **Conclusion:** This phenomenon shows us that in the prediction of prognosis in patients with GEP-NET, Ki-67 value can be more important evaluation factor relative to staging. **Keywords:** Grade, Stage, NET.

E18

Predictive Factors for Survival in Patients with Advanced Small Bowel Neuroendocrine Tumours

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Introduction: Tumour grade and hepatic metastases are negative prognostic factors for advanced small bowel neuroendocrine tumours (SBNETs), but data assessing other prognosticators at diagnosis (Dx) are lacking. **Aim(s):** To assess impact on survival of combined clinical and biochemical factors at time of Dx. **Materials and Methods:** 572 patients with advanced SBNETs including symptoms at Dx, carcinoid heart disease (CHD), biomarkers and initial treatment were retrospectively analysed, using Cox proportional hazards models. **Results:** Median survival was 128 months. Symptom presence at Dx [carcinoid syndrome, gastrointestinal (GI)] vs. incidental Dx was a negative prognosticator (hazard ratio (HR)=1.8, standard error (SE): 0.54; $p = 0.05$). On adjustment for grade, metastases and age, severe CHD at Dx was linked to shorter survival (HR = 5, SE = 2.26; $p < 0.001$), with 3 and 5-year survival of 38% and 25% respectively. Chromogranin-A and 5-hydroxyindoleacetic acid did not appear to affect survival. Contrarily, elective GI surgery (primary ± mesenteric metastases) prolonged survival (HR = 0.42, SE = 0.13; $p = 0.006$). For solitary primary resection HR was 0.35 with SE = 0.19; $p = 0.05$. Commencement of SSAs for tumour control improved outcomes, HR = 0.23, SE = 0.09; $p < 0.001$. **Conclusion:** Severe CHD is the most important negative prognostic factor. Symptom presence is associated with shorter survival. Elective GI surgery and commencement of SSAs for tumour control improve survival. Prospective studies are required to validate those predictive factors. **Keywords:** Small bowel NETs, Prognosis.

E19

Additional Value for Urinary 5-Hydroxyindoleacetic Acid as Prognostic Marker in Neuroendocrine Tumors?

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Introduction: 5-Hydroxyindoleacetic Acid (5-HIAA) is of value for diagnosis of NETs and correlates with severity of carcinoid syndrome. However its value for determining prognosis is uncertain, particularly in combination with other biomarkers. **Aim(s):** To determine prognostic value of 5-HIAA for overall survival (OS) in patients with a midgut NET or unknown primary and to compare prognostic value with patient characteristics, grade, stage, chromogranin A (Cga) and neuron-specific enolase (NSE). **Materials and Methods:** Data were collected from all patients with a midgut

NET or a NET from unknown primary with available 5-HIAA in 24 hour urine samples. Results were stratified for 5-HIAA and CgA: <2x upper limit of normal (ULN), 2-10x ULN or >10x ULN. For NSE this was reference range or >1xULN. OS was compared using a Kaplan Meijer with log rank test and hazard ratios were calculated using Cox-regression for univariate and multivariate analyses. **Results:** 449 patients were included, 53.7% male, mean age 59.9 years and 74.4% midgut tumors. OS was shortest in patients with >10xULN 5-HIAA vs. <2ULN (median 84 months vs. 152 months, p = 0.002). In univariate analysis, >10xULN 5-HIAA was a negative predictor (HR 1.94, CI: 1.34–2.82). However in multivariate analysis only grade 3 disease (HR 6.50, CI: 3.05–13.83), NSE (HR 2.19, CI: 1.29–3.74) and CgA >10xULN (HR 4.03, CI: 1.83–8.89) remained predictors. **Conclusion:** 5-HIAA >10xULN is a negative predictor for OS. However when added to other biomarkers and grading it is no longer a predictor for OS. **Keywords:** Prognosis 5-HIAA.

Epidemiology/Natural History/ Prognosis – Descriptive Epidemiology

F1

Pancreatic Neuroendocrine Tumors: Experience of a Tertiary Care Center

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Introduction: Pancreatic neuroendocrine tumors (PNET) are rare functionally and biologically heterogeneous tumors accounting for less than 5% of pancreatic cancer. **Aim(s):** To study the characteristics and outcomes of patients with PNET at AUBMC. **Materials and Methods:** We conducted a retrospective review of 27 patients diagnosed between 2005 and 2015. **Results:** Of these, 17 were male and 10 were female. Median age at diagnosis was 52 years. The most common presentations were abdominal pain (59%) and weight loss (48%) while 11% were asymptomatic. 4 patients had MEN1 syndrome. The tumor was multifocal in 59% of cases. 11 (40%), 14 (50%), and 3 (10%) patients had G1, G2, and G3 respectively. 26% of patients had lymph nodes involvement. 15 out of 27 had upfront metastates (stage IV), 14 to the liver and 1 to the bones. Of these 15 patients, 8 received chemotherapy and/or Somatostatin analogues (SSA), without surgical resection; 2/8 (25%) responded with tumor regression, 4/8 (50%) with stable disease, and 2/8 (25%) progressed. In 5 patients, the primary was surgically resected followed by chemotherapy and SSA; 2/5 had complete remission and 1/5 had a stable disease. The most frequently used regimen was Capecitabine and Temozolomide. One and two-year survival rates of stage IV were 93% and 74% respectively. The mean survival of stage IV was 61 months. Stage, grade and Ki-67 were independent predictors of poor outcomes. **Conclusion:** Prognosis improved in patients who underwent surgical resection including those with stage IV disease. **Keywords:** pNET stage IV surgery Ki-67.

F2

Epidemiology of NENs and miRNA-224/ LDL-C Level as an Independent Risk Factor in Jiangsu People's Hospital

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Introduction: Studies show an increasing incidence trend in the neuroendocrine neoplasms (NENs). However, diagnosis and treatment of NENs are still big challenges. It has not been realized that deficiency of serum low density lipoprotein cholesterol (LDL-C) is a risk factor of NENs. **Aim(s):** To investigate incidence trends of NENs in Jiangsu People's Hospital and uncover the role of LDL-C on NENs. **Materials and Methods:** The data of 164 patients with NENs were retrospectively analyzed. Human pancreatic NENs cell line BON-1 was used to explore the role of miR-224/LDL-C/glucocorticoid (GC) on NENs. **Results:** We concluded 164 NENs of which 58% were in men. The incidence of NENs was rapidly increasing. The most common primary site was pancreas (35%). Patients with Ki-67 index of 20–40, 40–70, >70 showed differences in survival rate ($P < 0.05$). LDL-C levels in NENs patients were significantly lower than healthy examinees ($P < 0.001$). Patients in digestive NENs (89 cases) with low level of LDL-C (<2.6 mmol/L) showed a lower survival rate ($P < 0.05$). miR-224 directly bound to the 3'UTR of proprotein convertase subtilisin/kexin 9 (PCSK9) which regulated LDL-C ($P < 0.05$). miR-224 antagmir promoted PCSK9 expression, induced cellular apoptosis ($P < 0.05$) and inhibited GC secretion ($P < 0.05$). There was no tumor formation in nude mice with subcutaneous injection of 5×10`6 cells. **Conclusion:** The incidence of NENs is increasing. In phase G3, it is necessary to include three parts according to Ki67 index, that is, 20–40, 40–70, >70 miR-224/LDL-C level is a risk factor of NENs. **Keywords:** NEN, miR-224, LDL-C, Survival.

F3

Epidemiology Survival and Prognosis of Neuroendocrine Tumors: A Multidisciplinary Single-Center Study

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Introduction: There is no certain consensus about prognostic factors of NETs. **Aim(s):** We evaluated epidemiology, survival and especially prognostic factors in NETs. **Materials and Methods:**

Patients were included who had a NET and were diagnosed between 2000 and 2014 at a tertiary care center. Demographic data, tumor characteristics, treatment modalities and survival rates were evaluated. Survival rates were calculated using Life-Table, Kaplan-Meier, and Cox-Regression methods. **Results:** 233 patients (123 male, 110 female; median age, 55 years) took part in the study. Primary NET sites were lung (n = 56), stomach (n = 50), pancreas (n = 39), colorectal (n = 21), small intestine (n = 19), and appendix (n = 19), and unknown in 19 patients. According to NET classification by the World Health Organization (WHO) in 2010, 60% of patients were grade (G) 1, 15% were G2, and 25% were G3. According to TNM staging, 88 patients were stage 1, 30 patients were stage 2, 22 patients were stage 3, and 93 patients were stage 4. Univariate analysis revealed significant associations between gender, age, grade, lymph node-distant metastasis, stage, and the number of metastatic organs. However, with multivariate analysis only age, grade, and curative surgery were found to be associated with survival. Five-year survival was 81% in G1 NET, 34% in G2 NET, and 9% in G3 NET. **Conclusion:** Age of more than 55 years, advancing grade, and inoperable tumors were significantly associated with shortened survival. **Keywords:** Grade, Ki-67 index, Prognostic factor, NETs.

F4

Nutritional Status and Nutritional Risk in Patients with Neuroendocrine Tumors

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Introduction: Malnutrition is common in patients with cancer and is associated with impaired function. No data are available on nutritional status (NS) and nutritional risk (NR) in patients with neuroendocrine tumors (NET). **Aim(s):** We aimed to assess: 1) NS, 2) NR and 3) whether nutrition impact symptoms (NIS) encompassing nausea, dry mouth, pain that affects appetite, swallowing difficulties and early satiety are related to NS or NR in NET patients. **Materials and Methods:** We performed a cross-sectional study in NET outpatients at Aarhus, ENETS NET Center of Excellence. Handgrip strength (HGS) was used as a marker of NS. Nutritional risk score (NRS) was determined by the NRS-2002. NIS was assessed by the eating symptoms questionnaire (ESQ), and the disease related appetite questionnaire (DRAQ). Data are presented as median (IQR) or %. **Results:** We included 186 patients (51% women). Age 66 (55–73) years. A low HGS was found in 25%. Thirty-eight percent were at NR. Both a low HGS and an NRS score >3 were associated with specific NIS: Nausea, stomach ache, dry mouth, pain that affects appetite, changes in taste, swallowing difficulties, early satiety and poor appetite (all $p < 0.05$). **Conclusion:** Totally 38% of our cohort of NET outpatients were at NR or had impaired NS and this was associated to specific NIS that preclude food intake. We therefore recommend that NET patients are screened with HGS and NRS-2002 and that specific NIS are investigated in patients at nutritional risk and with a low HGS. **Keywords:** NRS-2002, Nutrition impact symptoms.

F5

VIPomas, A Rare Entity

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Introduction: VIP secreting pancreatic neuroendocrine tumors (pNETs) are rare and controlled studies are lacking. **Aim(s):** To assess their prevalence and response to treatment. We performed a retrospective study using the case notes of a tertiary care center. **Materials and Methods:** Records from 172 patients with pNETs were reviewed for the presence of clinical, biochemical and histopathological evidence of a VIPoma. **Results:** Among 172 pNETs,33 (19.2%) were functioning and 4(2.3%) had histologically confirmed VIPomas; overall,12.1% patients with a functioning pNET had a VIPoma. All patients presented with diarrhea and in 3 the pancreas was the primary site whereas in another the primary site was not identified. The median tumor size was 4.9 cm (range 1.4–9) and 3/4 patients had hepatic metastases at diagnosis. The median VIP level was 270 pg/ml. Three patients had stage IV and 1 stage I disease and the median Ki67 index was 8% (range 1–18%). SSAs alone were insufficient to control the diarrhea in patients with stage IV disease and treatment with chemoembolization, PRRT and chemotherapy was administered. Overall, 2/3 patients received temozolomide based chemotherapy and the patient with unknown primary 5 cycles of 177Lu radionuclide treatment. Following a median period of follow-up of 30 months (range 2–70) all patients are alive exhibiting clinical, biochemical and radiological response. **Conclusion:** VIPomas represent 2.3% of our referral material, may not always originate from the pancreas and exhibit an overall good response to treatment. **Keywords:** VIPoma, pNET.

F6

Gastroenteropancreatic Neuroendocrine Tumors. Ten Year Experience at Instituto Oncologico Nacional. Panama 2004–2015

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Introduction: Gastroenteropancreatic neuroendocrine tumours (GEP-NET) are rare neoplasm with a rising incidence worldwide. **Aim(s):** The aim of this study was to analyze demographic, tumor, therapy, and clinical outcomes of patients presenting with GEP-NET in our institution. **Materials and Methods:** The cases of 152 patients with histological proven GEP-NET evaluated between 2004 and 2015 were reviewed retrospectively. **Results:** Median age at diagnosis was 59.0 years. 63 male and 89 female. Primary tumors localization was gastrointestinal tract in 60 patients (54.7%), 18 patients (11.8%) in pancreas and 48 patients (31.6%) unknown primary (liver metastasis). 13 patients (8.6%) had carcinoid syndrome. Stage at diagnosis was:

metastatic disease 52.2%, locoregional disease 7.4%, and localized in 40.4%. WHO classification was 53.1% grade 1, 17.0% grade 2 and 29.9% grade 3. Median survival not reached for primary resectable tumors and in irresectable/metastatic tumors was 26.21 ± 6.6 months (95% CI 13.2–39.2 months) (log rank test $p < 0.0001$). Median overall survival in grade 1 tumor according WHO classification: not reached, grade 2: 15.8 ± 5.4 months (95% CI 5.1–26.4) and grade 3: 5.9 ± 1.5 months (95% CI 2.8–8.9) (log rank test $p < 0.0001$). Among patients with irresectable/metastatic (grade 1–2) Octreotide) was associated with better overall survival ($p < 0.001$). **Conclusion:** Tumor grade and stage at diagnosis correlated with overall survival in patients with gastroenteropancreatic neuroendocrine tumors. **Keywords:** Grade, Prognosis, Neuroendocrine tumor.

F7

Reduced 25-OH-Vitamin D Levels in Patients with Chronic Autoimmune Atrophic Gastritis

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Introduction: Chronic atrophic autoimmune gastritis (CAAG) is characterized by parietal cells disruption leading to hypochlorhydria and vitamin B12 malabsorption. An increased risk of osteoporosis was reported in patients with long-standing hypochlorhydria. Only few studies reported a possible association between CAAG and 25OHVitamin D (25OHvitD) deficiency. **Aim(s):** To evaluate the prevalence of 25OHvitD deficiency in CAAG. **Materials and Methods:** From 2012 to 2015, 25OHVitD and calcium were measured in all the CAAG patients followed at our Centre. Results were compared with a group of 1234 subjects (958 F; median age 62 yrs). Subjects with abnormal calcium values, known VitD supplementation, primary hyperparathyroidism or renal failure were excluded. **Results:** 86 CAAG patients (64F; median age 65 yrs) showed median 25OHvitD level significantly lower than control group (17.9 vs. 23.9 ng/ml, $p < 0.0001$). 25OHVitD deficiency was observed in 57 CAAG patients (66%) considering 20 ng/ml as a cut-off and in 22 (26%) considering 12.5. In detail, 25OHvitD was significantly lower in CAAG patients in decades 36–45 (17.7 vs. 22 ng/ml, $p = 0.02$), 46–55 (17 vs. 22.5 ng/ml, $p = 0.03$), 56–65 (18.7 vs. 24.2 ng/ml, $p = 0.0043$), 66–75 (17.7 vs. 24.3 ng/ml, $p < 0.0004$) and 76–85 (13.9 vs. 24.3 ng/ml, $p = 0.003$). No differences were observed for decades below 35 and above 86 yrs. **Conclusion:** 25OHVitD deficiency was highly prevalent in CAAG. These observations suggest a possible impairment in vitamin D absorption, which could lead to an increased risk of bone loss. **Keywords:** Vitamin D, CAAG.

F8

Clinicopathological Features and Prognosis of Neuroendocrine Tumors: Analysis from a Single-Institution in Brazil

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Introduction: In Brazil, information on neuroendocrine tumors (NET) is scarce. We summarized data in our center to increase knowledge of this disease in Brazilian population. **Aim(s):** To describe clinicopathological features and prognosis for NET in Brazilian patients. **Materials and Methods:** We investigated retrospectively patients with histological diagnosis of NET treated in a single Brazilian institution between 2007 and 2015. **Results:** Of the 160 cases analyzed, the mean age was 51 years, and 53.8% were male. The gastroenteropancreatic tract was the most common site of involvement (77.5%), with the small intestine being the most prevalent among them (27.5%). Fifty percent of patients presented with distant metastasis, and liver was the most common site (65%). Surgery of the primary tumor was performed in 52.5% of metastatic tumors. Sixty-nine percent of patients had information avaiable about both Ki67 and Mitotic Rate: 52.3% were G1, 35.5% G2 and 8.1% G3. Univariate analysis showed that tumor grade ($p < 0.001$), tumor necrosis ($p = 0.006$), distant metastasis ($p < 0.001$), non resection of primary tumor in metastatic patients ($p = 0.007$) and 18-FDG-PET-CT positivity ($p = 0.02$) were predictors of poor prognosis. The overall 5-year survival rate of G1, G2 and G3 was 87.6%, 76.6% and 30.6%, respectively ($p < 0.001$). Median follow up was 44 months. **Conclusion:** These findings can be useful for better understanding the behavior of NET in Brazilian population and offer subsidies for planning future studies. **Keywords:** Neuroendocrine, Epidemiology, Prognosis.

F9

A Descriptive Cross-Sectional Study of Pain in Patients with Neuroendocrine Tumors

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Introduction: Pain is a feared symptom in cancer patients and is reported in 30% of patients during treatment and in 70–90% with advanced disease. **Aim(s):** Our aim was to determine the extent and the severity of pain in outpatients with NET as this has previously never been investigated. **Materials and Methods:** We conducted a cross-sectional survey of 207 NET patients between March 2014 and March 2015 at our tertiary NET Center. We used a validated questionnaire to investigate the prevalence, severity and character of pain along with demographic, clinical and pathological data from medical records. **Results:** One hundred and thirty-seven patients had undergone surgery (66%), 88 patients (64%) were cured. The group with residual disease after surgery or comorbidity at diagnosis con-

tradicting surgery comprised 119 patients. Eighty-five patients (41%) reported any pain within the past week with a median pain intensity of 5.0 (0.0–10.0, NRS 0–10). Forty-seven (23%) of all included patients reported pain within the past week that developed in relation to NET or its treatment and half of them had pain descriptors consistent with neuropathic pain. **Conclusion:** More than 40% of our NET patients suffer from moderate pain every week. Approximately 25% have pain in relation to NET and its treatment, 50% of these have neuropathic pain. This illustrates a need for pain screening during follow up. The WHO pain ladder or treatment with TCA or antiepileptic drugs should be considered according to the patients pain descriptors. **Keywords:** Pain, Screening, Neuropathic pain.

F10

Understanding a Neuroendocrine Tumors' Impact on Health Systems: A Population-Based Economic Analysis of Patterns of Costs

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Introduction: Little is known on resource utilization and health care costs in NET care. **Aim(s):** To define patterns of costs in NET management and compare them to a more common malignancy, colon cancer (CC). **Materials and Methods:** We identified all NET in a cancer registry (2004–2012). They were matched to CC patients (1:3). 2012 CND$ costs were obtained for 4 phases of care around diagnosis: pre-diagnostic (PrDx: –2 years to –181 days), diagnostic (Dx: –180 days to +180 days), post-diagnostic (PDx: +181 days to +3 years) and prolonged post-diagnostic (PPDx: +181 days to +9 years). Mean costs per patient were compared. Costs predictors were analyzed with quantile regression. **Results:** 3355 NET were matched to 9320 CC. Mean NET cost was higher than CC in PrDx phase ($5877 vs. $5368; $p = 0.06$), driven by higher non-drug costs including physician encounters, emergency room visits. Mean NET costs were lower in Dx and PDx phases ($p < 0.01$). In PPDx, drug costs were significantly higher in NET ($26788 vs. $7827; $p < 0.01$), accounting for 41% of costs (Vs 16% for CC). Older age, lower income, and comorbidities were predictors of higher NET costs in all phases. Gastroenteric NET was associated with higher costs in PrDx (parameter estimate – PE $62), and lower costs in Dx (PE $13644). Pancreatic NET was associated with higher costs in PDx (PE $3348) and PPDx (PE $1548). **Conclusion:** NET cost pattern is unique, with maximal costs during PrDx and PPDx phases. Primary NET site affected costs differently at different time points. **Keywords:** Costs, Care patterns.

F11

Clinical Characteristic and Treatment Options of Patients with G3 Gastroenteropancreatic Neuroendocrine Neoplasms in China

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Introduction: Well differentiated neuroendocrine tumor G3 (NET G3) patients are a special part of neuroendocrine neoplasms with a different biological behavior comparing with other G3 patients. **Aim(s):** This study was to investigate the clinical pathological features, the impact of different treatment strategies on their clinical outcomes of NET G3 and neuroendocrine carcinoma (NEC) patients in Chinese populations. **Materials and Methods:** We retrospectively collected 28 NET G3 patients from oncology departments of three hospitals in China and 38 NEC patients for comparison. **Results:** The most common primary site of NET G3 was pancreas (71.4%) followed by stomach and rectum. Esophageal and colon origin consisted almost 1/3 of NEC but in none of NET G3 patients. Significantly more NET G3 had hormone related symptoms and localized disease comparing with NEC. Median Ki-67 of NET G3 was 30% and median mitotic count was 12/10HPF which was lower than those of NEC and of the WHO criteria. In NET G3, the overall response rate of temozolomide and capecitabine (TEMCAP) and platinum-based therapy in first line or second line settings was 13.3% and 18.2% ($p = 0.735$), DCR was 78.6% and 50.0% ($p = 0.143$), median PFS was 8.4 months and 2.6 months ($p = 0.054$) respectively. The PFS of platinum-based therapy in NEC was 3.6 months in first line settings. **Conclusion:** The clinical pathological features, histological characteristics and treatment response varied markedly between NET G3 and NEC. TEMCAP might to be a promising treatment regimen for NET G3. **Keywords:** NET G3, NEC, TEMCAP.

F12

Analysis of Oesophageal Neuroendocrine Tumour Outcomes

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Introduction: Oesophageal Neuroendocrine Tumours (NETs) are rare neoplasms accounting for <2% of Gastroenteropancreatic NET (GEP NETs). **Aim(s):** To present our patients' group clinicopathological features, treatment and prognosis. **Materials and Methods:** Retrospective analysis from a GEP NET database of 1700

patients treated from October 2007 to November 2015. **Results:** 10/1700 (0.58%) with a GEP NET referred to our hospital were diagnosed with an Oesophageal NET.5/10 were male;8/10 presented with dysphagia (no information was available for 2) as the main presenting symptom. All were high grade Neuroendocrine Carcinoma (NEC) with Ki67 proliferation index >60%. At diagnosis, 2/8 had distant organ metastases and 3/8 had distant nodes involved (no complete data for 2). Regarding management, data was not available for 2 patients;a recently diagnosed third patient commenced chemotherapy. Among the rest,4/7 were managed with elective surgery and adjuvant chemotherapy;3/7 were treated with chemotherapy alone, consisting of a platinum-based regimen. In the group that had a combination of surgery and chemotherapy, survival was 22, 38*, 48* and 54 months; (*two of the above are still alive). All three treated with chemotherapy alone progressed within 8 months of treatment with the longest survival being 26 months. **Conclusion:** Oesophageal NETs are rare and commonly high grade NECs, where a combination of tumour resection and adjuvant chemotherapy may be beneficial. Further prospective studies should be performed to understand their biology and optimal management. **Keywords:** Oesophageal NEC.

F13

Peritoneal Metastases from Gastroenteropancreatic Neuroendocrine Tumors: Frequency, Treatment and Prognosis

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Introduction: Data on peritoneal metastases (PM) in patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are scarce. **Aim(s):** The aim of this study was to present population-based data on the frequency of occurrence, risk factors and survival of patients with PM from GEP-NETs. **Materials and Methods:** Data from all patients diagnosed with a GEP-NET during 2007–2013 were collected from the Netherlands Cancer Registry. **Results:** Synchronous PM were diagnosed in 234 patients (19% of patients with metastasized disease). Risk factors for PM were age (>60 yrs) (OR 1.4 95% CI 1.0–2.0), and primary tumor located in the small intestine (OR 3.5 95% CI 2.1–5.7) or colon (OR 2.5 95% CI 1.4–4.4). Small intestinal NETs with PM had the best survival; appendiceal NETs with PM the poorest (5-year survival rates 67% vs. 7%). Prognosis was associated with resection of the primary tumor (5-year survival rates 54% with vs. 34% without resection). Multivariate analysis showed that survival of patients with metastatic disease was independent of the presence of PM. **Conclusion:** Patients with metastasized GEP-NETs were frequently diagnosed with PM. Survival of patients with PM depended on the location and resection of the primary tumor. In further research, primary tumor location should be taken into consideration to determine if patients with PM of GEP-NETs qualify for potentially effective multimodal treatment strategies. **Keywords:** Peritoneal metastases, Peritoneal carcinomatosis, Gastroenteropancreatic neuroendocrine tumors, GEP-NETs, Prognosis.

F14

Gastrointestinal Neuroendocrine Tumors of Unknown Primary Site: Report from a Series at a Single Institute

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Introduction: Neuroendocrine neoplasms of unknown primary (NENs-UP) account for 10–13% of all NENs and show different biologic behavior, histologic appearance and clinical outcome. **Aim(s):** To describe clinical, histologic characteristics and the diagnostic work-up of NENs-UP. **Materials and Methods:** Between 2005 and 2015, among 93 metastatic NENs, 17 (11M; median age 64 yrs) presented with histologically proven NENs-UP. **Results:** Of the 17 NENs-UP patients, 14 (82%) showed hepatic and 3 nodal metastases. 16/17 had a well-differentiated tumor (5 G1 and 11 G2), whereas one patient had a poorly-differentiated carcinoma. Hormone-related symptoms were present in 11 cases (65%). In 14/17 cases (82%), liver or nodal metastases were incidentally diagnosed by abdominal ultrasound. After an in-depth work-up, the primary tumor was diagnosed after a median of 8.5 months in 12 cases (71%), 8 of whom (67%) had a functioning form. The primary site was: pancreas (#4), terminal ileum (#2) and colon (#1); central ileum (#1). Laparoscopy identified a jejunal, ileal, Meckel's diverticulum and pancreatic primary tumor in further 4 patients, whereas the remaining 5 were still classified as NENs-UP. **Conclusion:** NENs-UP represent a clinical challenge. Despite the continuous advances in diagnostic nuclear medicine imaging, endoscopic techniques, and immunohistochemical methods, NENs remain of unknown primary in a notable proportion of cases (5.3%). The presence of hormone-related symptoms may help to better localize the primary site. **Keywords:** Neuroendocrine tumors, Unknown primary.

F15

High Grade Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET). Instituto Oncologico Nacional. Panama City, Panama. 2004–2015

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Introduction: Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are relatively rare and complex neoplasms that present many clinical challenges. High grade at diagnosis is an adverse prog-

nostic factor. **Aim(s):** We conducted a study, to analyze the characteristics of patients being treated with a high grade GEP-NET at our institute. **Materials and Methods:** A retrospective review was performed, including 44 cases with histological proven high grade GEP-NETs, treated at our institution between 2004 and 2015. Demographic, clinical, therapeutic and prognostic variable were studied. **Results:** Median age at presentation was 59.5 ± 14.4 years. 56.8% of patients were females. The most frequent site of primary lesion was stomach 15.9%, rectum 15.9% and pancreas 13.6%. A 34.1% of cases were of unknown primary. 66.7% were metastatic at diagnosis, with a 70.8% of cases with unique site. Liver was the most frequent site of metastasis, affecting 83.3% of patients. Carcinoid syndrome was present in 6.7%. A 43.2% (19/44) received a first line of chemotherapy, being CDDP/VP-16 used in 73.7% of cases. 21.1% of partial response was achieved. Median survival time was 5.9 months (95% CI 2.9–8.9). Few patients were able to continue with a second or third line of treatment. **Conclusion:** High grade GEP-NETs have a poor prognosis. New agents are urgently needed to improve outcomes. **Keywords:** Neuroendocrine tumors, Neoplasm, Unknown primary, High grade.

F16

Duodenal Neuroendocrine Tumors – Data from a Single Centre

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Introduction: Duodenal neuroendocrine neoplasms (D-NENs) are heterogeneous tumors, whose prognosis is highly variable. Their optimal management remains to be clarified. **Aim(s):** Present series was aimed at reporting a single-centre experience. **Materials and Methods:** Retrospective analysis of patients with histologically confirmed D-NEN managed at our Institution. **Results:** From 2004 to 2014, 12 patients (9 M, median age 67 years) were diagnosed and treated. The D-NEN was single in all but one patient who was diagnosed with MEN1 syndrome. Two patients had a peri-ampullary D-NEN. The median diameter was 2 cm. A non-functioning D-NEN was incidentally diagnosed in 7 cases, a gastrinoma in 3, a somatostatinoma in 2 cases, respectively. D-NEN was G2 in 3 cases, G1 in 9. At enrollement, 4 patients (33%) had metastases, to lymph nodes (#2), liver (#1), both (#1). D-NEN was removed in 10 cases (83%), endoscopically (#3) or surgically (#7). An elder patient, with 8 mm non-metastatic gastrinoma unsuitable for surgery was only followed-up. One patient was lost at follow-up. Over a median follow-up of 33 months (range 2–133), 2 patients died of the disease. **Conclusion:** D-NENs may be metastatic at the diagnosis in up to 33% of the cases, thus nuclear imaging should be performed to exclude distant metastases. Endoscopy and surgery play a primary role in the management of the disease. Further studies are needed to define standardized dedicated guidelines for D-NENs, including the optimal management and the follow-up intervals. **Keywords:** Duodenal neuroendocrine neoplasms.

F17

Do Medical Oncology Services Receive More Patients with Neuroendocrine Tumors? Assessment of This Tendency and Reflections about Its Aid Complexity

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Introduction: Neuroendocrine tumors meant a change in the clinical practice, multidisciplinary approach (MA) is the gold standard today. **Aim(s):** We developed an analysis of patients referral with NET to Endocrinology (E) and Medical Oncology (MO) in order to evaluate treatments and follow-up. **Materials and Methods:** 120 patients, treated in La Fe Hospital: 3 temporal intervals: 1990–1999 (A), 2000–2004 (new WHO classification), (B) and 2005–2015 (new targets), (C). **Results:** 51% men, average age 55 years old. 63% pancreatic, 38% extrapancreatic (ileum most common). Metastatic at diagnosis: 43%. Medical departments received during A period, 18 patients (39% stage IV, 2patients/year), B, 22 (41% stage IV, 5 patients/year), and C, 80 (45% stage IV,10patients/year). During the A interval 3 patients received medical treatment (MT), only 1 was controlled by MO and E simultaneously; during B, MT was received by 4 patients and 3 of them were controlled by MO and E. During C period most of patient received MT, 19 patients were treated with new targets and 15 patients were evaluated by MO and E. MA: 11% A period, 13% B period and in the C period 34% of patients. **Conclusion:** Our data show an increase in MA, due to stages IV. Nowadays suitable therapeutic targets are available and need to be considered, this, has contributed to an increase in the number of patients referred to MO. MA represents an improvement in treatment quality, and therefore the trend should be the development of centers of excellence. **Keywords:** Neuroendocrine tumors, Epidemiology.

F18

Bone Metastases in NEN Patients – Frequency, Clinical, Therapeutic and Prognostic Relevance

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Introduction: Up to 73% of patients with neuroendocrine neoplasms (NEN) present with distant metastases at diagnosis. Advanced stage negatively correlates with prognosis. Bone metastases (BM) are usually reported in less than 10% of patients. Improved imaging results in more frequent detection but information in general is very limited. **Aim(s):** Presentation of a single-center experience on frequency, clinical and therapeutic relevance of BM. **Materials and Methods:** All patients treated in the ENETs center in Marburg, Germany, between 2000 and June 2015 listed in our NEN-database were evaluated for inclusion. Out of 709 patients 414 had distant metastases (58.4%) including 109 with BM (15.4%). 84 patients qualified for inclusion in our study. **Results:** Mean age was 61.9

years with a slight male predominance (53.6%). The small intestines (32.2%) and the pancreas (27.4%) were the most common location of the primary tumor. The mean Ki 67% value was 16.7%. BM were most frequently detected by MRI (40.5%). Bisphosphonates (57.1%) and peptide radio receptor therapy (27.4%) were mainly employed. 31% of the patients presented with pain at initial diagnosis. Fractures or neurological deficits occurred in 13.1% and 3.6% respectively. **Conclusion:** Incidence of BM in NEN is most probably underestimated, as they are often asymptomatic, and is going to increase in light of new imaging techniques. Severe complications such as fractures or neurological deficits are infrequent. Bisphosphonates are the most common treatment. **Keywords:** Bone metastases, Frequency, Relevance.

F19

Epidemiological Factors at Diagnosis in a Large Cohort of Patients with Small Bowel Neuroendocrine Tumours

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Introduction: The incidence of small bowel Neuroendocrine Tumours (SBNETs) has been increasing. Despite previous reports, epidemiological data regarding several clinical factors are limited. **Aim(s):** To present epidemiological data at the time of diagnosis (Dx) in a large cohort of patients with SBNETs. **Materials and Methods:** 572 patients with SBNETs were included. Follow-up was complete. Diagnosis was defined as the date of the first histopathological data. **Results:** Mean age at Dx was 59.4 years. 46% were females and 54% were males. In 16%, the tumour was diagnosed incidentally, 11% presented with carcinoid syndrome (CS) only, 51% had only gastro-intestinal (GI) symptoms, whilst 22% had both. 22% of patients with CS had carcinoid heart disease. In symptomatic patients, symptoms were present < 12 months prior to Dx in 45.5%, >36 months in 36.5%, and 12–36 months in 18%. 314 (52.3%) patients had surgery at Dx, emergency in 30.8% of them, due to small bowel obstruction. 18% had documented mesenteric desmoplasia. 15% had a history of other malignancies. Chromogranin-A was normal in 32.3% at Dx. 65% had Grade (G) 1 SBNET, 33.5% had G2, and 1.5% had G3. Median survival was 128 months. 5-year-survival in G1 was 83%; in G2 (Ki67<10%): 72%; in G2 (Ki67 10–20%): 67%; and in G3: 33%. **Conclusion:** GI are the most common symptoms at Dx in SBNETs. In more than half of patients, there is a substantial delay in Dx. Chomogranin-A can be normal in a third of patients. The vast majority of SBNETs are either G1/G2. **Keywords:** Small bowel NETs, Epidemiology, Diagnosis.

F20

Epidemiology and Treatment Strategy of Neuroendocrine Neoplasms in North China

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Introduction: Few studies had focus on the epidemiology of neuroendocrine neoplasms (NENs), a rare disease, in China. **Aim(s):** This study was to illustrate the epidemiology and treatment strategy of NENs in north China. **Materials and Methods:** Two hundred and fourteen NEN patients admitted to gastrointestinal oncology department in our center from January 2010 to December 2015. **Results:** The most common primary sites were pancreas (32.2%), rectum (13.6%) and stomach (11.2%), and 21 (9.8%) patients were primary unknown. They were classified as G1 (12.6%), G2 (47.7%), NEC (36.0%) and NET G3 (2.8%), respectively. Half of gastric NENs were G3. The most common metastatic sites were liver (62.1%), followed by lymph node (40.2%), peritoneum (22.4%), and bone (15.0%). One hundred and thirty five (63.1%) of patients had received either SRS or 68Ga-DOTANOC PET/CT with a positive rate of 80.6% in G1/G2 patients, of 54.2% in G3 or NET G3 patients. Among the 185 stage IV patients, 21 (41.2%), 12 (23.5%) and 4 (7.8%) out of 51 pNETs had received SSAs, sunitinib and everolimus respectively. Thirty one (53.4%), 3 (5.2%) and 12(20.7%) out of 58 extra-pNETs received SSAs, sunitinib and everolimus respectively. Twenty (39.2%) of pNETs and 24 (41.4%) of extra-pNETs had participated in a clinical trial (Sulfatinib). Forty seven (61.0%) of G3 had received EP regimen, and 20 (26.0%) had received CAPTEM regimen. **Conclusion:** In conclusion, the most common primary sites of NET were pancreas. Patients with different grade received different treatment settings. **Keywords:** Neuroendocrine neoplasms, Clinical pathological features, Treatment strategy.

F21

A Clinicopathological Study of Malignant Insulinoma in a Contemporary Series

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Introduction: Malignant insulinoma is traditionally considered extremely rare and its natural history variable. **Aim(s):** To summarize our institutional experience on malignant insulinoma in the last 15 years. **Materials and Methods:** Retrospective review of medical records and immunostaining of surgical specimen. **Results:** Between 2000 and 2015, 9 of 26 patients with sporadic insulinoma (35%; 4 F and 5 M, mean age 51) had malignant insulinoma. All 9 patients already had liver metastasis and large tumor burden at hypoglycemia presentation. Six patients had de novo diagnosis of malignant insulinoma, 2 had previously known metastatic clinically non-functioning pancreatic neuroendocrine tumor (PNET), and 1 had a known pancreatic mass. Proinsulin levels were markedly elevated, the median molar ratio of proinsulin to insulin 2.1, and median primary tumor

size 2.1 cm. Tumor grade was G1 in 4 patients, G2 in 4, and unknown in 1. Four patients died at 2–32 months after presentation. Tumor proinsulin expression was much stronger than insulin expression but overall, proinsulin- or insulin-expressing tumor cells were infrequent. **Conclusion:** Malignant insulinoma is not uncommon at our center in the new millennium, and produces proinsulin predominantly and sporadically, thus behaves like clinically non-functioning PNET at its early stage but causes hypoglycemia after tumor bulk grows large if the tumor originally produces proinsulin, or after the tumor metachronously produces proinsulin, at its late stage. **Keywords:** Malignant insulinoma, Proinsulin, Contemporary series.

F22

Clinical Epidemiology Study of Gastric Neuroendocrine Neoplasms in China

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Introduction: Tumor grade is a major indicator of prognosis for neuroendocrine neoplasms. **Aim(s):** To evaluate the clinical epidemiology features of gastric neuroendocrine neoplasms (GNEN) by grade. **Materials and Methods:** GNEN patients with the pathology results of mitotic count or Ki-67 index were selected in a nationalwide study, which retrospectively surveyed 2010 GEP-NEN patients in seven Chinese regions. According to ENETS grading system, epidemiological and clinical features were compared between G1/G2 group and G3 group. **Results:** The mean age of 475 GNEN patients was 59.2 ± 11.3 years, and the peak age for diagnose was 55–65 years. The sex ratio was 3.75/1. Patients in G1/G2 group took 32.8% in all, and the rest 67.2% were at G3. Male took a significant larger proportion in G3 than G1/G2 group ($P = 0.009$). More neoplasms in G3 group originated from gastric cardia than gastric body ($P < 0.001$). Ultrasound and CT were widely used with average detection rates of 51.5% and 92.8%. About 90% patient undergone surgery in all with more G3 patients took chemotherapy ($P = 0.042$). Target therapy, biotherapy and radio therapy were rarely used. The immunohistochemistry results were compared and the detection rates of synaptophysin, CD 56, etc were all around 70% with no significant differences. Only choromogranin A were higher expressed in G1/G2 group than in G3 group ($P < 0.001$). **Conclusion:** The disparities in demography and clinical characteristics indicate different pathogenesis in two groups. **Keywords:** Gastric neuroendocrine neoplasms, Grading, Clinical epidemiology.

F23

Vitamin D Deficiency as a Risk Factor in Pancreatic Neuroendocrine Neoplasms: Report from a Series at a Single Institute

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Introduction: Vitamin D deficiency (VitDdef) is hypothesized to represent a risk factor in several neoplasms. To date, vitamin D levels have not been previously evaluated in patients with pancreatic neuroendocrine neoplasms (pNENs). **Aim(s):** To determine whether VitDdef may represent a risk factor for pNENs and may be associated with overall survival (OS) and progression-free survival (PFS). **Materials and Methods:** From September 2009 to September 2014 pNEN was newly diagnosed in 47 patients (F = 30, median age 61 yrs). Grading was G1, G2 and G3 in 32, 14 and one patient, respectively. Again, TNM stage was I, II, III and IV in 16, 17, 2 and 12 cases, respectively. Serum 25-hydroxyvitamin D (25OHvitD) levels were measured at baseline in all the patients and its deficiency was defined when facing with values <20 ng/mL. The possible association of 25OHvitD levels with PFS and OS was evaluated by the Cox proportional hazards regression. Finally, the possible correlation between 25OHvitD and disease grading and staging was also considered. **Results:** Median 25OHvitD levels were 12.5 ng/ml (range 4–29.5); in detail, 38 patients (80%) had <20 ng/ml, with 20 cases having <10 ng/ml. No correlation was observed between 25OHvitD and disease grading, staging, OS or PFS. **Conclusion:** Among patients with pNENs VitDdef was highly prevalent. The role of VitDdef in both the disease pathogenesis and progression remains to be clarified. Further studies are needed to confirm this observation. **Keywords:** Pancreatic neuroendocrine tumor, 25OHvitamin D.

Pathology, Grading, Staging

G1

Study of the Biological Significance of the IGF-IEc (MGF) in Well and Poorly Differentiated Neuroendocrine Neoplasms

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Introduction: Insulin-like growth factor-I (IGF-I) has a key role in cell proliferation, differentiation, migration, and survival. Different IGF-I mRNA transcripts, such as IGF-IEc (mechano growth factor, MGF), are produced by alternative splicing. MGF has been implicated in muscle regeneration process as well as in the pathophysiology of various types of cancer. **Aim(s):** The role of MGF in the pathophysiology of neuroendocrine neoplasms (NENs). **Materials and Methods:** We have used an anti-MGF specific antibody to examine by immunohistochemistry the expression status (rate, %) of MGF in 39 specimens of patients with NENs [8 gastric, 11 pancreatic, 2 appendiceals, 7 small intestine, 1 colic and 1 retrosigmoidal, 1 gallblader and 3 lung NENs, 2 undifferentiated unknown primary (UPO), 3 UPO]. Proliferation index ki-67 MIBI (%) was also evaluated. **Results:** No MGF staining was found in 19 specimens while cytoplasmatic staining was found in 20 specimens: focal staining in 13 (65%), diffuse in 6 (30%) and dot-like in 1 (5%) specimen. Ki-67 was ≤2% in 15, 2–20% in 15, and >20% in 9 NENs. Ki-67 and MGF expression was positively correlated in all the samples studied reaching a trend difference ($r = 0.29$, $p = 0.07$); similarly, a correlation was seen in NENs with ≤2% ($r = 0.48$, $p = 0.07$) but not in the other subgroups studied. **Conclusion:** Our preliminary data suggest that MGF expression may be involved in the pathophysiology of well differentiated NENs. Further studies will shed light to the exact role of MGF in NENs. **Keywords:** Neuroendocrine neoplasms, MGF, IGF-IEC, Ki-67.

G2

Reassessment of Proliferative Activity at Disease Progression in Neuroendocrine Neoplasms

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Introduction: Ki67 is a key factor influencing prognosis and treatment in NENs. However, whether repeating histology at time of progression of disease (PD) is debated. **Aim(s):** To investigate Ki67 changes at time of PD in NENs. **Materials and Methods:** Sporadic NENs in which histology was repeated at time of PD. Values expressed as median (range). Wilcoxon test used to compare data. **Results:** 29 pts who repeated histology at time of PD were included: 41.4% (12 pts) had disease recurrence (DR) after radical surgery, 58.6% (17 pts) had increase in lesions number/size. Primary sites were: jejunum/ileum (48.3%,14 pts), pancreas (31%,9 pts, pNENs), other (20.7%,6 pts). At initial evaluation, 51.7% of pts (n = 15) had NET G1, 48.3% (n = 14) had NET G2. Median Ki67 was 2% (1%–20%). Interval between initial and repeated histology was 51 months (5–128). During this period pts received SS analogs (65.5%, 19 pts), PRRT (24.1%,7 pts), chemotherapy (17.2%,5 pts), everolimus (17.2%,5 pts). At time of PD 58.6% of pts (n = 17) showed increase in Ki67: 9 pNENs, 6 jejunum/ileum NENs, 2 others. A grading step-up occurred in 8 pts (5 pNENs, 3 non-pNENs): 5 pts G1>G2, 3 pts G2>G3. Overall, median Ki67 increased to 5% (range 1%–70%; $p = 0.006$ vs. Ki67 at initial assessment). Ki67 significantly changed in pNENs from 3% to 15% ($p = 0.004$) whereas it remained 2% in non-pNENs. **Conclusion:** Ki67 increase occurred in 58.6% of NENs at time of PD. A significant change was observed in pNENs. Ki67 reassessment at time of PD could help to plan proper patients' management. **Keywords:** Ki-67, Tumor progression.

G3

PD1 and PDL1 Expression in Midgut Neuroendocrine Tumors

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Introduction: PD1/PDL1 inhibitors have shown promising results in different carcinomas, and correlation between PDL1 expression and response to immunotherapy has been reported. No studies thus far have investigated the expression of PD1 or PDL1 in midgut NETs. **Aim(s):** To investigate the expression of PD1/PDL1 in midgut NETs, and its relation to the presence of peritumoral lymphoid cell aggregates containing germinal centers (lymph node-like structures; LLS). **Materials and Methods:** PD1 and PDL1 expression

was assessed by immunohistochemistry in 32 patients with midgut NET. All cases with moderate or strong staining by Allred score were considered positive. The presence or absence of LLS was evaluated on H/E stained sections, and characterized by immunohistochemistry. **Results:** PDL1 was expressed in 22/32 (69%; 95% CI, 51–82%) tumors. Infiltration of PD1-positive lymphocytes was observed only in PDL1-expressing NETs (17/22). A strong cytotoxic LLS response was observed in all PDL1-expressing NETs ($p < 0.0001$). CD21+ dendritic cells were present within the LLS follicular germinal centers, while CD3+PD1+ T cells were dispersed in the LLS parafollicular cortex zone. There was a negative correlation between the presence of LLS and metastatic status ($p = 0.04$). **Conclusion:** A majority of midgut NETs express PDL1. There appears to be an association between PDL1 expression and LLS formation around primary midgut tumors. PD1 and/or PDL1 antibodies should be studied in this population. **Keywords:** Midgut NETs, PD1, PD-L1, Lymph node-like structures.

G4

Expression of m-TOR Pathway Components in Gastric Neuroendocrine Neoplasms: A Pilot Study

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Introduction: The mammalian target of rapamycin (mTOR) signaling pathway plays a key role in the regulation of cell proliferation, protein synthesis and neuroendocrine tumor growth. **Aim(s):** This study aimed to assess the activation of the mTOR pathway in the different types of gastric neuroendocrine neoplasms (gNENs) and to correlate expression with clinicopathological variables and prognosis. **Materials and Methods:** Immunohistochemistry (IHC) was performed to assess the expression of phosphorylated mTOR (p-mTOR) and its downstream target, the eukaryotic initiation factor 4E-binding protein 1 (4EBP1) in 34 surgically resected gNENs. **Results:** Positive p-mTOR and 4EBP1 immunostaining was seen in 27 (79.4%), and 29 (85.3%) of 34 examined gNENs, respectively. Distribution of p-mTOR and 4EBP1 was heterogeneous among the various gNEN types. Strong cytoplasmic expression of p-mTOR and 4EBP1 was detected in type I, type III tumors and high-grade carcinomas of either large or small cell types. The IHC score of p-mTOR and 4EBP1 was higher but not significantly in G3 carcinomas than in G1/G2 tumors. Preliminary evaluation did not reveal correlation of marker expression levels in tumors with clinicopathological features or unfavorable prognosis. **Conclusion:** These data demonstrate a variable mTOR activation status in the different types of gNENs, suggesting that mTOR-targeted therapy may play a role in the treatment of gNEN patients. The prognostic role of these molecules should be further evaluated. **Keywords:** Neuroendocrine, Neoplasm, Gastric, Immunohistochemistry.

G5

Tissue Prognostic Markers in Pancreatic Neuroendocrine Tumours

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Introduction: Pancreatic neuroendocrine tumours (pNETs) are a rare, heterogeneous class of neoplasms, with a rising incidence. Prognosis is variable with 5-year survival as low as 16% in inoperable tumours. **Aim(s):** The role of the microenvironment in influencing prognosis is poorly described is the focus of this research. **Materials and Methods:** A thorough literature review has performed to identify important aspects of pNET microenvironments. A database of 131 patients with pNETs has been generated including all clinical, histopathological and survival data. Tissue Microarrays (TMAs) have been produced from paraffin-embedded primary and metastatic tumour tissue. These have been immunohistochemically stained for immune, stromal, signalling and vascular markers to identify prognostic markers. **Results:** High Ki67 ($p = 0.007$), lymph ($p = 0.044$) and liver ($p = 0.004$) metastasis were significantly associated with worse outcomes. Immunohistochemical staining is currently underway; staining will be scored with staining intensity correlated with survival and treatment modalities received (in progress). **Conclusion:** A large dataset of pNETs with matched TMAs has been generated using primary and metastatic tissue. Pre-existing clinicopathological factors known to influence prognosis have been confirmed. TMA staining, scoring and correlation with patient outcome will allow further exploration into novel prognostic markers yet to be examined in pNETs and may open avenues to potential targeted treatment strategies. **Keywords:** Pancreatic, Microenvironment, Prognosis.

G6

Three Cases of Ectopic Adrenocorticotropic Hormone Syndrome Due to Medullary Thyroid Carcinoma

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Introduction: Cushing's syndrome (CS) in medullar thyroid carcinoma (MTC) is rare. Among patients with MTC 0.7% developed ectopic ACTH-syndrome (EAS). EAS due to MTS occurs in 2,2–8% of cases. **Aim(s):** We report 3 cases of MTC with EAS. **Materials and Methods:** It was 2 men (16 and 21 years old) and 1 woman 40 years old. **Results:** All patients had a clinical presentation of hypercorticoidism. Blood analysis showed high serum ACTH and calcitonin. In one case EAS appeared 4 years after surgery (thyroidectomy about MTC), when there had been metastases in the liver. One men was diagnosed with MEN 2A. Metastases were present at diagnosis in all patients (local lymph node in all cases and liver metastasis in 1 case, bone metastases in other). Histopathology revealed nests of round or oval tumor cells with hyperchromatic nuclei and scant cytoplasm. Immunohistochemistry (IHC) with ACTH and calcitonin antibodies was positive in all cases. The IHC research for somatostatin receptors of subtype 2 and 5 was performed in 1 case and showed expression SSTR5. In this case index of Ki-67 was 22%. **Conclusion:** EAS due to MTC is a rare disease and it is difficult to diagnose and the prognosis is poor because of frequency of metastasis at diagnosis. **Keywords:** Nushing's syndrome, Medullary thyroid carcinoma.

G7

Gastric Neuroendocrine Tumors – From Clinicopathologic to Immunophenotype Features

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Introduction: Type 3 Gastric Neuroendocrine tumors (GNET3) natured in the absence of a specific gastric background of pathologic changes, while with poorer outcome due to a high rate of distant metastasis. **Aim(s):** To investigate a potential effective therapy for GNET3. **Materials and Methods:** We retrospectively observed 16 cases of GNET3 treated in our hospital, including 12 surgical cases and 4 endoscopic submucosal dissection (ESD) cases from 2005 to 2014. **Results:** In our data male/female ratio was 12 to 4, with median age 62y (42~85). They are all single, average size 2 cm (0.8~5 cm), and located in any part of the stomach. GNET3 was usually well-differentiated, with Ki67 index mean 16% (1% ~60%) and median mitoses 5/10HPF (0~20), and G1 (3/16,18.75%), G2 (7/16,43.75%), G3 (6/16,37.5%) according to 2010 WHO criteria. Two cases were found lymph nodes metastases at present. Four cases showed liver metastasis during follow-up (1~94 months, median 15 months). In 4 cases treated with ESD, no recurrence in the endoscopic follow-up over an average following time of 13 months. Different from pancreatic neuroendocrine tumors, GNET3 showed ATRX/DAXX negative (1/10,10%). Whie the mTOR pathway proteins, such us mTOR (6/10,60%), pmTOR (1/10,10%), PS6 (2/10,20%), p4EBP1 (4/10,40%), PTEN (4/10,40%) showed high expression, and both of P53 and RB are intact in GNET3. **Conclusion:** GNET3 was composed of some well-differentiated NET with elevated proliferation-The high expression of mTOR pathway related protein in advanced patients. **Keywords:** Gastric, Neuroendocrine tumor, mTOR.

G8

Evaluation of ENETS and AJCC Staging Systems for Pancreatic Neuroendocrine Neoplasms: A Multicenter Study in China

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Introduction: Accurate staging system is crucial for p-NENs management. The European Neuroendocrine Tumor Society (ENETS) and the International Union for Cancer Control/American Joint Cancer Committee/World Health Organization (UICC/AJCC/WHO) advocated their TNM staging system for pancreatic neuroendocrine neoplasms (p-NENs) respectively. **Aim(s):** To evaluate the prognostic validity of two TNM staging systems of ENETS and AJCC for p-NENs in Chinese. **Materials and Methods:** From January 2001 to April 2015, data of patients who were pathologically diagnosed as p-NENs were retrospectively reviewed from 8 institutions in China. Cox model was used to assess the prognostic value of included patients. **Results:** 520 patients with p-NENs met our criteria and were analyzed. By using ENETS staging system, Cox regression analysis demonstrated an equal distribution of patients in four risk groups that were statistically significantly different. (with stage I as the reference; HR of stage II = 5.15, P = 0.034; HR of stage III = 22.27, P < 0.001; and HR of stage IV = 43.58, P = 0.035). While the AJCC staging system distributed patients into three differently populated groups and failed to distinguish the tumor-related death rate from stage III and stage IV (with stage I as the reference; HR of stage II = 4.011, P = 0.001; HR of stage III = 13.391, P = 0.03; and HR of stage IV = 16.131, P = 0.699). **Conclusion:** In Chinese patients with p-NENs, ENETS staging system is superior to the AJCC TNM staging system in prognostic prediction. **Keywords:** p-NENs, AJCC, ENETS, TNM staging system.

G9

A Comparative Analysis of Ki67 Index of the High Grade Neuroendocrine Neoplasms Arising in the Gastrointestinal Tract and the Pancreas

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Introduction: A common classification has been used for NET in gastrointestinal tract (GI-NET) and pancreas (P-NET), but heterogeneity has been reported in high grade tumors; well-differentiated G3 (WDG3), poorly differentiated NEC (NEC), and mixed adeno-neuroendocrine carcinoma (MANEC). **Aim(s):** The morphological varieties of the high grade tumors among organs are further to be studied. **Materials and Methods:** We reviewed morphology and Ki67 index of 230 GEP-NET; 86 (39%) GI-NET and 134 (61%) P-NET cases. **Results:** WDG3/NEC and MANEC were 22 (25%) and 5 (6%) of the GI-NET cases and 12 (9%) and 1 (1%) of the P-NET cases, respectively. 24 (89%) of GI-WDG3/NEC/MANEC demonstrated Ki67 index higher than 55% and its great majority (26 cases, 96%) were NEC. However, only 5 (38%) of P-WDG3/NEC/MANEC had Ki67 index above 55% and NEC detected only in 6 (46%). Among the other P-WDG3/NEC/MANEC cases, 4 (31%) were WDG3 and 3 (23%) presented 'intermediate' morphological differentiation. The mean Ki67 index of pancreatic NEC was 87%, compared with 29% in WDG3 and 31% in 'intermediate' morphological differentiation. **Conclusion:** Results of this study indicated heterogeneous nature of WDG3/NEC/MANEC among organs. In the gastrointestinal tract little variation was detected – WDG3 was rarely observed. In contrast, in the pancreas, three distinctive types were detected; well-, intermediate, and NEC, of which the former two were more closely related to each other than to the latter. **Keywords:** High grade tumors, Morphological differentiation, Ki-67 index.

G10

PD-L1 Expression Is Associated with Grade of Neuroendocrine Tumors

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Introduction: Neuroendocrine neoplasms are divided into well-differentiated neuroendocrine tumors (WDNETs) and poorly differentiated neuroendocrine carcinomas (PDNECs). The correlation between Gastroenteropancreatic Neuroendocrine Neoplasms (GEPNENs) and immunocheck point molecule-PD-L1 is still unclear now. **Aim(s):** This study want to explore the relationship between PD-L1 expression and clinical-pathological parameters of GEPNENs. **Materials and Methods:** Totally 59 GEPNENS patients who

received surgery were involved in this study. The patients included 21 cases from stomach (4 WDNETs and 17 PDNECs), 2 cases from duodenum (2 PDNECs), 8 cases from colon (8 PDNECs), 4 cases from rectum (4 PDNECs), and 24 cases from pancreas (10 WDNETs and 14 PDNECs). PD-L1 expression was detected by Immunohistochemistry on Tissue Microarray (TMA) of these cases. **Results:** PD-L1 was mainly expressed in the membrane and cytoplasm of tumor cells. 13 out of 45 (29%) PDNECs were positive for PD-L1 staining, 14 WDNETs were all negative for PD-L1 staining. There was a significant correlation between PD-L1 expression and tumor grade ($p = 0.018$). No significant correlations were detected between PD-L1 expression and other clinical-pathological parameters (age, gender, tumor site, tumor invasion, nodal status, metastasis, TNM staging, vascular invasion). In logistic regression model, tumor grade was the only independent factor which affected PD-L1 expression ($p < 0.001$). **Conclusion:** PD-L1 expression is associated with the grade of GEPNENs. **Keywords:** PD-L1, Neuroendocrine tumor, Grade.

G11

Expression of Oncofetal Protein IMP3 in Lymph Node Metastases of Small Intestine Neuroendocrine Neoplasms: A New Predictor of Recurrence

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Introduction: Small intestine neuroendocrine neoplasm (SINENs) are heterogeneous neoplasms arising from endocrine cells of the intestinal mucosa. Ki67 is the main determinant of prognosis in NENs. However, the research for new prognostic makers represent a key-point. The oncofetal protein IMP3 plays a role in cell growth and its expression has a prognostic value in lung neoplasms. **Aim(s):** To text IMP3 expression in SINENs. **Materials and Methods:** From January 1998 to August 2015, 51 consecutive SINENs patients (34M, median age 68 yrs), suitable for surgery were studied. In all cases IMP3 expression was evaluated on primary tumors and, when available, on nodal and distant metastases. The medical records and pathological slides were used to determine clinical characteristics, pathological diagnoses, and outcome information. **Results:** The overall 5-year and 10-year survival rate was 53.9% and 42%. At Cox proportional hazards regression grading was the major factor influencing both OS and PFS at univariate ($p = 0.0002$ and 0.005, respectively) and multivariate analyses ($p = 0.0003$ and 0.005, respectively). Also IMP3 expression at the nodal metastases resulted a factor significantly associated with PFS at both univariate ($p = 0.006$) and multivariate analysis ($p = 0.023$, HR 2.39). IMP3 expression did not correlate with Ki67 (p = n.s.). **Conclusion:** IMP3 at nodal site resulted to be associated with a low PFS in SINENs, independently on Ki67 index. The combination of IMP3 and Ki67 could help to better stratify the risk of progression in SINENs. **Keywords:** IMP3, Intestinal nens.

G12

Morphological Differentiation and Ki67-Index Are Predictive of Prognosis Independently of the Type of Therapy in Gastroenteropancreatic Neuroendocrine Carcinomas (NECs)

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Introduction: Gastroenteropancreatic (GEP) neuroendocrine carcinomas (NECs) are considered an heterogeneous category. **Aim(s):** To clarify the prognostic role of different morphological characteristics and the impact of medical therapy on survival. **Materials and Methods:** 136 patients with GEP-NEC were retrospectively studied. **Results:** At multivariate analysis, three prognostic categories of NECs were identified according to morphological differentiation, well vs. poorly-differentiated, (MD) and Ki67% (20–55% vs. ≥55%). Median OS was: 43.6 months in well-differentiated neoplasms with Ki67 20–55% (Type A NECs), 24.5 months in poorly-differentiated neoplasms with Ki67 20–55% (Type B), and 5.3 months ($P < 0.0001$) in poorly-differentiated neoplasms with Ki67 ≥55% (Type C). Differences in PFS across morphological groups paralleled those of OS. No differences in PFS were detected among treatment groups (log-rank $P = 0.89$) (CDDP/CBDCA + VP16, n = 56: Median PFS = 7.4 months; Other CT with platinum, n = 31: Median PFS = 6.1 months; Other CT without platinum, n = 12: Median PFS = 7.6 months; Non CT, n = 8: Median PFS = 10.5 months). Intra-group differences in PFS and OS were reported according to prognostic category: NECs treated with CDDP/CBDCA + VP16 and type A, Median PFS was 19 months; Type B: 8 months; Type C: 4 months and OS was 45 months for Type A, 26 months for Type B and 9 months for Type C. **Conclusion:** In to the three prognostic GEP NECs categories identified, the differences in survival were independent from type of first-line therapy. **Keywords:** Ki-67, OS, PFS, NEC.

G13

Distribution of T-Cell Infiltrate in G1, G2 and G3 NENs

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Introduction: The identification of T-cell infiltrate and the expression of inhibitory molecules in the tumor microenvironment could lend support to the use of immunotherapy in the treatment of gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs). **Aim(s):** Study of T-Cell infiltrate in GEP NENs. **Materials and Methods:** Immunohistochemistry for CD3, CD4, CD8, HLA1, HLA DR and PDL1 was performed in primary and metastatic lesions from 52 patients with GEP-NENs classified according to ENETS/WHO 2010 as follow: 20 NET G1, 20 NET G2 and 12 NEC G3 and 39 Stage IV and 13 Stage IIIb). The expression (E) of each antibody was defined as follows: 1+, immunoreactivity in <25% of neoplastic cells; 2+, 26–50%; 3+, 51–75%; 4+, 76–100%. Intensity (I) was ranked as low (1+), normal (2+), or strong (3+), as compared with internal controls. E and I were combined into a single score (E×I). IHC was positive if score >1. **Results:** No significative difference in expression of CD3, CD4 and CD8 were detected. HLA1 was expressed in 39/52 (75%) Stage IV specimens and in only 13/52, (25%) p = 0.0001, Stage II e III specimens. HLA1 score was lower in specimens with Ki67 >20%. PDL1 positivity was revealed only in Stage IV specimens with Ki67 >20%. HLADR was absent in all specimens. **Conclusion:** Patients with Ki67 >20% and loss of HLA1 may have a poorer prognosis than those with Ki67>20%, retention of HLA1 expression and presence of T cell infiltrate. Expression of PDL1 in stage IV patients with Ki67>20% may prompt studies on checkpoint inhibitors. **Keywords:** Ki-67, T-Cells, NEN.

G14

Pancreatic NENs <2 cm Could Represent a New Entity Worth of Further Investigation

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Introduction: Surgical approach to the treatment of well-differentiated pancreatic neuroendocrine neoplasms (pNENs) is based on tumor size and Ki67. Surgical removal is not recommended for tumors <2 cm, due to their indolent nature. Ki67 ≤2% and size <2 cm are considered indicative of benign tumors. However, size and Ki67 may not correctly predict the prognosis of patients with pNENs <2 cm. **Aim(s):** The combined use of Ki67 and morphological parameters could allow different prognostic categories in pNENs <2 cm. **Materials and Methods:** 75 patients (33≤2 cm, 42>2 cm; 35 G1, 36 G2, 4 G3) were evaluated. All patients with <2 cm tumor had received surgical treatment. **Results:** No difference in PFS were observed between NENs ≤2 cm and those >2 cm, whereas Ki67<2% was predictive of longer PFS irrespective of tumor size (p = 0.001). Parenchymal infiltration (p = 0.040), perineural infiltration (p = 0.005), tumor necrosis (p = 0.034) were predictive of shorter PFS. We then defined two distinct morphological categories for NENs, namely 'good' (no parenchymal infiltration, perineural infiltration and tumor necrosis) and 'bad' (presence of any of these features). 40/42 (95.2%) of NENs >2 cm were classified as 'bad'; 16 NENs (48.4%) <2 cm were classified as 'good' and 17 (51.6%) as 'bad'. 'Bad' NENs were associated with shorter PFS than 'good' tumors (p = 0.024). **Conclusion:** Prognosis of pNENs <2 cm is better defined by combining Ki67 and morphological parameters. PFS differences emerged also among pNENs <2 cm, usually considered an unique clinical entity. **Keywords:** NEN, <2 cm, Prognosis.

G15

The Relation between GEP-NEN Prognosis Re-Stratification and Ki-67 Variability: From a Single Institution Study

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Introduction: Ki-67 has been identified as a prognostic factor for GEP NEN. The variability of Ki-67 during the disease course has been reported, but there's few about its effects on prognosis. **Aim(s):** We sought to study the association between Ki-67 variations and prognosis via survival re-stratification with one institution cohort. **Materials and Methods:** A total of 225 patients were enrolled in our cohort, We revised the survival classification on Ki-67 index (decision tree), and evaluated the patients with primary and metastasis specimens, compared the survival of Ki-67 variable group and those not (Kaplan –Meier method). **Results:** The reclassification of the survival with Ki-67 index (intervals 0–27.5;27.5–55;55–75;75–100) in our cohort suggested a higher prognosis hazard ratios (2.508, 2.921) than WHO2010'S classification. Of the 20 patients were retrieved, two were identified with Ki-67 falling, and 9 were identified up-regulated. The rectum and WHO G3 suggested the most variable primary site and variable interval. The group with Ki variability showed a worse prognosis with those not (P = 0.0074). **Conclusion:** The revision of the prognostic stratification in our cohort suggested the WHO G3 further be separated into 3 groups with an elevated Ki67 index and worse prognosis. The group with Ki67 variability suggested a worse prognosis than those not. Re-assessment of Ki67 in metastasis site may prove be significance to the GEP NEN patients' prognosis, especially for those primary G3. **Keywords:** GEP-NEN, Prognosis, Ki-67 variability.

G16

Somatostatin Receptors Profile in Pulmonary NETs Associated with DIPNECH

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Introduction: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare entity characterised histologically by the proliferation of neuroendocrine cells along the distal bronchiolar epithelium, associated with small tumourlets and usually found in association with pulmonary carcinoid tumour. This can be clinically silent or may be associated with symptomatic obstructive bronchiolitis. **Aim(s):** To study the pattern of expression of the somatostatin receptors1–5 is in pulmonary NETs associated with DIPNECH by immunohistochemistry. **Materials and Methods:** We retrospectively reviewed histologically proven DIPNECH (recent definition by Marchevsky AM, 2015), and examined the pattern of expression of the five SSTRs by immunohistochemistry on archival paraffin-embedded tissue. **Results:** After lobectomy (right 50%) the nodule were typical carcinoid (TC) in 6, primary pulmonary adenocarcinoma in 1 and metastatic renal cell carcinoma in 1. Using the immunoreactive score (≥3 as positive), TCs expressed mainly SSTR1 (66%), SSTR2 (0%), SSTR3 (88%), SSTR4 (100%) and SSTR5 (0%). In DIPNECH, staining was positive for SSTR1 (100%), SSTR2 (20%), SSTR3 (88%), SSTR4 (88%) and SSTR5 (0%). **Conclusion:** This preliminary report shows an unexpected pattern of somatostatin receptor subtype staining using IRS score for NETs associated with DIPNECH with very low IRS for SSTR2. These different SSTR expression profiles may help explain some of the clinical variation observed in pulmonary NETs associated or not with DIPNECH. **Keywords:** SSTR, DIPNECH, Carcinoid.

G17

Evaluate the Accuracy of Pathological Diagnosis on Biopsy Specimens from Gastrointestinal Neuroendocrine Tumors

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Introduction: Gastrointestinal neuroendocrine neoplasms (GI-NENs) is a highly heterogeneous tumor. The accuracy of pathological diagnosis on the biopsy is crucial for GI-NENs but rarely investigated. **Aim(s):** To investigate the accuracy of pathological diagnosis on biopsy samples of GI-NENs. **Materials and Methods:** Totally 54 paired biopsy and surgical GI-NENs cases from our hospital were retrospectively analyzed, 21 cases of low differentiated adenocarcinoma of the same period were randomly selected as control. We have used Immunohistochemistry (IHC) of Synaptophysin (Syn), Chromogranin-A (CgA), CD56(NCAM), CK, Ki-67 and special staining (AB-PAS, Mucus card red) to confirm the neuroendocrine component and the grade of the tumor. The consistence of the diagnosis between the biopsy and surgical samples was further evaluated. **Results:** The diagnostic accuracy of Neuroendocrine Carcinoma (NEC), Mixed Adenoneuroendocrine Carcinoma (MANEC), and Adenocarcinoma (ADC) was 4.5% (2/22), 0 (0/32), and 100% (21/21) respectively. The diagnostic accuracy of GI-NENs was significantly lower than that of ADC ($P < 0.001$). Combined with the results of IHC and special staining, the accuracy of diagnostic rate of biopsy specimens of GI-NENs was significantly improved ($P < 0.005$). **Conclusion:** Due to the poorly differentiated morphology, IHC staining and special staining were useful to improve the accuracy of pathological diagnosis on biopsy samples of GI-NENs. **Keywords:** Gastrointestinal neuroendocrine neoplasm, Morphology, Immunohistochemistry.

G18

Two Cases of Parathyroid Cancer with Pulmonary Metastasis

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Introduction: Parathyroid cancer (PC) is a rare disease accounting for less then 1% of all patients with primary hyperparathyroidism. The prognosis of patients with parathyroid carcinoma is variable; more than 50% have a persistent or recurrent disease due to a regional or distant disease. **Aim(s):** We describe 2 cases of PC with metastases in the lungs. **Materials and Methods:** Two women there are 27 and 75 years old with primary hyperparathyroidism (pathological osteoporosis, hypercalcemia, markedly high parathyroid hormone levels). **Results:** Parathyroidectomy was performed. In the first case we detected PC with extensive fibrosis of the stroma and single vascular invasion.

Tissue samples from second PC consist of chief clear cells showing atypia and nuclear pleomorphism with high mitotic activity. This tumor demonstrated evidence of capsular, thyroid and vascular invasion. Pulmonary metastasis was diagnosed in 7 years (in the first case) and in 1 year (in the second) after the initial surgery. Surgical resection of the metastases was made only to the young patient. Tissue metastasis had solid-trabecular structure from basophilic cells (which predominate) and clear chief cells (simulation neuroendocrine tumor) with increased mitotic activity and high expression of PTH. In this case we also examined the index of Ki-67. It was 18%. **Conclusion:** PC is a difficult disease for diagnosis and treatment. We should expect a PC, when we have a high level of PTH and tumors in the lungs. **Keywords:** Parathyroid cancer, Primary hyperparathyroidism.

Biomarkers

H1

Expression of Mutated p53 Protein in Gastroenteropancreatic Neuroendocrine Carcinoma (WHO G3)

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Introduction: Gastroenteropancreatic neuroendocrine carcinomas (GEP-NECs) are aggressive, highly proliferating tumors. Therapeutic response to current chemotherapy regimens is usually short-lasting. **Aim(s):** The aim of this study was to examine the expression and potential clinical importance of mutated p53 in GEP-NEC. **Materials and Methods:** Tumor tissues from 125 GEP-NEC patients (median age 64 years) treated with platinum-based chemotherapy were collected from Nordic centers and clinical data from the Nordic NEC register. All specimens were immunostained for p53 using commercially available antibodies. Kaplan Meir and cox regression were used to assess overall survival (OS). **Results:** Tumor tissues were positive for either one or both of chromogranin A and synaptophysin. Ki67 was >20% in all patients. Immunostaining for p53 was positive in 39% of the cases and negative in 61%. Foregut primaries (n = 77) with a p53 mutation were significantly correlated to better OS in univariate analyses (mOS 27.5 m vs. 14 m, p = 0.026) as well as when adjusting for Ki67. Presence of a p53 mutation in hindgut primaries (n = 48) seem to be associated with a shorter OS (mOS 10 m vs. 12 m, ns). **Conclusion:** The results show heterogeneity in the expression and clinical relevance of mutated p53 in GEP-NEC. The results may suggest an advantage of p53 mutation for a subset of GEP-NEC patients. Further studies are needed to understand the underlying biology and mechanism for the prolonged OS in the presence of p53. **Keywords:** Neuroendocrine carcinoma, Mutation, p53, Overall survival.

H2

Validation of Lysyl Oxidase-Like 2 (LOXL2) as Prognostic Marker for Gastro-Entero-Pancreatic Neuroendocrine Tumours (GEP-NET) Using an Independent Cohort

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Introduction: LOXL2 is a key protein to epithelial to mesenchymal transition. We showed LOXL2 has a role as a prognostic marker in 115 GEP-NET cases (training cohort (TC)). **Aim(s):** Validation of LOXL2 expression by immunohistochemistry (IHC) in an independent cohort. **Materials and Methods:** Formalin-fixed paraffin-embedded samples (FFPE) of consecutive GEP-NET patients from 1999 to 2010 who underwent surgery in a different Spanish institution constituted the validation cohort (VC). Tissue microarrays were constructed from 2 non-necrotic areas of tumour foci. LOXL2 expression was studied by IHC and classified as presence (P) vs. absence (A). Log rank test and Cox regression were used to study Disease Free Survival (DFS) and Overall Survival (OS). Univariate and multivariable analysis (MVA) were performed. **Results:** A total of 91 FFPE samples were included in the VC. Median follow up was 77 months. LOXL2 P was associated with better OS ($p = 0.023$) and showed a trend for better DFS ($p = 0.066$) in the VC. DFS at 3 years was 85% in LOXL2-P group vs. 45% in LOXL2-A group. OS at 5 years was 82% vs. 51% respectively. LOXL2 P was associated with better DFS and OS ($p < 0.001$) when the combined series (TC+VC; $n = 206$) was analysed. LOXL2 remained as an independent prognostic factor of OS adjusted for grade and stage in MVA in the VC (HR: 0.2, 95% CI: 0.1–0.6) and in the TC+VC (HR: 0.2, 95% CI: 0.1–0.5). **Conclusion:** Our results confirmed LOXL2 as prognostic biomarker candidate for GEP-NETs in an independent cohort. Further testing in prospective studies is needed. **Keywords:** LOXL2.

H3

NT-proBNP Is Superior to ST2 and Galectin-3 Cardiac Markers in Identifying Carcinoid Heart Disease in Small Bowel NET Patients

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Introduction: Carcinoid heart disease (CHD) develops in small bowel neuroendocrine tumour (sbNET) patients with carcinoid syndrome (CS). NT-proBNP (NTP) is suggested as the best current biomarker to screen and monitor for HF from CHD. A number of other markers, such as Galectin-3 (GAL3) and ST2 (or IL-1 R4), have been explored to diagnose and prognosticate in HF but have not been explored in NET patients with CS and CHD. **Aim(s):** To explore the value of markers NTP, GAL3 and ST2 in identifying CHD in sbNET patients. **Materials and Methods:** 3 groups of sbNET patients ($n = 37$) were identified from the Liver Research BioBank; CHD (Group A, $n = 10$), non-functional (Groups B, $n = 12$, normal chromogranin A (CgA), 5HIAA, BNP), functional (Group C, $n = 15$, increased CgA & urine 5HIAA, normal BNP). Analysis was performed using NTP (<125 ng/L), GAL3 (2.4–15.7 ug/L) and ST2 (6.74–20.4 ug/L) assays. **Results:** Median values (IQR) for the CHD, non-functional and functional groups respectively were: ST2 17.2 (21.2), 12.7 (12.6), 12.6 (4.0); GAL3 5.1(2.9), 6.6 (3.4), 5.4 (1.9); NTP 537.5 (533.4), 65 (68.4), 117 (110.5). The Kruskal–Wallis test across the 3 groups was significant for NTP ($p \leq 0.001$) but not for ST2 ($p = 0.12$) and GAL3 ($p = 0.71$). The Mann-Whitney test for NTP was significant ($p \leq 0.05$) between the CHD and both the functional/non-functional groups groups. **Conclusion:** The results corroborate the role of NTP in CHD. GAL3 and ST2 require further evaluation in larger studies at various stages of CHD to ascertain their value. **Keywords:** Carcinoid heart disease, Biomarker.

H4

The Clinical Utility of Blood Neuroendocrine Gene Transcript Analysis, the NETest, in Paragangliomas and Pheochromocytomas

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Introduction: Diagnosis of disease and identification of progression are critical issues in paraganglioma (PGL) and pheochromocytoma (PCC) management. An accurate blood biomarker that defines tumor biology irrespective of biochemical activity is lacking. **Aim(s):** Evaluate a 51-gene blood analytic (NETest) to diagnose and assess PCC/PGL. **Materials and Methods:** PCC/PGLs comprising HNP ($n = 15$), adrenal ($n = 7$), extra-adrenal ($n = 11$), and metastatic ($n = 7$). Median age 33 yrs. PCC/PGL were well-differentiated, had SDH

mutations (76%) and were biochemically inactive (67%). Transcripts assessed by qPCR and multianalyte algorithmic analysis compared to age/sex matched GEP-NETs and controls (n = 24). NETest measures disease activity risk0–100% with low (<40%) and high activity risk cutoffs (>80%). CgA was by ELISA (normal <109 ng/ml). Mann-Whitney and X2 tests used. **Results:** PCC/PGL exhibited NETest scores (45 ± 7%) comparable to GEP-NETs (44 ± 7%) but higher than controls (14 ± 3%, $p < 0.01$). Metastatic/progressive disease had significantly higher scores (64 ± 11%) than localized clinically stable disease (32 ± 7%) ($p < 0.005$) or disease free patients (12 ± 6%, $p < 0.01$). NETest was +ve in 100% (24/24) irrespective of biochemical activity. CgA was +ve in 7/24 (29%) of PCC/PGL and no correlation with stage or biochemical activity was evident. The NETest accuracy for PCC/PGL compared to CgA was (100% vs. 29%, Chi2 = 18.1, $p < 0.0001$). **Conclusion:** NETest diagnoses PCC/PGL (100%) irrespective of biochemical activity and accurately identifies metastatic, progressive disease. **Keywords:** NETest, PCR.

H5

Midkine Is a New Novel Serum Biomarker in Small Intestinal Neuroendocrine Tumors (SI-NETs)

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Introduction: SI-NETs are often diagnosed late, which limits curative treatment options. **Aim(s):** Our aim was to identify new novel biomarkers in SI-NETs, in order to enable early diagnosis, prognostication and monitoring of treatment response. **Materials and Methods:** Ninety-two biomarkers were screened in blood serum from 67 patients with SI-NETs and 23 age-matched healthy controls using multiplex proximity ligation assay (PLA). Confirmation of findings by multiplex PLA was performed by immunohistochemistry (IHC) on tumors, followed by ELISA assays in blood serum. **Results:** Multiplex PLA exhibited 13 biomarkers with higher serum levels in SI-NET patients than in controls. Midkine (MK), Colony Stimulating Factor 1 (CSF-1), C-X-C motif chemokine 9 (CXCL9) and C-X-C motif chemokine 10 (CXCL10) had the highest positive univariate hits in patient serum and were also significant biomarkers by multivariate classification. IHC staining demonstrated that MK, CXCL9 and CXCL10 were strongly expressed in primary tumors and metastases whereas ELISA analysis only confirmed increased MK ($p = 0.007$) in serum. ROC analysis for the ability of MK to discriminate between patients and controls displayed an AUC = 0.694. MK is a multifunctional cytokine involved in angiogenesis, innate immunity and inflammation, over-expressed in other malignant tumors, and also an emerging target to drug development. **Conclusion:** MK is a new potential biomarker for early diagnosis of SI-NET with an obvious need for testing in a larger prospective series. **Keywords:** Biomarker, SI-NET.

H6

Blood-Based Prognostic Biomarkers in Neuroendocrine Tumour: A Retrospective Study

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Introduction: Markers of systemic inflammation –such as the neutrophil:lymphocyte ratio (NLR), platelet:lymphocyte ratio (PLR) and lymphocyte:monocyte ratio (LMR) – have been shown to correlate with poor prognosis in multiple solid organ tumours. Analysis of CLARINET showed no significant association between NLR and progression-free survival. **Aim(s):** To investigate the prognostic value of NLR, PLR and LMR in patients with metastatic NET. **Materials and Methods:** We identified patients with histologically diagnosed NET, who had a full blood count in the 7 days prior to biopsy or resection. The prognostic impact of NLR – NLR >5 vs. NLR <5 (NLR5) and NLR >3 vs. NLR <3 (NLR3), PLR (PLR>median vs. PLR<median) and LMR (LMR > median vs. LMR<median) on overall survival (OS) was assessed using the log-rank test. **Results:** 71 patients (median age 57 years, 51% female; 31 Grade 1, 23 Grade 2, 9 Grade 3, 8 unknown) were eligible for inclusion, with median follow-up 12 months. There was no significant correlation between OS and NLR5 ($p = 0.74$), NLR3 ($p = 0.97$), PLR ($p = 0.81$) or LMR ($p = 0.79$). NLR was not significantly associated with histological grade ($p = 0.63$). Restriction of analysis to patients with gastroenteropancreatic NETs did not alter the significance of the results. **Conclusion:** NLR, PLR and LMR do not predict for OS in NET, in contrast to their demonstrated utility in other tumours. Given that neuroendocrine carcinomas are aggressive and potentially associated with more inflammation, further investigations of the above markers could focus on this cohort. **Keywords:** NLR, Biomarker.

H7

Graph-Theoretic Definition of Neuroendocrine Disease – A Tumor Specific Mathematical Toolbox for Assessing Neoplastic Behaviour

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Introduction: Widespread availability of high throughput screens has led to the rapid adaptation of mathematics in biomedicine. **Aim(s):** Holistically evaluate the pathobiology of GEP-NENs and model disease processes using Eulerian concepts. **Materials and Methods:** Public microarray collections: NEN tissue (n = 15), NEN peripheral blood (n = 7), and adenocarcinomas (n = 363). Bayesian modelling: reverse-engineer intracellular signalling networks. Hub genes identified using degree (number of interactions) and betweenness (number of shortest paths). A random forest algorithm was used to assess hub gene expression in 130 blood samples (NENs: n = 63)

and to differentiate healthy controls and GEP-NENs. The model was validated in two independent sets (Set 1 [n = 115, NENs: n = 72]; Set 2 [n = 120, NENs: n = 58]). Comparison with CgA (ELISA) was undertaken in 176 samples (NENs: n = 81). **Results:** 51 genes were identified using a graph theoretic analysis of GEP-NEN transcriptomes. Gene-based classifiers detected NENs in independent sets with high sensitivity (85–98%), specificity (93–97%), PPV (95–96%) and NPV (87–98%). The AUC for NEN-classifiers was 0.95–0.98 vs. 0.64 for CgA. The gene-based classifier was significantly ($\chi^2 = 12.3$, $p < 0.0005$) more accurate than CgA. **Conclusion:** Graph Theory is an ideal hypothesis-generating platform for assessment of clinically diverse systems such as GEP-NEN disease. Additionally, multi-transcript based machine learning algorithms substantially outperform single analyte assays such as CgA. **Keywords:** NETest, Biomarker, Algorithm.

H8

Role of TSC22D1 (TGFβ-Stimulated Clone 22 Domain Family Member 1) in Bronchial Carcinoids

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Introduction: Neuroendocrine tumors (NETs) include bronchial carcinoids, either typical (TC) or atypical (AC). Tsc22d1 encodes for a member of TSC22 domain family of leucine zipper transcription factors; the protein (TSC22D1) is stimulated by TGFβ. Microarray data analysis obtained comparing a pool of TC tissue specimens with a pool of AC tissue specimens shows TSC22D1 down-regulation in AC samples. These data were confirmed by real time PCR and Western blot in vitro models of TC (NCI-H727 cells) and AC (NCI-H720 cells). **Aim(s):** To evaluate the influence of TSC22D1 on cell proliferation, cell viability and apoptosis in NCI-H727 cell line. **Materials and Methods:** TSC22D1 was silenced by shRNA in NCI-H727 cell line to obtain a stable clone (shTSC22D1-NCI-H727). NCI-H727 and shTSC22D1-NCI-H727 cells were treated with TGFβ. Cell viability, caspase activation and cell proliferation were evaluated in both cell lines. **Results:** TGFβ reduced cell viability by 67% with a concomitant increase in apoptosis in NCI-H727 cells, while it did not affect cell viability and apoptosis in shTSC22D1-NCI-H727 cells. On the contrary, shTSC22D1-NCI-H727 cells showed an increase in cell proliferation as compared to NCI-H727 cells. **Conclusion:** TSC22D1 silencing determined a higher proliferation rate in NCI-H727 cells. Furthermore, TSC22D1 may affect the antiproliferative and pro-apoptotic effects induced by TGFβ. Further studies are necessary to better understand the role of TSC22D1 in bronchial carcinoids. **Keywords:** TSC22D1, bronchial carcinoid, TGFβ.

H9

C-Reactive Protein as a New Prognostic Factor for Overall Survival in Patients with Pancreatic Neuroendocrine Neoplasia

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Introduction: For many cancer entities, inflammation has been shown to play an important role in pathogenesis and progression. **Aim(s):** To investigate the association between preoperative plasma levels of C-reactive protein (CRP) and overall survival (OS) in patients with pancreatic neuroendocrine neoplasia (pNEN). **Materials and Methods:** A prospective database of patients with pNENs was retrospectively analysed with focus on initial preoperative CRP blood levels (<5 mg/l vs. ≥5 mg/l). Among 149 patients with sporadic pNEN, Kaplan-Meier method and Cox regression were used to evaluate the relationship between CRP and clinical outcome, defining overall survival as primary endpoint. Possible association between CRP-levels and the other prognostic factors was investigated via crosstabulation and Pearson-χ^2-test. **Results:** Elevated CRP levels were associated with poorer OS (hazard ratio 3.27; 95% CI 1.74–6.16; $P < 0.001$). This finding persisted after multivariable adjustment. Furthermore, OS was associated with presence of liver metastases (hazard ratio 3.17; 95% CI 1.88–5.35; $P < 0.001$), R-Status (hazard ratio 3.99; 95% CI 2.16–7.35; $P < 0.001$) and Ki-67 percentage (hazard ratio 5.05; 95% CI 2.17–11.76; $P < 0.001$) in log rank test and univariate regression analysis. **Conclusion:** CRP is an independent prognostic marker in patients with pancreatic neuroendocrine neoplasia. Pretreatment CRP measurement should be considered for incorporation into prospective studies of outcome in patients with pNENs and clini. **Keywords:** CRP, Prognosis, pNEN, Survival.

H10

Detection within a Neuroendocrine Tumor of High Levels of B-Lymphocyte Stimulator (BLyS) Correlates with a Greater Disease Severity

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Aim(s): Potential prognostic role of cytokine B-Lymphocyte Stimulator (BLyS) in follow-up of NET patients. **Materials and Methods:** 124 unselected patients (disease duration 5.9 ± 4.4 yrs) with NET: 36 lung NET, 47 gastrointestinal NET and 41 pancreatic lesions. In 23 cases BLyS was repeatedly assessed during follow-up, the disease was monitored according to RECIST criteria. Patients

were compared with a group of 77 healthy blood donors, matched for age and sex. Serum levels of BLyS and CgA were analyzed using ELISA. **Results:** BLyS serum levels were significantly higher in patients than controls (1274 ± 808.6 pg/ml vs. 666.5 ± 240.3 pg/ml; $p < 0.0001$). A cut-off value, by ROC curve analysis, of 932 pg/ml discriminates between patients and controls with sensitivity of 96% and specificity of 67%. BLyS levels showed significant but weak correlation with CgA ($r = 0.19$, $p = 0.035$). No correlation was found with Ki67, grading, NET site. In patients with sustained remission after surgery, BLyS levels showed gradual reduction over time ($p = 0.08$). Patients with metastases tended to show higher levels of BLyS compared to those without ($p = 0.052$). Patients with stable disease disclosed lower levels of BLyS compared to those with progressing disease ($p = 0.046$). More elevated BLyS levels at baseline did not predict progressing disease in follow-up. **Conclusion:** Increased levels of BLyS are significantly associated with NET presence. They do not seem to have prognostic value at baseline, but they may identify a more severe disease during follow-up. **Keywords:** Tumor marker.

H11

Evaluation of the Somatostatin, CXCR4 Chemokine and Endothelin A Receptor Expression in a Large Series of Paragangliomas

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Introduction: Paragangliomas are predominantly benign tumors, but in some cases invasive growth and also metastasis is observed. Given the limited number of nonsurgical treatment options, novel target structures for diagnostics and therapy of this tumor entity are urgently needed. **Aim(s):** In the present study, the expression of the five somatostatin receptor (SSTR) subtypes as well as of the chemokine receptor CXCR4 and of the endothelin receptor A (ETA) was evaluated. **Materials and Methods:** Receptor expression was assessed by means of immunohistochemistry using a panel of novel rabbit monoclonal antibodies in a total of 54 paraffin-embedded paraganglioma tumor samples from 43 patients. The stainings were rated by means of the Immunoreactive Score and correlated to clinical data. **Results:** The SSTR2 was by far the most prominent receptor in the paragangliomas investigated. It was present in all samples at a high intensity, followed by the SSTR5, the SSTR1, the SSTR3 and the SSTR4. The CXCR4 and the ETA were seen only in a few cases on the tumor cells. However, with respect to the tumor blood vessels, in all cases an exceptionally strong staining for the ETA and in the majority of the samples also for the CXCR4 was noticed. **Conclusion:** Due to the high expression rate found in the present study, paragangliomas seem to be well suited for SSTR2-based diagnostics and therapies. Additionally, an indirect targeting of these highly vascularized tumors via the CXCR4 or the ETA may represent a promising future strategy. **Keywords:** Paraganglioma, Somatostatin, CXCR4.

H12

Is True Non-Secretion of Chromogranin A an Unfavorable Prognostic Factor in Patients with ENETs TNM Stage IV Gastroenteropancreatic Neuroendocrine Tumors?

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Introduction: Chromogranin A (CgA) is the best available serum marker for the work-up of gastroenteropancreatic NETs (GEP-NETs) and correlates with tumor volume & biological activity. During diagnosis & follow-up we found patients with elevated CgA levels and patients without elevated CgA levels (='true non-secretors'). We postulated that lack of secretion is a sign of dedifferentiation with a poorer prognosis. **Aim(s):** To determine whether true non-secretion of CgA is an unfavorable prognostic factor in patients with ENETs TNM Stage IV GEP-NETs. **Materials and Methods:** Patients using PPIs & MEN-1 patients were excluded. Baseline & follow-up CgA were measured in a large single-center cohort with one assay (IRMA). Cut-off values for baseline & follow-up CgA: normal (reference range (RR)), intermediate (≤2x upper limit of normal (ULN)), high (2-10x ULN) and very high (>10x ULN). Overall survival (OS) was estimated using Kaplan–Meier methods & hazard ratios with a Cox proportional hazards model. **Results:** 692 patients were included, 50.8% male. OS was significantly shorter in patients with high baseline CgA (median 103.9 vs. 222.4 months, $p < 0.01$) and very high baseline CgA vs. RR (56.2 vs. 222.4 months, $p < 0.0001$). For follow-up CgA, OS was only significant shorter in the very high follow-up CgA vs. RR (62.9 months vs. not reached). **Conclusion:** True non-secretion of CgA has been proven to be a favorable biomarker for OS in patients with ENETs stage IV well-moderately differentiated GEP-NETs, at first referral and during follow-up. **Keywords:** GEP-NET, CgA, Prognosis.

H13

Circulating Neuroendocrine Tumor Gene Signature, the NETest, Defines Therapy in GEP-NETs

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Introduction: Early and precise delineation of therapeutic responses are key issues in GEP-NET management. Imaging has limitations in sensitivity while secretory biomarkers e.g., CgA is controversial. **Aim(s):** Evaluate whether NETest predicts responses to somatostatin analogs (SSAs) in a prospective clinical trial. **Materials and Methods:** Test set: n = 35 SSA-treated (RECIST-evaluated) to establish cut-offs to differentiate stable from progressive disease. Prospective trial set: n = 28 SSA-treated Grade 1 (n = 12)/Grade 2 (n = 16) GEP-NETs. CgA (ELISA, normal <109 ng/ml) and NETest (qRT-PCR with multianalyte algorithmic analyses: scale, 0–100%). Blood was evaluated monthly prior to SSA injection. CT/MRI were undertaken at entry and 6 monthly until progression (RECIST 1.0). **Results:** Test set: NETest (80%) differentiated stable (SD) and progressive (PD) disease ($p < 0.0001$). In the prospective set, PFS was 315 days. NETest ($p = 0.002$) and grade ($p = 0.054$), but not CgA associated with treatment response. NETest predicted disease progression ($p = 0.0002$, multiple regression). NETest changes (to levels >80%) identified progression in 100% vs. 57% with CgA elevations ($p = 0.02$). This rise occurred significantly earlier (146 days before progression vs. 56 days with CgA; $p = 0.0001$). **Conclusion:** A rise in blood NETest values (80–100%) during SSA therapy defined treatment response and correlated accurately (100%) with disease progression. These changes occurred at a significantly earlier time point (~5 months) than image-proven disease progression. **Keywords:** NETest, CgA, PCR.

H14

Blood Gene Transcript Analysis Diagnoses Bronchopulmonary NETs and Identifies Progressive Disease

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Introduction: Broncho-Pulmonary (BP) NETs are pulmonary neoplasms with indolent to aggressive behavior. Imaging, histology and biochemistry are limited in defining malignancy or progression. **Aim(s):** Assess the NETest in BPNET diagnosis and progressive disease delineation. **Materials and Methods:** BPNETs (n = 36), controls (n = 38) and cancers (n = 38). Measurements were NETest (positive >14%) and specific gene 'omic' analysis: growth factor signaling (GFS: N-Ras, K-Ras, BRaf, Raf1) and somatostatin receptor (SSR1,3,5) expression by qPCR; CgA by ELISA (normal <109 ng/ml); disease status by imaging. Tumors were typical TC: n = 14, atypical AC: n = 22 and stable (SD n = 18) or progressive disease (PD n = 18). 55% AC were PD, 42% TC were PD. Clinico-histological groups were AC/SD or AC/PD; TC/SD or TC/PD by RECIST. Analysis by X2 tests and ROC-statistics. **Results:** NETest was +ve in all BPNETs (100%) irrespective of TC or AC. Controls were 95% –ve (AUC: 0.94 ± 0.03) and –ve in other cancers 90% ($p < 0.001$; AUC: 0.90 ± 0.04). NETest >40% differentiated PD vs. SD (accuracy 70%, $p = 0.03$). Combination of NETest and 'omic' gene expression (SSR/GFS) defined clinico-histological groups with 94% accuracy: PD/AC (92%), PD/TC (100%), SD/AC (67%), SD/TC (100%). CgA was +ve in 50% ($X2 = 20.1$, $p < 0.001$). CgA increase did not predict SD/PD. **Conclusion:** A blood-based NETest accurately identified BPNETs (100%), controls and cancers (~95%). NETest/omic analysis accurately identified clinico-histological groups in 94%. Blood-based genomic information will facilitate TC/AC characterization. **Keywords:** PCR.

H15

Neutrophil-Lymphocyte Ratio Predicts Survival in Pancreatic Neuroendocrine Tumors

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Introduction: Although the prognostic role of neutrophil-lymphocyte ratio (NLR) has been confirmed in a variety of tumors, the prognostic role of NLR in pancreatic neuroendocrine tumors (PNETs) has not been examined. **Aim(s):** The study was performed to assess the role of NLR as a prognostic factor in patients with PNETs. **Materials and Methods:** Clinical data were retrospectively retrieved from a single institution. The best cut-off value for baseline NLR levels was determined by the receiver operating characteristic (ROC) curve and area under the ROC curve. The primary event was overall survival and event times were assessed by the Kaplan–Meier method. Potential factors associated with the elevation of NLR in PNETs were examined. **Results:** A total of 165 consecutive patients with pathological confirmed PNETs were included in this study. The cutoff value of NLR was 2.4 by ROC curve (area under ROC curve, 0.70). NLR >2.4 was found to be a poor prognostic factor in both univariate and multivariate analyses. Patients with a NLR value >2.4 had a higher proportion of tumor size >3 cm ($P = 0.001$), TNM stage III or IV ($P = 0.019$), and G2/G3 ($P = 0.003$). **Conclusion:** NLR is an independent predictor of overall survival for patients with PNETs. Aberrant elevation of NLR identifies high-risk patients with aggressive characteristics. **Keywords:** pNET, Prognosis, Pancreatic neuroendocrine tumor, NLR.

H16

CA19-9 as a Prognostic Biomarker in Pancreatic Neuroendocrine Tumors

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Introduction: Carbohydrate antigen19-9 (CA19-9) is generally not considered as a biomarker in pancreatic neuroendocrine tumors (pNETs) since most pNETs present with normal range of CA19-9. **Aim(s):** The current study was to evaluate the role of serum CA19-9 levels as a prognostic factor in a relative large number of patients with pNETs. **Materials and Methods:** Consecutive patients were retrospectively collected from a single institution between June 2006 and February 2015. The receiver operating characteristic (ROC) curve and area under the ROC curve were used to select the best cut-off values for baseline CA19-9 levels. The primary end point was overall survival. Potential factors related to abnormal elevation of CA19-9 in pNETs were also investigated. **Results:** The cut-off value of CA19-9 was 16 U/mL by ROC curve. Univariable analysis demonstrated that CA19-9 >16 U/mL was an adverse prognostic factor for patients' overall survival. The CA19-9 >16 U/mL group had statistically higher proportion of tumor node metastasis (TNM) stage III or IV, vessel invasion, and symptoms in non-functioning pNETs than the CA19-9 ≤16 U/mL group. **Conclusion:** Our study firstly indicates that CA19-9 is a prognostic biomarker of pNETs which could reflect its aggressiveness and severity. **Keywords:** pNET, Prognosis, CA19-9, Biomarker.

H17

Chromogranin A in the Follow-Up of Digestive Neuroendocrine Neoplasms: Is It a Useful Biomarker?

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Introduction: Chromogranin A (CgA) is the most frequently used biomarker in digestive neuroendocrine neoplasms (DNENs) but its real usefulness is still unclear. **Aim(s):** To identify CgA clinical usefulness and the most accurate cut-off to detect disease progression (DP) or recurrence (DR) in the follow-up of DNEN. **Materials and Methods:** Unicenter retrospective analysis of sporadic DNENs with ≥24-mos follow-up and ≥2 CgA assessments. Circulating CgA was measured by Cisbio CgA-RIA (Gif-sur-Yvette, France). For clinical usefulness we meant CgA accuracy in detecting DP/DR at least 3 mos before imaging tests, and considered only cases in which CgA was measured before DP/DR. We analyzed CgA accuracy using different CgA changes: increase ≥50% from previous CgA level, increase ≥30%, ≥2xULN. **Results:** 129 pts (median ki67 4%; 51.3% stage IV, 38.6% stage III, 10.1% disease free) with a total number of 384 measurements (median 3 per patient; range2–6). Imaging tests diagnosed DP at any time in 52 pts and DR in 13 (by CT/MRI in 70.1%, by Ga-PET/octreoscan in 29.9%); CgA early detected it in 47.4% of cases (median 6.5 mos before imaging). 50% increase in CgA showed sensitivity, specificity and accuracy rates of 71.3%, 82.9%, 78.4% respectively, and was superior than other CgA changes ($P < 0.05$) in detecting DP/DR. **Conclusion:** In our population CgA was clinically useful only in 47.4% of cases; CgA increase ≥50% seems the most accurate CgA change in DP/DR detection. A larger case series is needed to validate these data. **Keywords:** CgA, Clinical usefulness, ≥50% increase.

H18

Blood Measurement of NET Transcripts (NETest) Predicts Well-Differentiated Gastroenteropancreatic NET Disease Status and Is Prognostic for Disease Progression

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Introduction: A key issue in GEP-NETs is early identification and prediction of disease progression. Clinical evaluation and imaging are limited due to the lack of sensitivity and disease indolence. **Aim(s):** Assess the NETest as a predictive and prognostic marker of progression in a long-term follow-up study. **Materials and Methods:** GEP-NETs (n = 34) followed for a median 4 yrs (2.2–5.4). WHO tumor grade/stage Grade I: n = 15, Grade II: n = 17; 31 (91%): stage IV. Baseline and longitudinal imaging and biomarkers were available and progression defined (RECIST 1.0). NETest: qPCR and multianalyte algorithmic analysis (disease activity scaled0–100% with low <40% and high activity risk cutoffs >80%); CgA: RIA (normal <150 µg/l); PFS: Kaplan-Meier analysis. **Results:** At baseline, 100% were NETest+ and CgA was elevated in 50%. Baseline NETest (>80%) was significantly associated ($p = 0.01$) with disease progression (median PFS 0.68 yrs vs. to 2.78 yrs with <40% levels). NETest was more informative (96%) than CgA changes (>25%) in consistently predicting disease alterations (40%, $p < 2x10\text{-}5$, $X2 = 18$). NETest had an earlier time-point change than imaging (1.02 ± 0.15 yrs). Baseline NETest levels >40% in stable disease were 100% prognostic of disease progression vs. CgA ($X2 = 5$, $p < 0.03$). Baseline NETest values <40% accurately (100%) predicted stability over 5-yrs ($p = 0.05$, $X2 = 3.8$ vs. CgA). **Conclusion:** NETest correlated with well-differentiated GEP-NET clinical status. It identified clinically-actionable alterations ~1 year before image-based evidence of disease progression. **Keywords:** PCR.

H19

Somatic Variant Detection in Circulating Cell-Free Plasma DNA of Patients with Pancreatic Neuroendocrine Tumours

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Introduction: Cell-free DNA (cfDNA) as a type of 'liquid biopsy' represents an attractive alternative to tissue sampling for detecting tumour-specific changes (circulating tumour DNA; ctDNA). **Aim(s):** To investigate if pancreatic NETs (PNETs) release ctDNA for use in disease monitoring. **Materials and Methods:** We investigated the mutational landscape of 9 PNET tissue samples from 3 cases using exome sequencing. DNA from matched blood served as control. Common mutations in all samples from the same case were identified and prioritised for further plasma validation according to type of mutation, quality of sequence reads and mutant allele frequency. **Results:** We identified somatic variants in genes commonly mutated in PNETs (ATRX, DAXX, TSC1/2) and novel variants in cancer-related genes (e.g. NEBL, NPRL2, CSMD3). Droplet digital PCR (ddPCR) was used to validate chosen somatic variants in plasma cfDNA from the 3 cases. Positive controls included the same tissue DNA used in sequencing while assay background was estimated in gDNA from healthy donors. The same tissue somatic variants were detected in ctDNA from cases 1 (NEBL) and 3 (DAXX). The number of mutant copies/mL of plasma was 27 and 61-68 copies, respectively. TSC1 and NPRL2 variants found in tissue DNA from case 2 were not detected in plasma. **Conclusion:** This proof-of-concept analysis demonstrates that ctDNA from PNET patients can be detected in blood and warrants further investigation using multiple samples to study how ctDNA levels alter during treatment and clinical follow up. **Keywords:** ctDNA, PNET.

H20

Up-Regulation of the Immunoregulatory Enzyme Indoleamine-2,3-Dioxygenase (IDO) with Consecutive Tryptophan Depletion Predicts Death in Patients with Neuroendocrine Neoplasia

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Introduction: Data from a considerable number of malignancies demonstrate that depletion of the essential amino acid tryptophan via induction of the immuno-regulatory enzyme Indoleamine-2,3-dioxygenase (IDO) serves as an important tumour escape strategy and is of prognostical importance. **Aim(s):** Here we investigate the activity of IDO as well as serum levels of tryptophan and respective downstream catabolites in a large cohort of NEN patients. **Materials and Methods:** 142 consecutive Caucasian patients (62 male, aged 60.3 ± 11.9 years) with histologically confirmed NEN were systematically analysed in a retrospective blinded endpoint analysis. Patients were followed up for a mean period of about 3.9 ± 1.9 years and clinical outcome, levels of established biomarkers, and tryptophan degradation markers (assessed using tandem mass spectrometry) including estimated IDO-activity were recorded. **Results:** We found that baseline serum tryptophan levels were significantly lower and IDO-activity was significantly increased in non-survivors. The risk for death inclined stepwise and was highest in patients in the upper tertile of IDO-activity. Cox-proportional regression models identified IDO-activity as independent predictor for death. **Conclusion:** In this retrospective analysis, we observed that baseline activity of the immunoregulatory enzyme IDO is significantly increased in non-survivors. IDO-activity was identified as an independent predictor for death in this cohort of NEN patients. **Keywords:** IDO-1, Inflammation, Tryptophan catabolites, Predictor, Biomarker.

H21

The Usefulness of Assessment the Serum Concentrations of Vascular Endothelial Growth Factor (VEGF) and Its Soluble Receptor Type 2 (VEGFR2) in Patients with Neuroendocrine Neoplasm (NEN)

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Introduction: Angiogenesis plays an important role in tumour growth and disease progression. VEGF is a angiogenesis-stimulating factor. VEGFR2 has antiangiogenic properties. **Aim(s):** Assessment the usefulness of determining VEGF and VEGFR2 serum concentrations in patients with NEN. **Materials and Methods:** The study included 82 patients with NEN: 48 women aged 57,17± 12,11 years and 34 men aged 59,56 ± 13,06 years. The control group consisted of 48 healthy sex- and age-matched cases. VEGF and VEGFR2 serum concentrations were mesured using the ELISA method with R&D Systems kits. **Results:** VEGF serum levels were significantly higher in patients with NEN, as compared to the control group. The concentrations of VEGF but not VEGFR2 were associated with III and IV clinical stages of the disease (TNM Classification). Significantly higher levels of VEGF in poorly differentiated NEC were found. **Conclusion:** VEGF may be useful in biochemical diagnosis as a marker for differentiating patients with NEN according to clinical stage and histological grade. **Keywords:** Neuroendocrine neoplasms, VEGF, VEGFR2.

H22

Validation of a Blood Neuroendocrine Tumor Gene Signature, the NETest, in a Netherlands NET Cohort

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Introduction: The CgA has limitations as a monoanalyte biomarker. The introduction of a PCR-based multi-analyte analysis of 51 genes (NETest) has been proposed as more accurate. **Aim(s):** We evaluated the NETest and CgA in a Dutch cohort and evaluated diagnosis and prediction of disease status. **Materials and Methods:** 20 healthy volunteers and 133 patients with NET were included. G1: n = 100, G2: n = 33; positive Octreoscan: n = 104; non-progressive disease (NPD): n = 84, progressive disease (PD): n = 49. Transcripts assessment-real-time PCR (ULN: 14%) and CgA-Kryptor (ULN: 100 µg/l) were measured. Mann-Whitney tests and ROC-statistics were used. Values expressed as median (range). **Results:** Median NETest scores were for controls 10% (0–27%) and in NETs 33% (7–93%) with a discrete bimodal distribution. NETest of 24% had 95% specificity and 82% sensitivity for NETs vs. controls (ROC AUC: 0.94 ± 0.02). In patients with NET, NETest and CgA were elevated in 85% and 46% respectively ($p < 0.001$). Neither differentiated between G1 and G2. In NPD median NETest was 33% (7–93%) and in PD 80% (13–93%) ($p < 0.001$). Median CgA in NPD was 75 µg/l (12–13950) and 260 µg/l (33–44150) in PD ($p < 0.001$). Identification of progression by ROC AUC analysis was NETest: 0.81 ± 0.04 and CgA 0.69 ± 0.05 ($p = 0.05$). **Conclusion:** The NETest was validated in an independent, blinded Dutch cohort and exhibited high sensitivity (82%) and specificity (95%). NETest is significantly higher in PD as compared to NPD. NETest better predicts disease activity than CgA ($p = 0.05$). **Keywords:** NETest, CgA, PCR, Progressive disease.

H23

iFiT: An Integrative Bioinformatics Platform for Biomarker and Target Discovery. A Case Study in Neuroendocrine Tumors

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Introduction: iFiT (Ipsen Focused-on-new bIological enTities and biomarkers) is a Bioinformatics platform integrating systems biology functionalities together with semantic & logic-based artificial intelligence within a high-scale computing environment. **Aim(s):** Key applications are the discovery of potential therapeutic targets as well as the identification of patient stratification candidate biomarkers. **Materials and Methods:** Given the limited OMICs characterization of neuroendocrine tumors, the identification of driver genes and pathways is challenging: To help circumvent this paucity of molecular information, iFiT was built on the postulate that co-expressed genes participate in the same biological processes. Furthermore, we fed the platform with curated heterogeneous datasets, pre-clinical and clinical, including molecular and phenotypic information. We focused our search on drugable GPCRs and microRNAs involved in mechanisms such as pancreas islet cells lineage, differentiation, multiplication and hormone secretion. **Results:** As a result, we identified 42 GPCRs and 10 microRNAs, including well-known NETs-associated genes such as SSTR2 and DRD2. iFiT predicted the driver role of SSTR2 in both proliferation and secretion before the release of the CLARINET study (ESMO 2013). Remarkably, 90% of candidate genes were validated on tumor tissues from 40 GEP-NET patients. **Conclusion:** In conclusion, iFiT achieves an excellent detection rate, and is proving suitable to uncover hidden information and mine translational knowledge in NET. **Keywords:** Targets iFiT.

H24

Biomarker and Target Identification in GEP-NET: From in Silico Prediction to Validation on Patient Tissues

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Introduction: Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a heterogeneous group of tumors. Somatostatin agonist treatment has a key role in the management of GEP-NET. However, the prognosis of these tumors varies between individuals. There is, therefore, a need to identify novel prognostic and predictive biomarkers of therapeutic efficacy, as well as to propose novel therapeutic strategies. **Aim(s):** To optimize this approach, we adopted a strategy that uses a curated biological knowledge source coupled with a proprietary data mining methodology (iFit) followed by wet lab experiments. In this poster, we highlight some of the results of the experimental validation. **Materials and Methods:** We selected 10 miRs and 42 mRNAs coding for G protein coupled receptors (GPCRs) that were identified with iFiT, for evaluation in tumor functioning or not from 40 metastatic or not patients (20 pancreatic NET and 20 ileal NET). The nanostring® platform was used for miRNAs and mRNAs analysis and immunohistochemistry was carried out for 11 GPCRs. **Results:** 90% of the in silico predictions were verified. We observed a significantly higher SSTR2 expression ($p = 0.034$) in non-functioning tumors. In contrast, DRD2 was found to be significantly more expressed in metastatic patients ($p = 0.009$). **Conclusion:** Taken together these results suggest that targeting SSTR2 and DRD2 might be a promising strategy for the treatment of NETs expressing both receptors. Interestingly, our study confirmed that miRNA-196 could be a marker of metastatic patients. **Keywords:** GPCR, miR.

H25

In vivo Expression of Survivin and XIAP in Medullary Thyroid Carcimoma

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Introduction: Medullary thyroid carcinoma (MTC) accounts for approximately 5% of all thyroid malignancies. Although surgery remains the first line therapy with curative intention, for advanced MTC current chemotherapeutic regimes do not provide promising results. Consequently, the identification of biologically relevant biomarkers that are associated with MTC progression may provide novel therapeutic targets. **Aim(s):** Aim of this study was to analyze the expression of Inhibitor of apoptosis protein (IAP) family members survivin and XIAP in MTC specimen. **Materials and Methods:** Tissue microarrays were constructed from MTC tissue specimens of 79 patients who underwent curative surgery for MTC between 1986 and 2003. The percentage of immunohistochemically positive cells and staining intensity of survivin and XIAP was evaluated by using immunoreactivity score (IRS). **Results:** In contrast to MTC tissue specimen, normal thyroid tissue stained negatively for survivin or XIAP. Overexpression of survivin or XIAP was significantly associated with an advanced T-stage and metastatic disease. In addition, expression of survivin strongly correlated with serum calcitonin levels. Interestingly, XIAP was highly expressed in patients with sporadic MTC. Importantly, multivariate Cox regression analysis demonstrated that overexpression of both IAPs correlated with a poor prognostic outcome. **Conclusion:** This study provides first evidence that survivin and XIAP are valuable biomarkers in patients with progressive and metastatic MTC disease. **Keywords:** MTC, IAP, Survivin, XIAP.

H26

Expressions of CK19 and CD117 in Hepatic Metastatic Pancreatic Nonfunctional Neuroendocrine Neoplasms

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Introduction: The expressions of CK19 and CD117 in pancreatic neoruendocrine neoplasms were considered dismal prognostic factors in some studies, but inconsistent in others. **Aim(s):** To determine the expressions of CK19 and CD117 in hepatic neuroendocrine lesions. **Materials and Methods:** A total of 22 patients with pancreatic neoruendocrine neoplasms with liver metastases underwent hepatectomy in our center from June 2005 to April 2015. The tissue microarray of 22 surgical samples was manufactured. **Results:** This cohort contains 12 males and 10 females. The mean age was 54.59 years old. Single-lobe was involved for 31.8% patients, and the others were bi-lobe lesions. All the patients underwent pancreatectomy and hepatic cytoreduction. According to the WHO standard, G1, G2 and G3 accounted for 4.5%, 72.7% and 22.7%, respectively. The mean Ki-67 index was 13.71%. The percentage of lymph node metastases was 22.7%. All samples of normal control group were negative for CK19 and CD117. The positive expression rates of CK19 and CD117 in observe group were 86.4% and 0%, respectively. The mean follow-up time was 34.5-mo and the median overall survival time was 12.89-mo. The expressions of CK19 and CD117 were not correlated with their survival. Ki-67 index >20%, higher grades and poor differentiation were dismal predictors ($P < 0.05$). **Conclusion:** The expression rate of CK19 in hepatic metastatic pancreatic neuroendocrine lesions was high, but its expression did not influence their survival. No expression of CD117 was found. **Keywords:** CK19, CD117, pNEN, LM, TMA.

H27

Expressions of ATRX and DAXX in Hepatic Metastatic Pancreatic Nonfunctional Neuroendocrine Neoplasms

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Introduction: Loss of ATRX or DAXX is common in well-differentiated pancreatic neuroendocrine neoplasms, and is correlated with higher tumor stage and shorter survival time. **Aim(s):** To determine the incidence of the loss of ATRX or DAXX in hepatic metastatic pancreatic neuroendocrine lesions. **Materials and Methods:** We collected 22 patients who underwent partial hepatectomy in our center from June 2005 to April 2015, and manufactured tissue microarray with their samples. **Results:** Of those 22 hepatic samples, 5 samples were well-differentiated G3 lesions, and the other 17 samples were well-differentiated G1/G2 lesions. For those 17 patients: 8 were males and 9 were females; the mean age was 51.94 years old; single-lobe was involved for 35.3% patients, and the others were bi-lobe lesions; according to the WHO criteria, G1, G2 accounted for 11.8%, 88.2%, respectively; the mean Ki-67 index was 13.71%; the percentage of lymph node metastases was 17.6%; the mean follow-up time was 38.7-mo, the median overall survival time was 21.07-mo. Overall, the incidence of loss of ATRX or DAXX was 76.5%. Meanwhile, the percentages of loss of ATRX, DAXX, ATRX and DAXX were 64.7%, 47.1 and 35.3%, respectively. Our data did not demonstrate that loss of ATRX or DAXX was correlated with their survival. **Conclusion:** Loss of ATRX or DAXX was frequent in hepatic metastatic pancreatic neuroendocrine neoplasms. This event could further indicate that loss of ATRX or DAXX was correlated with disease progression of those patients. **Keywords:** ATRX, DAXX, Hepatic lesion, pNEN, TMA.

H28

Immunohistochemical Expressions in Hepatic Nonfunctional Neuroendocrine Neoplasms with Unknown Origins

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Introduction: Liver metastasis is common in neuroendocrine neoplasms, but many patients could not reveal their origins during their career. **Aim(s):** To determine the immunohistochemical expressions in those hepatic neuroendocrine lesions with unknown origins and explore if they can help us to sreach for the primary lesions. **Materials and Methods:** The samples of 29 patients who underwent hepatectomy in our center from June 2005 to June 2014 were collected, and the tissue microarray were manufactured. **Results:** This cohort contains 15 males and 14 females. The mean age was 59.79 years old. Single-lobe was involved in 75.9% patients, and the others were bi-lobe lesions. According to the WHO criteria, G1, G2 and G3 accounted for 17.2%, 34.5% and 48.3%, respectively. The mean Ki-67 index was 24.32%. The percentages of well, intermediate and poor differentiation were 31%, 31% and 37.8, respectively. The incidence of loss of ATRX or DAXX was 31%, the other 69% samples were positive expressions of both ATRX and DAXX. The positive expression rates of p53, CK19, CD117, mTOR and cyclin D1 were 65.5%, 75.9%, 6.9%, 65.5% and 17.2%, respectively. Ki-67 index ≥10%, high grade and poor differentiation lesions were dismal prognostic factors ($p < 0.05$). No immunohistochemical expressions of TMA were correlated with their prognosis. One patient with loss of ATRX was diagnosed metastases from the pancreas recently. **Conclusion:** According to analyze the abnormal immunohistochemical expressions in hepatic lesions maybe helpful to search for the origins. **Keywords:** IHC, TMA, LM, NEN.

H29

Expression and Clinical Significance of Alpha-Internexin in Gastroenteropancreatic Neuroendocrine Neoplasm

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Introduction: Alpha-internexin is a 66-kDa neuronal intermediate filament protein, data on its role in gastroenteropancreatic neuroendocrine neoplasm (GEP-NEN) are limited. **Aim(s):** To explore the expression and the epigenetic regulation mechanism of α-internexin in GEP-NEN and investigate its clinical significance. **Materials and Methods:** α-internexin was detected by immunohistochemistry in 286 GEP-NEN specimens. The methylation of α-internexin promoter was evaluated by bisulfite genomic sequencing. **Results:** The positive expression rate of α-internexin in GEP-NEN was 26.6%, while the reduced/loss of expression rate was 73.4%. Reduced/loss of α-internexin was significantly different at different sites of gastrointestinal NEN ($P < 0.001$), and much higher in poorly differentiated G3 or metastases tumors ($P < 0.001$). KM survival curves showed that patients with reduced/loss of α-internexin had significantly shorter survival ($P < 0.001$). The median methylation degree of α-internexin promoter was 66.0% in 116 tissues. Hyper-methylation of the promoter was not correlated with the loss expression of α-internexin ($P = 0.525$). **Conclusion:** The expression of α-internexin was highly heterogenous in different sites of GEP-NEN. The reduced/loss of α-internexin was significantly related to the malignant biological behavior of GEP-NEN. Hyper-methylation of gene promoter may be not an important epigenetic regulation mechanis of reduced/loss of α-internexin expression in GEP-NEN. **Keywords:** Gastroenteropancreatic neuroendocrine neoplasm, Alpha-internexin, Prognosis, Methylation.

Imaging (Radiology, Nuclear Medicine, Endoscopy)

I1

Interim Results on the Influence of Lanreotide on Uptake of [68Ga]-DOTATATE in Patients with Metastatic or Unresectable NET: No Evidence for Discontinuation of Lanreotide before [68Ga]-DOTATATE PET/CT

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Introduction: Somatostatin receptor imaging with [68Ga]-DOTATATE PET/CT has become common practice in patients with NET. Current guidelines recommend discontinuing treatment with SSAs before obtaining a [68Ga]-DOTATATE PET/CT scan. The assumption is that unlabeled somatostatin may lower the detectability of lesions. **Aim(s):** To investigate the influence of lanreotide on the uptake of [68Ga]-DOTATATE in tumor- and normal tissue. **Materials and Methods:** 34 patients with metastatic/unresectable NET being treated with lanreotide and scheduled for [68Ga]-DOTATATE PET/CT are included. The PET/CT scan is made on the day before and the day after lanreotide injection in each patient. [68Ga]-DOTATATE uptake in the primary tumor, metastases, and normal tissue are quantified (SUVmax, mean, peak). **Results:** 17/34 patients were included up to 11–2015. No difference was seen in the uptake of [68Ga]-DOTATATE in tumor lesions, neither in primary tumors nor metastatic lesions, before or after injection of lanreotide. This was observed in all metastatic sites investigated. In normal tissue, the uptake of [68Ga]-DOTATATE in spleen, liver, and thyroid gland were significantly lower after injection of lanreotide. **Conclusion:** The administration of lanreotide does not alter the uptake of [68Ga]-DOTATATE in tumor lesions, but lowers physiological uptake in the liver, spleen, and thyroid gland. This contradicts the guidelines for [68Ga]-DOTATATE PET/CT imaging and suggests that cold somatostatin does not negatively affect somatostatin imaging. **Keywords:** Dotatate. *Supported by Ipsen.*

I2

The Role of Ga68-DOTATOC-PET-CT in Routine Screening of Multiple Endocrine Neoplasia Type 1

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Introduction: Multiple endocrine neoplasia type 1 is a tumor syndrome characterized by NENs of the pancreas, duodenum, parathyroid, pituitary, adrenal, thymus and bronchi. Gene carriers are recommended participation in prospective screening programs at expert centers. Ga68-DOTATOC-PET-CT is an increasingly used very sensitive imaging technique for GEP-NENs. **Aim(s):** Aim of the present study was to evaluate the role of Ga68-DOTATOC-PET-CT in routine screening of MEN1. **Materials and Methods:** In addition to established imaging techniques (CT thorax, MRI abdomen and brain, endoscopic ultrasonography (EUS), ultrasound of the neck) Ga68-DOTATOC-PET-CT was performed in all MEN1 patients undergoing regular screening in our hospital between January 2014 and September 2015. Findings were documented in a prospective database. **Results:** 33 MEN1 patients underwent screening. Ga68-DOTATOC-PET-CT detected 59 NENs in 27 of the33 patients. MRI of the abdomen and EUS detected 112 NENs in 31 of the 33 patients. 47% of the NEN found by established imaging techniques were missed by DOTATOC-PET-CT. The sensitivity of Ga68 PET/CT for NENs exceeding 20 mm was 100%. In one patient (3%) Ga68-DOTATOC-PET-CT detected a therapeutically relevant ileum-NET that was missed by the other imaging techniques. **Conclusion:** Ga68-DOTATOC-PET-CT may be of additional use, especially for the detection of NENs outside the primary target organs of MEN1. However, in regard of its expense and radiation its routine use for screening does not seem justified. **Keywords:** MEN1, GA68-DOTATOC-PET, Screening.

I3

The Role of 68Ga-DOTA-NOC PET in Evaluating Neuroendocrine Tumors: Real-World Experience from Single Lebanese Institution

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Introduction: Functional imaging with somatostatin analogues have been commonly used in NETs. **Aim(s):** To assess the role of 68Ga-DOTA-NOC PET-CT as a primary diagnostic tool for staging and follow-up of NETs. **Materials and Methods:** This is a retrospective study performed between 2010 and 2015, including patients having done PET for reasons related to NET:clinical, biological or radiological suspicion; staging; follow up of a primary tumor. **Results:** 129 patients were included. 68 (52.7%) were males with a median age at diagnosis of 54 (range3–88). 36 patients presented for primary detection: 19 presenting with clinical suspicion of NET, 3 with biological suspicion of NET, and 14 with a suspicious lesion discovered on another imaging modality. The most common indication was typical carcinoid syndrome (n = 12). PET was indicated mainly for staging (43.4%), followed by detection (27.9% based on clinical, radiologic or biologic suspicion 52.8%, 38.9% and 8.3% respectively), then by follow up (21.7%) and finally search for a primary (7%). Results based on histology were used as gold standard for diagnosis in 57% of patients and the remaining on the basis of follow up. Sensitivity, specificity, NPV and PP of PET were 87.1%, 97.7%, 79.6% and 98.7% respectively for the totality of the sample. Accuracy was measured using the ROC curve analysis with an AUC = 0.924

(CI: 0.874–0.974). **Conclusion:** 68Ga-DOTA-NOC PET is a highly sensitive and specific test for NETs. These results support its use as a primary diagnostic modality when evaluating NETs. **Keywords:** NET, Gallium PET.

I4

Staging of Neuroendocrine Tumors: Value of Hybrid Imaging With 111In-Pentetreotide

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Introduction: Neuroendocrine tumors (NET) are rare and can occur anywhere in the body. Ninety-eight percent of these tumors express the type 2 of somatostatin receptors, making possible the functional imaging of NET. 111In-labelled pentetreotide specifically binds to somatostatin receptors, with particular affinity to subtypes 2 and 5. **Aim(s):** The purpose is to show the value of Somatostatin Receptor Scintigraphy (SRS) with hybrid imaging in the management of NET. **Materials and Methods:** 49 patients (25 males and 24 female) aged 50.6 ± 14.3 years (16 to 78 years, median age 54 years) underwent 52 SRS. Indications were as follows, search for a primitive and staging in 23 cases (44.2%), preoperative with known primitive in 16 cases (30.8%) and post operative in 13 cases (25%). **Results:** In search for a primitive and staging, SRS was negative in three cases, diagnosed the primitive in 12 cases in whom 10 metastases were diagnosed. It failed to determine the primitive in 8 cases but established lesions cartography among theses latter's. Among the 16 patients with primary known lesions, SRS revealed abnormal radiotracer uptake in 12 patients with 10 metastatic sites, and was negative in 4 patients, in whom 2 metastatic sites were revealed. Post operative evaluation was negative in 8 patients and positive in 5 patients (with 3 distant metastases, one lymphatic node metastasis and one residual tumor site). **Conclusion:** SRS imaging with 111In-pentetreotide plays an important role in the diagnosis and the staging of patients with NET. **Keywords:** Neuroendocrine tumor.

I5

Dual 18F-Fluorodeoxyglucose/68Gallium DOTATATE (FDG/DOTA) PET Predicts Overall Survival in Neuroendocrine Tumours (NET)

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Introduction: 68Ga-DOTATATE (DOTA) and FDG PET have been utilised in NETs to aid diagnosis, prognostication and guide management. FDG PET avidity is associated with poor prognosis, but the prognostic significance of dual FDG/DOTA grading has not been explored. **Aim(s):** We investigated the prognostic value of a novel FDG/DOTA grading scheme in patients with metastatic NETs. **Materials and Methods:** We identified patients with histologically diagnosed NET, who had both FDG and DOTA PET scans within 31 days of each other. A novel scoring scheme (NETPET) was developed. Two experienced nuclear medicine physicians scored the scans based on FDG avidity, DOTA avidity and relative concordance/discordant sites. Paired scans were scored from 1 (DOTA+, FDG– disease) to 5 (FDG+, DOTA– disease). The prognostic impact of NETPET score on overall survival (OS) was assessed. **Results:** 73 patients (median age 60 years, 35% female; 17 Grade 1, 32 Grade 2, 16 Grade 3, 8 unknown) were eligible for inclusion, with median follow-up 12 months for patients still alive. When scores were considered as three groups (1 – DOTA+FDG–, 2–4 – DOTA+FDG+, 5 – DOTA–FDG+), increased NETPET score was associated with poorer overall survival (median OS for NETPET score 1: Not reached,2–4: 32 months, 5: 10 months; p = 0.0011, log-rank test). Increasing histological grade was also associated with poorer overall survival (p = 0.0081). **Conclusion:** NETPET grade correlates strongly with prognosis, with increasing FDG positivity/DOTA negativity predicting for poorer overall survival. **Keywords:** PET, Prognosis.

I6

Staging in Small Bowel Neuroendocrine Tumours: Roles and Shortcomings

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Introduction: Small bowel neuroendocrine tumours (SB NETs) frequently present with lymph node and/or distant metastases. **Aim(s):** To review the role of staging in 84 surgically treated SB NET patients, comparing yields of various imaging modali-

ties. We also compared pre-operative imaging with intra-operative findings in 20 patients undergoing surgery as the initial treatment. **Materials and Methods:** Retrospective review of our database of patients treated at 3 tertiary referral centres. Disease staging incorporated morphological (CT, MRI) and functional (68Ga DOTATATE PET/CT) modalities, and was tailored to each patient. **Results:** Seventy-eight patients had tumour grade data: 65 (83.3%) had G1, 11 (14.1%) had G2 and 2 (2.6%) had G3 tumours. Twelve patients (14.3%) had multifocal primary tumours. Nine patients (10.7%) showed no tumour dissemination; 74 (88.1%) had lymph node metastases and 51 (60.7%) had distant metastases (48 [57.1%] with hepatic disease). 68-Ga DOTATATE PET/CT identified at least 1 lesion in every patient, and demonstrated additional lesions in 51/80 (63.8%) of patients compared to morphological imaging. Pre-operative imaging understaged true disease burden in 14/20 (70%) of patients as discovered intra-operatively. Herein, imaging failed to identify primary tumour multifocality (7 patients) and additional hepatic metastases (4 patients). **Conclusion:** Currently available imaging heavily understages disease. Meticulous intra-operative exploration is superior to any pre-operative staging technique. **Keywords:** Neuroendocrine, Tumour, Staging.

I7

Pancreatic Neuroendocrine Neoplasms: Magnetic Resonance Imaging Features and Correlation with Their Histological Grade

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Introduction: Pancreatic neuroendocrine neoplasms (PanNENs) have different biological behavior and prognosis according to their histological grade. At present, few data are available regarding the value of imaging techniques in predicting the grade of PanNENs. **Aim(s):** To describe magnetic resonance (MR) imaging features including diffusion-weighted imaging (DWI) of PanNENs according to their histological grade. **Materials and Methods:** Preoperative MR examinations of 50 PanNEN patients were retrospectively reviewed. Qualitative and quantitative MR features were evaluated by two radiologists by consensus. All MR features were compared between histological grades using chi-square/Fisher's exact test and Student's T/ANOVA test. P values <0.05 were considered statistically significant. **Results:** Ill-defined margins, local infiltration, vascular involvement and liver metastases were significantly more common among G2-3 PanNENs compared to G1 tumors. G1 tumors were significantly smaller than G2-3 tumors (22.8 vs. 38.1 mm, p = 0.016); the mean ADC value was significantly lower among G2-3 tumors as compared to G1 tumors (1.03 ± 0.3 vs. 1.38 ± 0.6, p = 0.010). **Conclusion:** MR features of PanNENs vary according to their histological grade; MR imaging including DWI can differentiate G1 from G2-3 PanNENs. **Keywords:** Pancreas, Neuroendocrine neoplasms, Magnetic resonance imaging, Diffusion-weighted imaging.

I8

Small and Large Incidental Non-Hyperfunctioning Pancreatic Neuroendocrine Tumors: Spectrum of Magnetic Resonance Imaging Features

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Introduction: The improvement of imaging techniques significantly increased the detection of small incidental non-hyperfunctioning pancreatic neuroendocrine neoplasms (NF-PanNENs). Most NF-PanNENs <2 cm are likely benign lesions and a non-operative approach could be advocated in selected cases for these lesions. **Aim(s):** To analyze and compare magnetic resonance (MR) imaging features of incidental NF-PanNENs according to their size. **Materials and Methods:** MR examinations of 23 patients with incidental, histologically-proven PanNENs were retrospectively evaluated. Qualitative and quantitative MR features were analyzed and compared between small (<2 cm) and large (>2 cm) NF-PanNENs. **Results:** Fourteen small NF-PanNENs (mean size, 14.1 mm) and 19 large tumors (mean size, 40.9 mm) were included in this study. The percentage of G2/3 tumors was significantly higher among large NF-PanNENs compared to small neoplasms (57.9 vs. 21.4%, p = 0.040). Four large NF-PanNENs presented liver metastases at diagnosis. The percentage of tumor showing cystic/necrotic features on T2-weighted images, inhomogeneous enhancement and hypoenhancement during the arterial phase was significantly higher among large NF-PanNENs as compared to small tumors (26.3% vs. 0%, 36.8% vs. 0% and 42% vs. 7%, p = 0.049, 0.012 and 0.030, respec-

tively). **Conclusion:** Cystic/necrotic areas, inhomogeneous enhancement and arterial phase hypoenhancement are more frequent in large NF-PanNENs as compared to small NF-PanNENs. **Keywords:** Pancreas, Neuroendocrine neoplasms, Magnetic resonance imaging.

I9

Molecular Imaging of Late Somatostatin Receptor–Positive Metastases of Renal Cell Carcinoma in the Pancreas by Radiolabeled 111In SRS Octreotide Scan: A Rare Differential Diagnosis to Multiple Primary Pancreatic Neuroendocrine Tumors

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Introduction: Somatostatin-Receptor Scintigraphy (SRS) has a sensitivity and specificity for pancreatic NETs (pNETs) of 90 and 80% respectively. SRS is indicated as first staging procedure and one of the most sensitive imaging modalities for well-differentiated neuroendocrine tumors, based on imaging of somatostatin receptors (SSRTs). **Aim(s):** To report 111In SRS scan ability in detecting lesions of RCC origin. **Materials and Methods:** A radiolabeled 111In SRS scan was used. **Results:** Herein we report the case of a 45-year-old Caucasian lady with a previous history of left partial nephrectomy in 2005 for a G2 pT1b RCC, who presented with multifocal pancreatic disease and mediastinal and, perihilar lymphadenopathy 9 years later. Initial investigations with a 111In SRS scan detected strongly SSTR-positive pancreatic lesions which after biopsy histologically turned out to be ultra-late metastases of RCC (+ CD10 and +PAX-8, – CD56, CgA and synaptophysin). Given that the pancreatic lesions where initially deemed to be secondary to a pNET, the patient was offered a trial of long acting Somatostatin Analogs (SSAs) that were ultimately discontinued following histology report. **Conclusion:** Considering the somewhat surprising finding in the biopsy, a literature search in PubMed was performed, to discover limited reports of octreotide positive tumors of RCC origin in some cases even dealt with Peptide Receptor Radiotherapy (PRRT). This case highlights the spectrum of this diagnostic modality and the need for further research in the field. **Keywords:** SRS, pNET, SSRTs, RCC.

I10

Emergency Therapy for Liver Metastases from Advanced VIPoma: Surgery or Transarterial Chemoembolization

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Introduction: VIPoma is a rare neuroendocrine tumor (NET) with a high potential to develop hepatic metastases and poor prognosis. The primitive tumor is non-symptomatic and usually localized within the pancreas. Liver metastasis drove the prognosis and induced profuse watery diarrhea or renal failure. **Aim(s):** We herein present severe renal failure or diarrhea in 2 patients hospitalized in intensive care justifying emergency treatment of liver metastasis. **Materials and Methods:** Two patients experienced severe diarrhea due to a hyper secretion of vasoactive intestinal peptide (VIP) from liver metastasis released into the blood circulation. **Results:** Therapeutic management was discussed and liver transarterial chemoembolization (TACE) was performed with chemotherapy-loaded embospheres, which causes necrosis of tumor lesions. TACE permitted to control the hormonal syndrome and made patients eligible for curative surgery. Tumor necrosis occurred and VIP levels collapsed. Surgery was performed in one of the 2 cases after TACE and patient was considered in remission. They were still alive after 3-years follow up. **Conclusion:** TACE is feasible and appeared as an effective emergency treatment in patients with a VIP hormonal syndrome due to liver metastases. Despite the biological disorder due to the hormonal secretion, an aggressive approach is warranted in VIP liver metastasis. **Keywords:** VIPoma, hepatectomy, Trans arterial chemo embolization (tace), Neuroendocrine tumors (net), Vasoactive intestinal peptide (vip), Systemic chemotherapy.

I11

Biodistribution and Radiation Dosimetry of a Novel 18F-Fluoroethyl Triazole [Tyr3] Octreotate Analogue for PET Imaging Patients with Advanced Neuroendocrine Tumours

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Introduction: Despite advances, detection and quantification of NET activity by imaging remains a challenge. **Aim(s):** We present the first in-man study of 18F-fluoroethyl triazole [Tyr3] octreotate (18F-FET-βAG TOCA) in NET patients to evaluate biodistribution, dosimetry and safety. **Materials and Methods:** 18F-FET-βAG TOCA was synthesized via the click reaction. Nine patients were enrolled into study. Eight patients with sporadic NET and 1 MEN1 syndrome. Mean age 56 yr (range 35–73 yr) and weight 75.2 kg (91.2–66.3 kg). Patients underwent whole body PET-CT multi-bed scanning over 4 h and venous blood samples were taken at specific intervals to measure 18F radioactivity concentration in blood and plasma. Regions of interest were drawn, to derive individual and mean organ residence times; effective dose (ED) was calculated with OLINDA 1.1. **Results:** All patients tolerated 18F-FET-βAG TOCA with no adverse events. Over 60% parent tracer was present in plasma at 60 min. High tracer uptake was observed in tumours (primary and metastases). Physiological uptake was seen in pituitary, salivary, thyroid and spleen, with low background uptake in liver, an organ where metastases commonly occur. Organs receiving highest absorbed dose were gallbladder, spleen, stomach, liver, kidneys and bladder. ED over all subjects was 0.029 mSv/MBq (SD ± 0.004). **Conclusion:** The favourable safety, imaging and dosimetric profile makes it a valuable candidate in staging and management of NETs. Clinical studies in an expanded cohort are ongoing to clinically qualify this agent. **Keywords:** PET.

I12

Pretherapy Identification of Patients at Risk of Receiving a High Renal Dose Undergoing Peptide Receptor Radionuclide Therapy

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Introduction: 68GaDOTA TATE imaging of patients with neuroendocrine tumours has shown that tumour sequestration is a major factor leading to a sink effect that decreases activity concentration in healthy tissues, particularly the renal parenchyma. **Aim(s):** Based on this sink effect, we propose a quantitative method for pretherapy identification of patients at risk of receiving a high renal dose while undergoing peptide receptor radionuclide therapy (PRRT). **Materials and Methods:** 26 patients undergoing 177LuDOTA TATE PRRT received individual dosimetry via quantitative SPECT for their first cycle of treatment. For each patient, the mean renal dose was calculated and compared to pretherapy 68GaDOTA TATE PET imaging. **Results:** A relationship was found between the kidney absorbed dose from the 177LuDOTA TATE PRRT and the ratio of liver counts to whole body counts in the pretherapy 68GaDOTA TATE imaging. We also observed a weaker relationship between renal dose and glomerular filtration rate (GFR) before treatment which becomes stronger for the group of patients with lower liver uptake (i.e. a small sink effect). **Conclusion:** For routine clinical practice, the derived relationship provides a simple method to identify patients at risk of high renal dose before undergoing PRRT. While GFR before treatment provides some indication of risk of high renal dose, we demonstrate that characterisation of the tumour sink effect in pretherapy 68GaDOTA TATE imaging is a stronger determinant of renal risk across a broader range of patients. **Keywords:** Dosimetry, PRRT.

I13

Value of Octreoscan and 18FDG-PET for Clinical Prognosis of Patients with Neuroendocrine Neoplasms

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Introduction: Despite the existence of biological markers of aggressiveness, the clinical course of gastro-entero-pancreatic (GEP) neuroendocrine neoplasms (NEN) remains difficult to predict. Discrepancies between imaging data generated with 111In-pentetreotide scintigraphy (SRS) and 18 F-FDG-PET could reflect the degree of cellular de-differentiation. **Aim(s):** To test the overall prognostic value of the combined use of these two imaging modalities. **Materials and Methods:** NEN patients with both types of studies were identified retrospectively from the SwissNET database. Disease evolution was correlated with functional imaging results. **Results:** We identified 28 patients with both imaging studies, either on the primary tumour site (19/28) or for metastases (28/28). Median follow-up was 22 months (range: 1–80). With respect to primary tumor, 9/19 (47%) patients had a discrepant result, with 5 positive SRS and negative PET, and 4 negative SRS and positive PET. Among these patients, 3/4 (75%) with a positive PET had died at follow-up, compared to 0/5 (0%) with a positive SRS. For metastases imaging, only 6/28 patients had a discrepant result, thus not allowing drawing any definite conclusion. **Conclusion:** In good accordance with what has been described in the literature, these data suggest that a discrepancy between 18F-FDG-PET and scintigraphy, with a positive PET, could be predictive of an adverse outcome. **Keywords:** 111in-pentetreotide scintigraphy, 18F-FDG-PET, Prognosis, Clinical course.

I14

Clinical Value of Somatostatin Receptor Scintigraphy in the Management of Medullary Thyroid Carcinoma

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Introduction: Medullary Thyroid Carcinoma (MTC) is a rare form of thyroid cancer. It represents 5 to 10% of these cancers. MTC grows from specialized thyroid cells called para-follicular cells, or C-cells that secrete a hormone called calcitonin. Its prognosis is usually good. Recurrences can occur, requiring lifelong surveillance. **Aim(s):** The aim of this study is to evaluate the clinical value of Somatostatin Receptor Scintigraphy (SRS) in the management of patients with MTC. **Materials and Methods:** Four patients (2 man, 2 women) aged 28–67 years underwent a total of five SRS. All these patients had a total thyroidectomy for MTC. SRS was requested during an assessment of post-operative extension in two cases, research of recurrence in two cases and therapeutic evaluation in the last case. **Results:** In two patients, the post-surgical SRS showed the presence of lymphadenopathies: one right cervical in one case and two paraesophageal in the other case. In two other cases, the SRS has not objectified recurrence. In the last case, the patient had bone, lung, liver and left breast metastases not expressing the somatostatin receptor. So, the examination was not contributory to evaluate treatment response. **Conclusion:** SRS plays an important role in the management of patients with MTC by establishing the lesion cartography. It adapts treatment strategy in post-surgical period and after therapeutic evaluation. It allows also the detection of recurrences. **Keywords:** Medullary thyroid carcinoma, Somatostatin receptor scintigraphy, Management.

I15

Iodinated Exendin-4 Shows Improved Pharmacokinetic in Rat Insulinoma Model

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Introduction: GLP-1 receptor is an important marker for imaging benign insulinomas. **Aim(s):** The limitations of existing PET tracers are high kidney uptake and low specific activity. We attempted to improve these by using radioiodinated (Ex-4). **Materials and Methods:** Kd and Bmax of [Nle14,125I-Tyr40-NH2]Ex-4 (125I-Ex-4) were determined in in vitro binding assay using Ins-1E rat insulinoma cells. Biodistribution of 125I-Ex-4 was studies in nude mice bearing rat Ins-1E xenografts. **Results:** 125I-Ex-4 bound to Ins-1E cells with the Kd of 4.1 ± 1.1 nM and Bmax of 0.045 ± 0.002 nM. Biodistribution at 1 hour post injection (h p.i.) revealed the highest uptake of 125I-Ex-4 in Ins-1E tumor (72.7 ± 12.2%IA/g), pancreas (25.3 ± 4.2%IA/g) and lung (30.5 ± 3.6%IA/g). The specificity of tracer accumulation in these organs was confirmed by blocking experiment. Tumor-to-blood and tumor-to-muscle ratios were 25.5 and 169.2, respectively. The kidney uptake was only 7.5 ± 0.7%IA/g, and the tumor-to-kidney ratio (9.7) was much higher than for any other previously published tracer. Blocking the sodium/iodide symporter by irenat reduced the amount of radioactivity in the thyroid by 94%. After 4 h p.i. uptake of 125I-Ex-4 in tumor and pancreas decreased to 22.4%IA/g and 10.4%IA/g, respectively. After 24 h p.i. the tracer was almost completely cleared from the body, with 3.7 ± 2.5% IA/g remaining in the tumor. **Conclusion:** 125I-Ex-4 shows favorable pharmacokinetic with highly improved tumor-to-kidney ratio and excellent contrast to other normal organs. **Keywords:** GLP-1, Insulinoma.

I16

Evaluation of CT Prognostic Factors of Neuroendocrine Liver Metastasis Treated with Transcatheter Arterial Embolization

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Introduction: TAE has been shown to be effective in the management of metastatic NET. **Aim(s):** To screen CT prognostic factors of neuroendocrine liver metastasis treated with transcatheter arterial embolization. **Materials and Methods:** CT images of 22 patients with 32 neuroendocrine liver metastases (10 patients with two metastases) treated with transcatheter arterial embolization from July 2010 to January 2015 were retrospectively analyzed. CT features (location, number, boundary, long diameter, short diameter, hyper- or hypovascular, enhancement pattern, attenuation, absolute and relative enhancement of tumor) between the responder (CR and PR) and nonresponder (SD and PD) groups, the decrease of long diameter after embolization using RECIST and modified RECIST (mRECIST) criteria between the hyper- or hypovascular groups were compared by independent t test or Mann-Whitney test. **Results:** The decrease of long diameter were (12.31 ± 16.01)% and (17.99 ± 19.13)% for the hyper- and hypovascular groups using RECIST criteria, (43.95 ± 42.62)% and (47.84 ± 46.45)% using mRECIST criteria. There were no statistically significant differences between two groups (with P value of 0.388 and 0.824, respectively). None of the CT features showed statistically significant differences between the responder and nonresponder groups. **Conclusion:** None of the CT features can predict the response of neuroendocrine tumor liver metastasis treated with transcatheter arterial embolization. **Keywords:** CT, Neuroendocrine tumor, Liver metastasis, Transcatheter arterial embolization.

I17

Somatostatin Receptor PET/CT with Radiolabelled Antagonist Is Twice as Effective as the Agonist for Detecting Liver Metastases: Results of a Phase 1/2 Study Comparing 68Ga-OPS202 with 68Ga-DOTATOC PET/CT in Gastroenteropancreatic NET Patients

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Introduction: 68Ga-DOTATOC PET/CT is a reference method for imaging somatostatin receptor (sstr) expressing neuroendocrine tumors (NET). Presence and extent of liver metastases impact on patient management and prognosis. **Aim(s):** To investigate safety and diagnostic accuracy of 68Ga-OPS202, a radiolabelled sstr antagonist for PET/CT imaging of gastroenteropancreatic (GEP) NET (ClinicalTrials.gov NCT02162446). **Materials and Methods:** Twelve metastatic G1/G2 GEP-NET patients were enrolled in a prospective phase 1/2 imaging study to investigate two single doses of 68Ga-OPS202 (A: 15 μg & B: 50 μg) in comparison with 68Ga-DOTATOC PET/CT. Scans were reviewed by 2 independent blinded readers. Follow-up imaging and biopsy were used as standard of reference. **Results:** No adverse reaction to 68Ga-OPS202 required treatment. Both 68Ga-OPS202 doses showed lower uptake than 68Ga-DOTATOC in the normal liver, the pancreas and the gastrointestinal (GI) tract ($p < 0.05$) and similar uptake in malignant lesions, thus significantly improving the image contrast: e.g. liver-lesions-to-normal-liver uptake ratios (mean ± σ) were 5.7 ± 6.9 (A)/6.0 ± 7.4 (B) for 68Ga-OPS202 vs. 3.0 ± 4.1 for 68Ga-DOTATOC ($p < 0.05$). A total of 103 lesions were detected with 68Ga-DOTATOC vs. 179 (A) and 202 (B) with the antagonist. **Conclusion:** 68Ga-OPS202 is well tolerated, improves imaging contrast and tumor detection in the liver over 68Ga-DOTATOC PET/CT. The lower GI and pancreatic uptake may increase the PET accuracy for detecting sites of primary. **Keywords:** Radiolabelled somatostatin antagonist, PET, GEP-NET.

I18

68Ga-DOTATOC PET and Gene Expression Profile in Patients with Neuroendocrine Carcinomas

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Introduction: Somatostatin receptor expression on both protein and gene expression levels were compared with in vivo 68Ga-DOTATOC PET/CT in patients with neuroendocrine carcinomas (NEC). **Materials and Methods:** Twenty-one patients with verified NEC who underwent a 68Ga-DOTATOC PET/CT between November 2012 and May 2014, were retrospectively included. By quantitative real-time polymerase chain reaction (qPCR) we quantitatively determined the gene expression of several genes and compared these with 68Ga-DOTATOC PET. By immunohistochemistry we qualitatively studied the expression of selected proteins in NEC. **Results:** Median age at diagnosis was 68 years (range 41–84) years. All patients had WHO performance status0–1. Median Ki67 index was 50% (range 20–100%). Gene expression of somatostatin receptor subtype (SSTR) 2 and Ki67 were both positively correlated to the 68Ga-DOTATOC uptake ($r = 0.89$; $p < 0.0001$ and $r = 0.5$; $p = 0.021$, respectively). Furthermore, SSTR2 and SSTR5 gene expression were strongly and positively correlated ($r = 0.57$; $p = 0.006$). On the protein level SSTR2 stained positive in 33% ($n = 7$) and SSTR5 in 38% ($n = 8$) of the NEC patients. **Conclusion:** This study as the first verifies a positive and close correlation of 68Ga-DOTATOC uptake and gene expression of SSTR2 in NEC. SSTR2 gene expression had a stronger correlation to 68Ga-DOTATOC uptake than SSTR5. In addition, the results indicate that the gene expression levels of SSTR2 and SSTR5 at large follow one another. **Keywords:** Neuroendocrine carcinoma, Gene expression, 68GA-DOTATOC, IHC, SSTR2.

I19

[18F]FDG-PET/CT as a Predictive Tool for Response to Chemotherapy and Everolimus Treatment in Patients with Pancreatic Neuroendocrine Tumour

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Introduction: The predictive role of 18F-FDG-PET/CT (FP) in neuroendocrine tumours is debated. **Aim(s):** To evaluate the correlation between FP and response to chemotherapy (CHT) and everolimus (E) for pancreatic NETs (PanNETs). **Materials and Methods:** Baseline and post-treatment imaging studies (contrast enhanced CT/MRI and FP) of 31 patients (P) treated for advanced, G1-2 PanNETs were retrospectively reviewed. A per lesion analysis was conducted, separately for each treatment arm (CHT and E), selecting up to 6 lesions (L) for each P. Baseline FP results (positive if SUV max >3.5) and RECIST1.1 disease control rate (DCR) and objective response rate (ORR) were analyzed for possible correlations. **Results:** Thirtyfour treatments (15 E and 19 CHT) were conducted on 31 P, from which 107 lesions (L) were selected (mean 3.6 per P, range: 1–6). 66 and 41 L were FP positive (FP+) and negative (FP–). In the CHT arm, DCR and OR were higher in FP+ compared with FP– L: 82.4% vs. 46.6% (p 0.004) and 28% vs. 20% (p 0.53). In the E arm, a trend towards higher DCR and OR was found in FP– compared with FP+ L: 76.9% vs. 66.6% (p 0.54) and 19.2% vs. 0% (p 0.155). Similar results were found in the per patient analysis. **Conclusion:** FP may have a role in the prediction of response to CHT and E for PanNETs: the most relevant finding is the trend towards better DCR/OR in FP+ and FP– patients treated with CHT and E, respectively. These preliminary results deserve validation in prospective, larger series. **Keywords:** 18F-FDG-PET/CT, Predictive, Chemotherapy, Everolimus, Pancreatic NETs.

I20

[18F]FDG-PET/CT Heterogeneity in Patients with Metastatic, Well-Differentiated Pancreatic Neuroendocrine Tumours

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Introduction: 18F-FDG-PET/CT (FP) often shows an heterogeneous pattern of positivity in patients (P) with pancreatic neuroendocrine tumours (PanNETs). **Aim(s):** To evaluate the incidence of FP positivity (FP+) and FP heterogeneity (H) in P with advanced, well differentiated (WD) PanNETs, and to analyze possible correlations with tumour grade (G). **Materials and Methods:** Baseline FP of P treated for metastatic, G 1-2 or WD G3 (Ki67<55%) PanNETs were retrospectively reviewed. FP was defined positive if at least one lesion had SUV max >3.5. In a same FP+ P, categorical H (CaH: coexistence of FP positive and negative lesions) and continuous H (CoH: mean FP SUVmax difference between lesions) were calculated. FP+ and CaH rates were compared between G groups using Chi-square test. P values <0.05 were considered significant. **Results:** Thirty P were analyzed: seven, 15 and 8 were G1, G2 and WD G3, respectively. Between them, 70% were FP+, 38% of which with CaH; mean CoH was 3.7. Although not statistically significant, a trend towards higher FP+ rate was found according to grade: FP was positive in 57.2%, 73.4% and 75% of G1, G2 and WD G3 P, respectively (p 0.988). Conversely, CaH was observed in 50%, 36.7% and 33.3% G1, G2, G3 P, respectively (p 0.696). **Conclusion:** FP+ is a frequent event in the metastatic setting of WD PanNETs (70%). In P with FP+, the rate of CaH approximates 40%, and mean SUVmax CoH is 3.7. A non-significant trend was found for higher FP+ and lower CaH rates according to tumour grade. **Keywords:** 18F-FDG-PET/CT, Heterogeneity, Pancreatic NETs.

I21

Significance of Preoperative FDG-PET/CT Scan in Patients with Pulmonary Carcinoid Tumours

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Introduction: FDG uptake on PET/CT scan has been shown to be of prognostic significance in patients (pts) with metastatic neuroendocrine tumours (NET). **Aim(s):** The aim of the study was to determine the prognostic significance of preoperative FDG uptake in the primary tumour in pts who underwent radical surgical resection of their pulmonary carcinoids (PC). **Materials and Methods:** Pts were operated by a single surgeon and were followed-up in the Christie NHS Hospital from 2007 to 2015. Pathology diagnoses were centrally confirmed. Tumours with SUVmax >3 were considered FDG-positive(+). **Results:** 65pts, 55 with typical (TC) and 10 with atypical carcinoid (AC) were included. Thirty-nine pts (60%) had FDG(+) tumours, 25 pts (46%) with TC and 9 (90%) with AC ($p = 0.042$). Of the FDG(+) tumours, the median SUVmax for TC was 5.1 (range,3.1–14.1) and 5.4 (range,4.0–12.9) for AC ($p = 0.505$). The lowest whisker SUVmax value (boxplot) in the group of AC pts was 4.0 and was used as a cutoff for prognostic analysis. After a median follow-up of 34 months, no pt with FDG-negative or SUVmax < 4.0 relapsed. Pts with SUVmax ≥4.0 had significantly worse relapse-free survival (RFS, $p = 0.004$). Among TC pts, those with SUVmax ≥4.0 (compared to <4.0) showed significant overall trend for worse RFS ($p = 0.062$). **Conclusion:** To our knowledge, this is the first report showing that FDG uptake of the primary tumour is prognostic for RFS in pts with radically resected pulmonary carcinoids. Central review of FDG-PET/CT scan results will be presented. **Keywords:** Pulmonary carcinoids, FDG-PET/CT scan.

I22

Role of Preoperative Computed Tomography (CT) in Diagnostics and Disease Stage of Small Bowel NEN: Correlation with Pathology Based on pTNM WHO 2010 Classification

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Introduction: SbNEN are difficult to diagnose on standard CT without bowel preparation. Knowledge about specific radiological signs is essential. **Aim(s):** To evaluate the usefulness of CT in detection and staging of sbNEN based on pTNM (WHO 2010). **Materials and Methods:** We retrospectively analyzed 71pts from initially 117pts with pathologically proven sbNEN, 46 of them were excluded. Specific radiological signs of primary tumor, and stage of disease were evaluated using index scale and correlated with pathology. Separate analysis evaluated technical aspects of CT scans. **Results:** NENG1 and G2 both 34pts, 2pts NECG3 and 1pt had undetermined grade. Primary tumor detected in 58pts (sensitivity 82%). Additionally 10pts (14%) had mesenteric changes highly suggested sbNEN. Overall diagnostic sensitivity of CT in detection of primary was 96%. The correlation of pathologic findings with CT, in size of primary was 0.89. CT correctly T stage in 46%. Accuracy of N stage and M stage was 94% and 97%. Only 35% of exams were made using optimal protocol, others (65%) were only acceptable technically. In the group of exams made with optimal protocol only 1 case had no radiological signs of primary tumor. **Conclusion:** CT is able to detect sbNEN with sensitivity 96% if including mesenteric lesions. There is high correlation of CT in size of the primary. N and M stage of disease is also with high accuracy using CT. Appropriate CT protocol and interpretation of specific signs are mandatory. **Keywords:** Small bowel neuroendocrine neoplasm, Computed tomography.

I23

Double Balloon Enteroscopy in Detecting Small Bowel Neuroendocrine Neoplasms (SB-NENS)

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Introduction: Data describing the effectiveness of double-balloon enteroscopy (DBE) in the detection of small bowel neuroendocrine neoplasms (SB-NENs) are scanty. **Aim(s):** Present series was aimed at reporting the experience at a single referral centre for NENs. **Materials and Methods:** All consecutive patients with a suspected SB-NEN selected for diagnostic DBE were enrolled. **Results:** Between 2011 and 2015, among 45 patients with suspected SB-NEN or NEN from unknown primary, after an extensive work-up, six patients (4 M, 2 F, median age 50 years) underwent DBE (3 anterograde, 2 retrograde, 1 both; median time: 60 min; median insertion 200 cm). DBE was positive in two patients with evidence of an ileal lesion of 1 and 2 cm, respectively (biopsy: G1 NEN). Both patients underwent uneventful surgical resection. Of the four patients with negative DBE, two had metastatic NENs of unknown primary, one had primary jejunal NEN revealed by Gallium68-PET and then surgically removed; the last patient resulted a true negative as NEN was not confirmed at long-term follow-up. Overall, in absence of falsely positive results, DBE showed a sensitivity of 33%. No complications were observed during the procedure. **Conclusion:** Present series showed that DBE is a safe procedure in the diagnosis of SB-NENs. Further studies are needed to better clarify the diagnostic role of DBE in the neuroendocrine tumor setting and its relationship with other techniques, i.e. videocapsule endoscopy and nuclear imaging. **Keywords:** Small bowel neuroendocrine neoplasm, Double-balloon enteroscopy.

I24

Type I Gastric Neuroendocrine Tumors Diagnostics: 16 Years of Experience

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Introduction: In our institution from 1998 to 2014 we have identified 72 patients with type I gastric neuroendocrine tumors (NET). **Aim(s):** Majority of patients were woman – 85.7%. Most part (79.6%) of tumors were well-differentiated – G1 (Ki-67 lower than 2%) and only 14.3% were G2 (median Ki-67–4.3). In 3 (6.1%) patients G1 and G2 type I gastric NETs were found synchronously. **Materials and Methods:** More often tumors occurred in gastric corpus (93,88%), in 40.82% of them lesions diagnosed also in proximal parts of stomach and in 12.24% – in gastric antrum. Mean tumor size in G1 tumors was 0.58 cm (0.2–2.0 cm), whereas in G2 cases – 1.35 cm (0.5–3.0 cm), mean tumor amount in patients with G1 tumors was 11 (1–93), while in patients with G2 lesions – 2 (1–4). **Results:** In all cases severe atrophic gastritis in adjacent to NETs gastric mucosa was noted, and in 69.4% of them autoimmune gastritis with enterochromaffin like cells hyperplasia lesions was comfirmed. **Conclusion:** Serum gastrin-17 level raised along with tumor number: in cases with gastrin-17 level lower than 100 mkm/l mean tumor amount was 13, while in patients with gastrin-17 level 200–400 mkm/l – 21.1. Serum chromogranin A level was also raised in all cases: if it was within 100–200 ng/ml, mean tumor amount was 10,5, whereas in with serum chromogranin A more than 200 ng/ml – mean gastric NETs number was 26. **Keywords:** Gastric, NET, Neuroendocrine.

I25

Multimodal Endoscopic Diagnostics of Gastric Type I Neuroendocrine Tumors

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Introduction: From 1998 till 2014 in our institution we have diagnosed 72 type I gastric neuroendocrine tumors (NET) with upper gastrointestinal endoscopy. **Aim(s):** At early stage (up to 2006) only white-light endoscopy was used for gastric NET diagnostics and all of them appeared as flat or polypoid reddish lesions in proximal stomach or gastric corpus. Since 2007 we started use narrow-band imaging (NBI) endoscopy and it allowed more accurate gastric NET diagnostics. **Materials and Methods:** All lesions with NBI examination had altered mucosal pit pattern: tortuous or dot-type. Moreover, with NBI it is possible to review not only pit pattern, but microvessel pattern also, and in all type I gastric NET we observed pathologic arborescent dilated microvessels. Use of NBI endoscopy with x150 magnification allowed comprehensive diagnostics of very small (less than 0.1 cm) lesions, and additional 43.2% gastric type I NETs were found only with such diagnostic approach. **Results:** We have tried to use autofluorescence (AFI) endoscopy in gastric type I NET diagnostics, but none of them had specific autofluorescense extinction, unlike adenocarcinoma. **Conclusion:** In all patients with gastric NETs 20 MHz endoscopic ultrasonography was performed obligatory: 88.7% tumors located within mucosa, the rest – in submucosa. Last 4 years we started to use confocal laser endomicroscopy with x1000 magnification in gastric NET cases and it shows mucosal surface destruction and small round tumor cell infiltrates. **Keywords:** Confocal laser endomicroscopy, Mucosal surface destruction, Gastric net.

I26

Multimodal Endoscopic Diagnostics of Gastric Neuroendocrine Tumors

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Introduction: From 1998 till 2014 in our institution we have diagnosed 72 type I gastric neuroendocrine tumors (NET) with upper gastrointestinal endoscopy. **Aim(s):** At early stage (up to 2006) only white-light endoscopy was used for gastric NET diagnostics and all of them appeared as flat or polypoid reddish lesions in proximal stomach or gastric corpus. **Materials and Methods:** Since 2007 we started use narrow-band imaging (NBI) endoscopy and it allowed more accurate gastric NET diagnostics. All lesions with NBI examination had altered mucosal pit pattern: tortuous or dot-type. Moreover, with NBI it is possible to review not only pit pattern, but microvessel pattern also, and in all type I gastric NET we observed pathologic arborescent dilated microvessels. **Results:** Use of NBI endoscopy with x150 magnification allowed comprehensive diagnostics of very small (less than 0.1 cm) lesions, and additional 43.2% gastric type I NETs were found only with such diagnostic approach. We have tried to use autofluorescence (AFI) endoscopy in gastric type I NET diagnostics, but non of them had specific autofluorescense extinction, unlike adenocarcinoma. **Conclusion:** In all patients with gastric NETs 20 MHz endoscopic ultrasonography was performed obligatory: 88.7% tumors located within mucosa, the rest – in submucosa. Last 4 years we started to use confocal laser endomicroscopy with x1000 magnification in gastric NET cases and it shows mucosal surface destruction and small round tumor cell infiltrates. **Keywords:** Gastric, NET, Endoscopic, Diagnostics, NBI, Confocal, CLE.

I27

Analysis of 18FDG-PET/CT in Patients with Gastrointestinal Neuroendocrine Neoplasm

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Introduction: Gastrointestinal neuroendocrine neoplasm (Gi-NEN) comprised a wide and heterogeneous group of neoplasms. Diagnosis could often be challenging due to their rarity. 18FDG-PET/CT had a high accuracy for poorly differentiated NENs. **Aim(s):** This study aimed to assess the value of 18FDG-PET/CT in Gi-NEN patients and illustrate the correlation between glucose metabolism and differentiation degree of tumor. **Materials and Methods:** 37 patients (22 males, 15 females, age: 34-77 years) with definite histological diagnosis of Gi-NEN who underwent 18FDG-PET/CT were involved in this retrospective study. All the patients had primary lesions or metastases. **Results:** The positive rate of 18FDG-PET/CT in different grade of Gi-NEN was 42.86% (G1, 3/7), 46.67% (G2, 7/15) and 93.33% (G3, 14/15) respectively. Means of SUVmax in these three groups were 2.97 ± 1.16, 4.29 ± 3.57, and 14.41 ± 9.64. SUVmax was significantly correlated with Ki67 (r = 0.670, P = 0.000). 18FDG-PET/CT showed distant metastasis in 51.35% (19/37) patients, such as liver, skeleton and lungs. Ki67 values had no significant difference between distant metastasis group and non-distant metastasis group (P = 0.09). On the contrary, SUVmax was statistically different between the two groups (P = 0.009). **Conclusion:** There was a positive correlation between glucose metabolism and differentiation degree of Gi-NEN. 18FDG-PET/CT was valuable in staging Gi-NEN, especially G3 or metastatic tumors. **Keywords:** 18FDG, Gastrointestinal neuroendocrine neoplasm, Positron emission tomography, Standard uptake value.

I28

Analysis of 18FDG-PET/CT in Patients with Pancreatic Neuroendocrine Tumor

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Introduction: Neuroendocrine Tumor (pNET) comprised a wide and heterogeneous group of neoplasms. 18FDG-PET/CT was the most widely used functional imaging for cancer in general and had a high accuracy for poorly differentiated NENs. **Aim(s):** This study aimed to analyze the special performance of 18FDG-PET/CT in pNET patients and to assess the correlation between glucose metabolism and differentiation degree of tumor. **Materials and Methods:** 40 pNET patients (20 males, 20 females, age: 19-77 years) with histologically proven were enrolled in the study. All the patients had primary lesions or metastases. **Results:** The positive rate of 18FDG-PET/CT in different grade of pNET was 53.80% (G1, 7/13), 83.30% (G2, 15/18) and 100% (G3, 9/9) respectively. Even in relatively poor differentiation group (Ki67 ≥10%), the positive rate was also up to 100% (18/18), and the other group's (Ki67 <10%) was 59.09% (13/22). SUVmax was significantly correlated with Ki67 (r = 0.488, P = 0.001). 18FDG-PET/CT showed distant metastasis in 50.00% (20/40) patients, such as liver, skeleton and peritoneum. But Ki67 values and SUVmax had no significant difference between distant metastasis group and non-distant metastasis group (P = 0.208, P = 0.271). **Conclusion:** There was a positive correlation between glucose metabolism and differentiation degree of pNET. 18FDG-PET/CT was valuable in staging pNET, especially relatively poor differentiation tumors (Ki67 ≥10%). **Keywords:** 18FDG, Pancreatic neuroendocrine tumor, Positron emission tomography, Standard uptake value.

Medical Treatment – Chemotherapy

J1

Antitumor Efficacy of Temozolomide in Patients with Metastatic Pulmonary Carcinoids

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Introduction: Temodal (TMZ) is an oral alternative to dacarbazine. **Aim(s):** The aim of this study was to retrospectively analyze the efficacy and safety of TMZ in patients with metastatic pulmonary carcinoids (mPC). **Materials and Methods:** 34 patients pathologically reviewed mPC according to the WHO criteria, referred to Gustave Roussy from 1993 to 2014 were included. Treatment was given at a dose of 150 mg/m^2/day for 5 days (D1 = D28), escalated to 200 mg/m^2/day if well tolerated. Disease control rate, according to RECIST at 12 months was the primary endpoint. DCR was compared in patients who received both oxaliplatin-based chemotherapy (O-BC) i.e gemox or folfox, and dacarbazine (TMZ or deticene/DTIC-BC) in a subgroup of 16 patients referred to Gustave Roussy or Hospices Civils of Lyon. **Results:** 10 patients (29%) were functioning. 62% presented at least two metastatic sites. 18 (56%) underwent previous surgery on the primary tumour. They previously received a median number of 1 chemotherapy. 88% had RECIST progressive disease before TMZ. A median number of 6 [1–15] cycles of TMZ was given. 12 months DCR was 21%. Partial response was noted in 3 patients, lasting 30, 33 and 52 months. mPFS was 6 months [95% CI = 3–9]. Grade 3 or 4 toxicities occurred in 5 patients (15%). Within the subgroup of 16 patients, 12 months DCR was 19%, 31% or 19% under TMZ/DTIC-BC, O-BC or both regimens. **Conclusion:** Our study confirms tolerable antitumor efficacy of TMZ in mPC. Response to TMZ/DTIC-BC or O-BC were not exclusive. **Keywords:** Pulmonary carcinoids, Temozolomide, Safety.

J2

Radio-Chemotherapy vs. Surgery in Non-Metastatic Ano-Rectal Neuroendocrine Carcinoma: A Multicenter Study by the Association des Gastro-Entérologues Oncologues

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Introduction: Neuroendocrine carcinomas (NEC) of the anus or the rectum are a rare disease, accounting for less than 1% of all digestive malignancies. Most are metastatic at diagnosis and treated with a platinum-based chemotherapy. No guidelines for localized tumors exist. **Aim(s):** The purpose of this study was to describe the characteristics of ano-rectal localized NEC, their management and their outcomes. **Materials and Methods:** We retrospectively reviewed patients from 11 French centers with ano-rectal localized NEC. We compared two therapeutic managements: surgery (group A) versus chemotherapy with or without radiation (Group B). Progression-free survival (PFS) and overall survival (OS) were estimated with the Kaplan-Meier method. **Results:** A total of 24 patients were identified with a median follow-up of 25 months (3-60 months). Median age was 63 years old and seventeen had a rectal tumor (71%). Mean Ki-67 was 72% (range: 20–100), and 75% of the tumors had a high proliferative index (Ki-67>50%). Global PFS and OS were 13.1 and 44.1 months, respectively. 37% of patients were in group A and 63% in group B. There was no difference between group A and group B, whether in terms of PFS (13.0 versus 13.2 months, p = 0.75) or OS (49.1 versus 39.2 months, p = 0.42). **Conclusion:** In patients with ano-rectal localized NEC, chemotherapy with or without radiation obtained a similar outcome as surgery and this conservative approach could be deemed a reasonable option. **Keywords:** Neuroendocrine carcinoma, Ano-rectal tumor, Surgery, Radio-chemotherapy.

J3

Capecitabine and Temozolomide in NETs G1-2: The Experience of Various Hospitals in Spain

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Introduction: Treatment of neuroendocrine tumors (NETs) with capecitabine-temozolomide (CAPTEM) is an option yet to be confirmed in phase III trials. **Aim(s):** The experience of 12 centers in Spain with this scheme is presented. **Materials and Methods:** We retrospectively reviewed patients with NETs G1-2 of any origin treated with capecitabine (750-1000 mg/m^2 twice daily days 1-14) and temozolomide (150-200 mg/m^2 days 10-14) every 28 days, from June 2009 to August 2015. **Results:** 61 patients were included, 43 of them (70.5%) pancreatic NET (pNET). Mostly, they were second-line treatments (41%), positive octreoscan (90.2%) and 39.3% received concomitantly somatostatin analogs. Response rate (RR) was 49.2% (2 CR and 28 PR), with 39.3% (24) stable disease. Median progression-free survival (PFS) was 16.2 months (95% CI 12.0–20.3), and median overall survival (OS) was 38.3 months (95% CI 24.6–52.0). Although pNETs had higher RR (53.5% vs. 38.9%; p = 0.29), longer median PFS (18.4 vs. 15.3 months; p = 0.57) and shorter median OS (31.2 vs. 41.6 months; p = 0.67) than non-pNETs, differences did not reach statistical significance. Nine patients (14%) experienced G3-4 toxicities, mainly thrombocytopenia (11.5%) and neutropenia (8.2%). **Conclusion:** This is the largest reported series of NETs treated with CAPTEM. The achieved RR matches other retrospective series and is higher than that reached with targeted therapies. We are analyzing MGMT expression to study its predictive role. Prospective studies to validate these results are needed. **Keywords:** Capecitabine, Temozolomide.

J4

Capecitabine-Temozolomide in G3 Neuroendocrine Neoplasms

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Introduction: There is no standard second line treatment for G3 neuroendocrine neoplasms (NENs). The sensitivity to platinum combinations of G3 NENs with a Ki67 <50% remains unclear. **Aim(s):** We hypothesize that capecitabine-temozolomide (CAPTEM) could be a valid option in this setting. **Materials and Methods:** We retrospectively analyzed the outcome of NEN patients treated with CAPTEM in 12 sites in Spain between June/2008 and October/2015. **Results:** A total of 25 patients were included. Median age of 55 years, mostly men (72%). Primary tumor was predominantly located in the pancreas (40%), lung (12%) and colon (12%). Distant metastases were present at the liver (80%), lung (24%), peritoneum (20%) and bone (16%). Fifteen (60%) patients had Ki67 ≤50% and 12 (48%) positive octreoscan. Patients were treated in first (16%), second (44%) and subsequent lines (40%) of treatment. Disease Control Rate was 44% (4% PR + 40% SD). Median progression-free survival (PFS) was 4.4 months (95% CI, 3.9–4.9) and median overall survival (OS) was 8.0 months (95% CI, 5.3–10.7). No differences were found in DCR nor PFS when comparing Ki67 ≤50% vs. >50%, positive vs. negative octreoscan and treatment line (first vs. second vs. third and subsequent). Ki67 (≤50% vs. >50%) was found as a prognostic factor with a median OS of 12.1 months vs. 5.9 months (p = 0.009). **Conclusion:** CAPTEM could be an alternative option for G3 NEN. We need further prospective studies with this scheme in these patients. **Keywords:** Capecitabine, Temozolomide, G3 NEN, Ki-67.

J5

FOLFOX Chemotherapy: Efficacy and Tolerability in Advanced Digestive Neuroendocrine Neoplasms (NENs)

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Introduction: FOLFOX has been poorly investigated in digestive NEN (DNENs), mostly in small cohorts. **Aim(s):** To analyze efficacy, predictive factors of response and tolerability of FOLFOX in a consecutive series of advanced DNENs. **Materials and Methods:** Retrospective analysis of patients (pts) receiving FOLFOX IV in 2005-2015, with at least 3-mos follow-up. Objective response (OR) and progression-free survival (PFS) were assessed; prognostic factors analyzed by Cox-regression model. **Results:** 67 pts included; 41.6% NET G2, 21.5% NET G3, 35.4% NEC G3, 1.5% MANEC. 18 pts (26.9%) had FOLFOX as 1st line therapy. Median number of cycles was 8; OR (PR+SD) occurred in 76.1%. Median PFS was 8 mos, PFS-rates at 3 and 6 mos were 88.1% and 73.0%. Median PFS of pts with FOLFOX as 1st line was 10 mos compared to 7 mos for other lines ($P < 0.05$). PFS was not affected by Ki67. Predictors of worse outcome ($P < 0.05$) were reduced serum albumin (HR 0.60), reduced serum protein (HR 0.65) and elevated serum alkaline phosphatase (AP)(HR 1.003); predictors of better outcome ($p < 0.01$) were FOLFOX treatment for more than 6 mos (HR 0.51) and more than 9 cycles (HR 0.41). Multivariate analysis revealed AP and total number of cycles of FOLFOX as independent factors ($P < 0.05$). Toxicity (polyneuropathy, cytopenia) caused FOLFOX stop in 36.7%, pause in 13.9%, dose reduction in 32.9%. **Conclusion:** FOLFOX is effective in advanced DNENs with poor prognosis; efficacy is correlated with tolerability, duration of therapy and number of cycles. **Keywords:** FOLFOX, Tolerability, Tumor response.

J6

FOLFOX in Neuroendocrine Tumors

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Introduction: Favorable toxicity profile and significant antitumor activity of FU-oxaliplatin in several malignancies led us to evaluate FOLFOX in advanced neuroendocrine carcinomas (NETs). **Aim(s):** Evaluate the efficacy, Progression-free (PFS) and Overall survival (OS) respectively. **Materials and Methods:** We performed a retrospective study in 31 patients with metastatic digestive and lung well-differentiated G1-G2 NETs with progressive disease treated with FOLFOX regimen chemotherapy. Were registered improvement of clinical symptoms and radiological response. **Results:** FOLFOX was first-line therapy for 18 patients, further line for 8 and 5 cases respectively. Nine patients (29%) had partial response (PR) and 13 (42%) stable disease (SD). Disease control rate was 71%. Among patients, 22 had clinical benefit, although 20 patients had an initial poor performance status (>2) and 28 a clinical tumor syndrome (pain, hormonal secretions). Median OS was 25 months. One and 2 years OS were 84 and 65% respectively. Median PFS was 14 months. No significant difference in OS/PFS was observed between KI67 subgroups or primitive location. No unusual toxicity was noted.7/9 patients with PR and 12/13 with SD got benefit of a break in treatment, whose median duration was respectively of 9. **Conclusion:** Conclusion: FOLFOX chemotherapy exhibits promising efficacy and clinical benefit in patients with naïve or previously treated NETs, with the possibility of prolonged breaks. **Keywords:** Neuroendocrine tumors, FOLFOX, Clinical improvement, Break in treatment, PFS, OS.

J7

Aranoza in the Treatment of Metastatic Neuroendocrine Tumors (NETs): Single Institution Experience

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Introduction: Aranoza (3-α-L-arabinopyranosyl-1-methyl-nitrosourea) – nitrosourea derivative, as STZ. **Aim(s):** To evaluate the efficacy and safety of Aranoza in metastatic WD NETs. **Materials and Methods:** We performed a prospective analysis of all pts treated with Aranoza (500 mg/m^2 for 3 days every 3 weeks) at our center between July 2007 and July 2014. The median progression-free survival was calculated using Kaplan-Meier method. Treatment efficacy was evaluated according to RECIST. **Results:** 64 pts (27 pancreatic NETs, 32 non-pancreatic NETs and 5 NETs without primary) were included, median age was 56 years. 45 pts were chemotherapy-naïve. Overall RR was 21% (13/62: 8/26 in PNETs, 4/31 in non-PNETs and 1/5 NETs without primary). RR in patients with Ki-67 above 5% and ≤5% was seen in 23% (7/30) and 18% (5/28) pts respectively. Median PFS was 18.1 months (20.1 mo in PNETs and 15.3 mo in non-PNETs, $p = 0.4$). Toxicities grade 3–4 were noted in 23 pts, thrombocytopenia ($n = 12$) and neutropenia ($n = 11$). **Conclusion:** Aranoza demonstrated a moderate antitumor activity and good safety profile in WD NETs. **Keywords:** Aranoza, Neuroendocrine tumors, Chemotherapy.

J8

Use of Lanreotide LAR in the Case of Intolerance of Octreotide LAR in Patients Well-Differentiated NETs

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Introduction: Intolerance of Octreotide is about 10% of cases. **Aim(s):** To evaluate the tolerability of Lanreotide LAR in the case of intolerance of Octreotide LAR. **Materials and Methods:** 5 patients with metastatic well-differentiated (G1-G2) functioning EP-NETs (2 – pancreas, 1 – cecum, 2 – small intestine). **Results:** Patients received Octreotide LAR 30 mg for 5-8 mo. More frequent diarrhea, flatulence, abdominal pain developed. In one patient colitis identified by CT. Octreotide LAR was stopped and Lanreotide LAR assigned (Somatuline Autogel 120 mg). The patients' condition improved, abdominal pain stopped, the multiplicity of diarrhea reduced. 1 pts received Octreotide LAR 30 mg within one year with clinical effect, and bilateral abscesses in the soft tissues of the gluteal area apeared as a result of intramuscular injection of Octreotide LAR. Octreotide LAR was stopped and Lanreotide LAR subcutaneously assigned (Somatuline Autogel 120 mg). Clinical effect was maintained within 6 mo. All patients had stable disease with good tolerance of Lanreotide LAR. **Conclusion:** Lanreotide LAR can be successfully used in patients with intolerance of Octreotide LAR. **Keywords:** Octreotide, Lanreotide, Intolerance, NETs.

J9

3-Drugs Chemotherapy Regimen for G3 PanNENs with Ki67 below 55%: Single Institution Experience

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Introduction: To date no standard regimen of chemotherapy (CTH) is universally approved for advanced pancreatic neuroendocrine neoplasms (PanNENs) with Ki67<55% and no predictive selection criteria is available. **Aim(s):** To retrospectively assess the outcomes obtained with CHT in PanNENs with Ki67<55%. **Materials and Methods:** We retrospectively reviewed data from unresectable PanNENs patients (P) who received CHT during 2011-2015. Ki67% >55% or mixed hystological type were excluded. P underwent CHT with STZ/5FU (2C) or DTIC-5FU-CDDP (3C) and were separately analyzed. **Results:** 29 treatments were conducted on 27 P, with mean age at diagnosis of 55 years. 13.8%, 48.3% and 37.9% P had respectively G1, G2 and G3 (Ki67<55%) grading. Mean Ki67 was 11.4% and 22.1% in 2C and 3C respectively; Ki67 was among 20–55% in 15.8% and 80% of 2C and 3C treated-P. ORR and DCR were 36.8% (7/19) and 84.2% (16/19) vs. 40% (4/10) and 80% (8/10) in 2C and 3C treated-P respectively. mPFS was 9 and 6,3 months for 2C and 3C respectively; median OS was not yet reached in both groups. G3/4 hematologic toxicity occurred in 26.3% and 20% of P respectively for 2C and 3C regimen. **Conclusion:** 2C schedule performance is consistent with literature. To our knowledge this is the first report concerning activity of 3C schedule in a population enriched of PanNENs with Ki67 20–55%. Activity and safety of 3C regimen deserve further study in PanNENs with Ki67 among 20–55%. **Keywords:** 3-drugs chemotherapy regimen, Pancreatic NETs, Ki-67% <55%.

J10

O6-Methylguanine DNA Methyltransferase (MGMT) Expression by Immunochemistry May Help Predict Response to Streptozotocin-Based Chemotherapy in Pancreatic Neuroendocrine Tumours

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Introduction: Streptozotocin (STZ) is an alkylating agent inducing DNA damage mainly repaired by MGMT. STZ-based chemotherapy is the first line treatment of non-resectable well-differentiated PNET. As for temozolomide, tumour MGMT deficiency may predict the efficacy of STZ in PNET. **Aim(s):** Assessment of the predictive value of MGMT in a monocentric retrospective cohort of PNET treated with STZ-based chemotherapy. **Materials and Methods:** All patients with a well-differentiated PNET treated with a STZ-based chemotherapy according to the Moertel scheme between 01/2006 and 02/2014 were selected. Efficacy of the chemotherapy was assessed on CT-scan according to RECIST 1.1 and by PFS. MGMT expression was assessed by immunochemistry with a score (0–300) combining the % of positive cells by the intensity of the staining (0–3). **Results:** 18 patients (8 men, median age 52) with a PNET grade 1 (n = 3), 2 (n = 12) or 3 (n = 3), progressive in 50% of the cases, were selected. STZ-based chemotherapy (with doxorubicin n = 16 or 5FU n = 2) was mainly administered as first line (78%). Best radiological response was an OR in 28% (n = 5), SD in 56% (n = 10) or PD in 16% (n = 3). 5-year survival rate and median PFS were 61% and 14 months [3.7–28.3], respectively. Median MGMT was 85 [0–300]. A low MGMT expression was not associated with an objective response but patients with MGMT ≤120 had a longer PFS (19.5 [7.2–28.3] vs. 6.6 months [3.7–20.2]) (p = 0.03). **Conclusion:** A low MGMT score (≤120) can help selecting patients to be treated with STZ-based chemotherapy. **Keywords:** MGMT, Streptozotocin, PFS.

J11

Efficacy and Tolerance of a Simplified Combination of Streptozotocine and Epi-Adriamycine in Metastatic Foregut Neuroendocrine Tumor (NET). A Pilot Study

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Introduction: Since more than 30 years the combination of Adriamycine (A) and Streptozotocine (STZ) is considered as one of the standard chemotherapy regimens (Moertel et al, N Engl J Med 1992, 326 : 519–23) for patients with aggressive grade 2 metastatic pancreatic NET (PNET). **Aim(s):** To evaluate tolerance and efficacy of a simplified schedule in patients with progressive metastatic PNET. This simplified regimen used an equivalent dose/intensity of epi-A and STZ as in the Moertel's regimen : STZ 600 mg/m² in 1 hour perfusion d1 and d2 and Epi-A: 60 mg/m² d1 every 3 weeks. **Materials and Methods:** Between 2011 and 2015, 10 patients were treated and their data prospectively entered in the hospital data-base. All patients gave their consent before treatment. **Results:** Median number of cycles administered were 3 (1–7). 2 patients move to 5FU and STZ for toxicity (1 for atrial fibrillation and 1 for digestive bleeding and fatigue). Regimen tolerance was good: no case of renal toxicity, only 1/8 gr 3 vomiting, 1/8 gr 3 neutropenia, 1/8 gr 3 asthenia. No dose reduction was necessary. There were 4 objective response (RECIST 1-1) and 4 stabilizations, and 2 patients progressed after first evaluation. After chemotherapy 3 patients had their primary resected allowing secondary chemoembolization of their liver mets. PFS and OS will be presented. **Conclusion:** Compared to the traditional regimen of A and STZ on five days this regimen on 2 days every 3 weeks is more simple and appears to have a favorable tolerance profile. **Keywords:** Pancreatic net chemotherapy.

J12

Efficacy and Safety of Sunitinib as Long-Term Treatment in Japanese Patients with Advanced Pancreatic Neuroendocrine Tumors

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Introduction: The results from recent clinical trials have suggested the ethnical difference in antitumor activity of sunitinib against advanced pancreatic neuroendocrine tumors (PNET), which seemed to be higher in Japanese than those in Western patients. **Aim(s):** To evaluate the efficacy and safety of sunitinib in Japanese patients with advanced PNET. **Materials and Methods:** A total of 15 patients with advanced PNET (median age 57 years, 40% male, 33% NETG1) treated with sunitinib in our hospital were retrospectively reviewed. The primary endpoint was clinical benefit rate (CBR). The secondary endpoints included objective response rate (ORR), progression-free survival (PFS) probability and safety. **Results:** During the median observation time of 13.6 months (1.0–25.8), the CBR, ORR and PFS probability at 1 year were 67%, 40% and 89%, respectively. Grade 3/4 adverse drug reactions (ADRs) occurred in 67% patients. The most common ADRs were hand-foot syndrome (80%), neutropenia (67%) and diarrhea (60%). More than half of the hematologic ADRs were of grade 3/4 in severity. The dose of sunitinib in 8 patients whom continued more than 1 year was reduced to 25.0mg/day, and the relative dose intensities and drug resting rates were 46% (33–65) and 34% (3–50), respectively. **Conclusion:** Sunitinib demonstrated definite antitumor activity in Japanese patients with advanced PNET. Appropriate dose reduction and resting periods would enable long-term continuation and consequently maximize the efficacy of sunitinib. **Keywords:** Sunitinib, Pancreatic neuroendocrine tumor.

J13

Chemotherapy for Stage IV Sporadic Pancreatic Neuroendocrine Tumors (pNET): Are Partial Responses to Post-First Line Chemotherapy Predictable by Response/ Type of First Line Chemotherapy?

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Introduction: Three types of chemotherapy are recommended for stage IV pancreatic neuroendocrine tumors (pNETs): streptozocin (STZ)-, dacarbazine (DCZ)- and oxaliplatin (OX)-based. Whether cross resistance exists is unknown. **Aim(s):** To analyze RECIST-response to second-line chemotherapy as a function of antitumor activity and type of first line chemotherapy. **Materials and Methods:** Multicenter retrospective study. Inclusion criteria were: 1) Confirmed pNET naive of therapy 2) RECIST measurable disease 3) Sporadic tumor. STZ- and DCZ-regimens were grouped together as alkylating agents. **Results:** We included 81 patients. First line chemotherapy was STZ-, DCZ- or OX-based in 37, 14, and 30 patients. Thirty-seven of them received second-line chemotherapy (STZ-, DCZ- or OX-based in 8, 14, and 15 subjects). Rates of partial response to second-line chemotherapy was 20 and 30% in patients who respond or not respond to first-line chemotherapy, respectively. Rates of response to second-line alkylating agents in patients receiving first-line OX-regimens was 27%. Rates of response to post-first line OX-regimen in patients receiving first-line alkylating agents was 32%. By contrast when sequential administration of alkylating agents (STZ- or DCZ-based chemotherapy) was performed, no partial response were observed. **Conclusion:** Response to first-line chemotherapy does not predict the likelihood of responding to second-line cytotoxic agents when alternative family of cytotoxic agents are used. **Keywords:** Pancreatic neuroendocrine tumor, Chemotherapy.

J14

The Role of Interval CT Scanning in Patients Undergoing Palliative Chemotherapy for Metastatic Neuroendocrine Tumours (NETs)

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Introduction: In NET, radiological response to chemotherapy is often delayed and the importance of interval-imaging during treatment has not been determined. **Aim(s):** To asses whether interval-imaging alters clinical management. **Materials and Methods:** We performed a retrospective review of NET patients treated with chemotherapy between 2008-2011. Relevant data was extracted from the medical and radiological records. **Results:** 63/84 patients had sufficient data to assess clinical and radiological response. Common primary sites included pancreatic (36%) and bronchial (16%). 47% were grade 3. After three cycles of chemotherapy, 58%, 20% and 22% had clinical response (ClinR), stable symptoms (SS) or symptomatic progressive disease (PD) respectively. Of 36 patients with ClinR, 34 also had radiological response (1 CR, 15 PR and 18 SD (PPV 94%)). Two patients with a ClinR had PD on imaging; both high-grade tumours (Ki67 80% and 90%). 14 patients had clinical PD of which 2 died from PD and on imaging; 8 had PD, 1 a mixed response and 3 had SD but discontinued chemotherapy due to progressive symptoms. All patients with radiological progression had Ki67 ≥20%. All patients with SS had SD on imaging. Overall there was a discrepancy between clinical and imaging response in 5 cases (7.9%). **Conclusion:** In 97% of patients with metastatic NETs, interval-imaging would not have altered management based on clinical assessment. We recommend interval imaging only for patients with clinical PD or tumours with Ki67>20%. **Keywords:** NETs, Chemotherapy, Imaging.

J15

The Efficacy and Safety of Sunitinib in Heavily Pretreated Patients with NETs. National Cancer Research Center Experience

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Introduction: There was done monocentral trial. 19 pts with progressive well differentiated NETs (G1, G2) were treated with sunitinib. **Aim(s):** Evaluation efficacy and toxicity. **Materials and Methods:** All pts received long acting somatostatin analogs. The mean age was 55 years, 4 male, 15 female. The most of pts had pancreatic neuroendocrine tumor – 16 (84%) pts, kidney NET–1 pt, primary multiple synchronous panceatic+kidney had 2 patients. There was index proliferation Ki67% determination: Ki67 less 3% –1 pt, Ki67% = 3–20% had 15 pts; ki67% more than 20% had 2 pts. There were 3 pts with G1 NETs, 16 patients with G2 NETs. Cytoreductive

surgery was performed in 9–47.3% pts. 6/19 pts had 0-1-2 prior lines of CT and 13/19 patients were heavily pretreated with more than 3 lines of CT. Previous treatment included interferon α, octreotide LAR, XelOx, EP and of temozolomide, paclitaxel and fluoropyrimidines, everolimus. Sunitinib as a first line treatment was in 3 patients, after everolimus therapy was in 2 cases. **Results:** The efficacy was evaluated in 14/19 pts. There was 2 PR-14.3%, 11pts had stable disease-78.6% and 1 pt had progressive disease. The median of PR is not reached. The median of stable disease was 13 months AE III-IV grade included hematology 8 pts, hypertension 4 pts, bleeding from esophageal vessels 1 patient stopped treatment due to toxicity. Dose of sunitinib was reduced in 4 pts due to high blood pressure. **Conclusion:** Preliminary data suggests that sunitinib efficacy, the observed AE correlated with known. **Keywords:** NET, Sunitinib, Efficacy, Chemotherapy.

J16

Safety and Compliance of Capecitabine and Temozolomide in Patients with Advanced Neuroendocrine Tumours

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Introduction: Capecitabine-temozolomide (CAPTEM) is a treatment option in patients (pts) with neuroendocrine tumours. Although efficacy data has been reported, no detailed safety information exists. **Aim(s):** The aim of this retrospective study was to examine safety and treatment compliance in CAPTEM-treated pts with diverse advanced NETs. **Materials and Methods:** Pts were treated with CAP 750 mg/m^2 BD (day1-14) and TEM 200 mg/m^2 OD (day 10–14) orally in a 28 day cycle up to a maximum of 6 cycles. Alive pts completed retrospectively a treatment satisfaction survey. **Results:** 38 pts were included; primary sites were lung (18 pts), GI tract (6 pts), pancreatic (4 pts), other (4 pts) and unknown primary (6 pts). Twenty-eight pts (74%) had ECOG performance status (PS) 0–1 and 10 (26%) had PS 2. Fourteen pts (37%) had prior chemotherapy. Sixteen pts (42%) did not complete 6 cycles; due to progressive disease (11 pts), thrombocytopenia (3 pts), PS deterioration (1 pt) or pt decision (1 pt). Six pts (16%) had at least 1 dose deferral and 8 (21%) had dose reductions, all during first two cycles. Grade (G) 3/4 haematological toxicities were thrombocytopenia (16%), neutropenia (10%) and anaemia (5%), in 4 pts who received prior chemotherapy and 4 naive ($p = 0.433$). G2 non-haematological toxicities were nausea (5%) and diarrhoea (5%). **Conclusion:** CAPTEM is well-tolerated at full dose irrespective of prior chemotherapy, age or PS. A minority develop severe thrombocytopenia during the first 2 cycles. Pt survey data will be presented. **Keywords:** Capecitabine, Temozolomide, NET.

J17

Efficacy of the Combination of Capecitabine and Temozolomide in Patients with Advanced Pulmonary Carcinoid Tumours

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Introduction: Limited treatment options exist for patients (pts) with advanced pulmonary carcinoids (PC). Capecitabine-temozolomide (CAPTEM) has demonstrated significant efficacy in pts with pancreatic neuroendocrine tumours. However, its role in PC remains unexplored. **Aim(s):** The aim of this study was to examine the efficacy of CAPTEM in advanced PC. **Materials and Methods:** Pts were treated with capecitabine 750 mg/m^2 BD day1-14 and temozolomide 200 mg/m^2 OD day10-14 of a 4-week cycle up to maximum of 6 cycles. All pts were treated at the Christie NHS Hospital from 3/2014 to 11/2015. **Results:** 19 pts were included; 8 (42%) had typical and 11 (58%) atypical PC. Fourteen pts (74%) had ECOG performance status (PS) 0-1 and 5 (26%) PS 2. The number of involved organs was 1/2 in 8 pts (42%) and >2 in 11 (58%). The most frequent site of metastasis was the liver. Prior treatments included octreotide (10 pts, 53%), pasireotide (2 pts, 11%), chemotherapy (5 pts, 26%), interferon (2 pts, 11%) and everolimus (1pt, 5%). Five pts (26%) received CAPTEM as first line treatment and 8 (42%) as second line. Median number of cycles was 4. Seven pts (37%) completed 6 cycles. Among 17 assessable pts, 2 (12%) had partial response, 9 (53%) stable disease and 6 (35%) disease progression. After 8 months median follow-up, 11 pts progressed and 6 died. Median progression-free survival was 5 and overall survival 10 months. **Conclusion:** CAPTEM has moderate activity in PC. Predictive factors of efficacy could not be identified. **Keywords:** Pulmonary carcinoids, Capecitabine, Temozolomide.

J18

O6-Methylguanine DNA Methyltransferase (MGMT) Deficiency and Response to Aranoza-Based Therapy in Patients with Neuroendocrine Tumors

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Introduction: Aranoza (3-α-L-arabinopyranosyl-1-methylnitrosourea) – nitrosourea derivative, as STZ. O6-methylguanine DNA methyltransferase (MGMT) is an enzyme implicated in chemo-

therapy resistance to alkylating agents and its low levels are associated with sensitivity to them. **Aim(s):** To investigate the relationship between response to Aranoza-based therapy and MGMT expression. **Materials and Methods:** The MGMT expression was measured in 37 pts by immunohistochemistry using paraffin-embedded tissues. Tumors were scored as ''intact'' when the rate of positive cells was more than 10% with the intensity of staining 1+ and more. All consecutive pts with WD NETs treated with Aranoza alone or in combination with capecitabine, doxorubicin or temozolomide. Treatment efficacy was evaluated according to RECIST criteria v.1.0. The median PFS was calculated using Kaplan-Meier method. **Results:** In archival specimens, MGMT deficiency was observed in 17 of 19 pancreatic NETs (PNETs), 8 of 16 non-PNETs and 3 of 3 without primary. 12 of 27 pts with MGMT-deficient tumors (9 PNETs, 2 non-PNETs and 1 without primary) and 1 of 10 pts with tumors showing intact MGMT expression responded to treatment ($p = 0.06$). Pts with MGMT-deficient tumors had a median PFS of 16.5 months compared to 14.0 months for intact MGMT ($p = 0.17$). **Conclusion:** MGMT deficiency, measured by immunohistochemistry, is more common in PNETs than in non-PNETs ($p = 0.02$). Absence of MGMT expression may explain the sensitivity of some PNETs to treatment ($p = 0.06$). **Keywords:** Aranoza, MGMT, Chemotherapy, NETs.

J19

Oxaliplatin-Based Chemotherapy in Advanced Neuroendocrine Tumors: Clinical Outcomes and Preliminary Correlation with Biological Factors

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Introduction: The role of chemotherapy in low/intermediate grade neuroendocrine tumors (NETs) is still debated. **Aim(s):** To evaluate activity and toxicity of oxaliplatin-based chemotherapy in patients with advanced NETs in an Italian multicenter 'real world' retrospective study. **Materials and Methods:** Clinical records from 5 referral centers were reviewed. Disease control rate corresponding to PR+SD (partial response + stable disease), progression free survival (PFS), overall survival (OS) and toxicity were calculated. Ki67 labeling-index, grade of differentiation and excision-repair-cross-complementing group-1 (ERCC-1) were analyzed in tissue tumor samples. **Results:** 78 patients were included. Primary sites were: pancreas in 46%, gastrointestinal in 24%, lung in 19%, and unknown in 10% patients. The vast majority were G2. More than 80% patients were metastatic, pretreated and progressive to previous therapies. 65% received CAPOX, 6% GEMOX, 29% FOLFOX-6. Partial response occurred in 26% patients, half of them with pancreatic NETs, and SD in 54%. Responses were in both low/high-grade tumors, especially in pretreated patients. The median PFS and OS were 8 and 32 months respectively. The most frequent G3 toxicities were neurological and gastrointestinal. ERCC-1 immunohistochemical over-expression was positive in 4/28 evaluated sample. **Conclusion:** Oxaliplatin-based chemotherapy can be active with a manageable safety profile in advanced NETs irrespective of the primary sites and tumor grade, especially in pancreatic pretreated NETs. **Keywords:** Oxaliplatin, NETs.

J20

Temozolomide-Based Second-Line Chemotherapy in Patients with Advanced Bronchopulmonary Neuroendocrine Tumours

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Introduction: The management of advanced Bronchopulmonary Neuroendocrine Tumours (BP-NET) is not standardized. There are only few clinical studies of Temozolomide (TMZ) as monotherapy or in combination with other agents available for BP-NET. **Aim(s):** To evaluate the efficacy and safety of TMZ-based chemotherapy (CTX) in a cohort of patients (pts) with pre-treated advanced BP-NET. **Materials and Methods:** Twenty-five pts who underwent treatment with TMZ-based CTX at our institution for BP-NET, excluding small cell lung cancer, between 2010 and 2015 were included. The RECIST 1.1 objective response rates (ORRs) and toxicity following NCI-CTCv4 criteria were retrospectively assessed. **Results:** The median age at second-line treatment initiation was 63 years (range 41–83). Eleven pts (44%) had atypical carcinoid and 14 (56%) poorly differentiated neuroendocrine carcinoma. ORRs were 36% and disease control rate (PR+SD) was 48%. Median overall survival (mOS) was 10 mo (95% CI; 8.1–11.9), median progression free survival (mPFS) was 6 mo (95% CI; 1.0–11.1), while median time to progression (mTTP) was 3 mo (range 0–24). An exploratory responder (PR+SD) analysis showed that 7 (58%) pts experienced prolonged PFS (>12 mo) and 2 (17%) of them remained progression free after 2 years. Eight (67%) of responders had Ki67-index <55%. **Conclusion:** TMZ-based CTX is well tolerated and shows clinical activity in BP-NET with OR in 1/3 of pts. Our analysis suggest that BP-NET pts with Ki67-index <55% are most likely to respond to TMZ-based CTX. **Keywords:** Temozolomide, BP-NET, Ki-67 index.

Medical Treatment – SMS Analogues, Interferon

K1

Safety of High Doses Lanreotide Treatment in Patients with Progressive Neuroendocrine Tumors: Results from a Prospective Phase II Trial

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Introduction: Dose escalation (or interval reduction) of somatostatin analogs (SSAs) is a rather common strategy for patients (pts) with progressive metastatic neuroendocrine tumors (NETs). However, to date, no systematic prospective studies have been carried out to evaluate safety and efficacy of this treatment schedule in NETs. **Aim(s):** Evaluate high doses of lanreotide (LAN) in progressive (PD) NETs. **Materials and Methods:** A multicenter, prospective, open label, single arm phase II study with LAN ATG (180 mg/28 days for 12 months) has been completed in 35 pts with PD NET under standard maximal doses of SSAs. Primary endpoint was safety, while secondary was efficacy. **Results:** Here we present the results about primary endpoint. The planned recruitment of 35 pts was completed in November 2014. Mean age was 63 ± 11 years, 16% thoracic and 84% gastroenteropancreatic NET were enrolled and 49% were G2. Pts entered the study with radiological PD in 94% of cases. Nine serious adverse events (SAE) in 7 pts have been recorded, including 2 treatment-related (cholelithiasis and consequent cholecystitis were considered as 2 SAE, although concurrently occurred in the same case), with a SAE frequency rate of 21.8%. Statistical analysis for the verification of primary endpoint (binomial test with null hypothesis value at 65%) has shown that treatment with high dose lanreotide in NET is safe ($p < 0.0001$). **Conclusion:** The achievement of primary endpoint substantiates the treatment with LAN high doses in PD NETs. **Keywords:** High doses lanreotide safety. *Partially supported by industry.*

K2

Tumor Growth Rate (TGR) as an Indicator of Antitumor Activity with Lanreotide Autogel/ Depot (LAN) vs. Placebo (Pbo) in Intestinal/ Pancreatic NET: Post Hoc Analysis of CLARINET Data

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Introduction: TGR is a novel measure of tumor growth activity that may be more precise than RECIST for evaluating response to treatment of NETs. **Aim(s):** To evaluate TGR in patients from CLARINET study. **Materials and Methods:** Patients with metastatic intestinal/pancreatic NETs received LAN 120 mg or Pbo 4 wkly for 96 wks or until PD/death. TGR (% variation of tumor volume per month) was calculated from SLD of original target lesions (excluding new ones) on 2 CT scans during defined periods: 12 to 24 wks prior to randomization vs. baseline (pretreatment); and baseline vs. each visit or between consecutive visits. We analyzed changes in TGR during treatment, and relationship of TGR during different periods and PFS outcomes. **Results:** Mean (95% CI) pretreatment TGR was 4.1% (2.6, 5.6) and 3.3% (1.7, 4.8) in the LAN and Pbo groups ($p = 0.46$); and TGR at 12 wks' treatment was 1.2% (–0.4, 2.7) and 4.1% (2.6, 5.6) with LAN and Pbo, respectively ($p = 0.008$). This difference between groups was maintained throughout the treatment period. ROC analysis showed that pretreatment TGR≤/>4% was the best cut-off value for predicting risk of progression, independently of treatment; TGR >4% resulted in a 4-fold higher risk of progression than TGR ≤4% (HR 4.1; 95% CI 2.5, 6.5; $p < 0.001$). Regardless of pretreatment TGR, LAN was more effective than Pbo in delaying PD. **Conclusion:** TGR seems to be a more precise marker to assess NET response to therapy than RECIST, and has potential clinical utility as a novel parameter for tumor progression. Sponsored by Ipsen. **Keywords:** TGR, PFS.

K3

Dosimetry to Estimate the Effect of Gelofusine® on the Renal Absorbed Dose of Lutetium 177-DOTA-Octreotate

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Introduction: Lutetium-177 DOTA-octreotate (LuTate), a radiolabelled somatostatin analogue, delivers targeted radiation to neuroendocrine tumours and metastases. Healthy tissues also receive significant irradiation. Charged amino acids are routinely co-infused to block renal proximal tubular LuTate reabsorption. Gelofusine® (a succinylated bovine gelatin molecule), proposed to interact with the megalin/cubulin receptor-mediated transporter system, has been shown to reduce renal uptake of indium-111 octreotide. Routine Gelofusine® administration is limited by risk of allergic reaction. **Aim(s):** To utilise personalised dosimetry to assess renal radiation risk from LuTate therapy and the additional effect of Gelofusine® on renal absorbed dose of LuTate. **Materials and Methods:** Quantitative SPECT images are routinely acquired following the first therapy cycle to estimate accumulated radiation doses delivered to kidneys. Five patients demonstrated a higher than threshold renal radiation dose and received additional renal protection with Gelofusine® for future cycles of LuTate, with repeat dosimetry. **Results:** Gelofusine® administration resulted in a mean reduction in renal absorbed biologically effective dose of 34% (range 12%-51%), with standard deviation of 19%. **Conclusion:** While administration of Gelofusine® with LuTate therapy reduced renal absorbed radiation dose in all our patients, extent of reduction was quite variable. Further studies are required to understand the reasons for these variations. **Keywords:** Lutetium, Dosimetry, Renal, Gelatin, Somatostatin.

K4

Comparison of Somatostatin Analogue (SA) and Chemotherapy (CT) in Neuroendocrine Tumors (NET) Patients with Ki-67 ≤20%

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Introduction: SA and CT are the most important treatment options for grade (G) 1 and G2 NET patients. **Aim(s):** To compare SA and CT with progression-free survival (PFS), and to find patients group who are more effective of these treatments in NETs with Ki-67 index ≤20%. **Materials and Methods:** Patients who received SA or CT, were unresectabl and metastatic NETs with Ki-67 index ≤20%. These patients were selected from 13 centers between 2000-2014. The patients were evaluated retrospectively for factors effecting PFS by the Kaplan-Meire and Cox-Regression methods. **Results:** 165 patients were enrolled. The median duration of follow-up was 36 months. 59 (36%) had died during follow-up. The median age was 56 and male/female ratio 1.09. 74 (45%) patients were G1 and 91 (55%) were G2 NET. And also among these Ki-67 ≤20% cases, 89 patients (54%) were Ki-67 <5% and 78 (46%) were Ki-67 ≥5%. SA was given to 146 patients, 80 patients were treated with CT. Among these patients, both SA and CT were given to 61 patients. Response rate (RR) after SA was 16%; 71% had disease stabilization (SD) and RR after CT was 28%; 46% had SD ($p = 0.008$). The median PFS in patients receiving SA was 34 months and for patients receiving CT 8 months ($p < 0.001$). PFS of SA was longer than PFS of CT both the first-line and second-line in all Ki-67 values ($p < 0.001$). PFS was longer (51 months versus 20 months) when Ki-67 was <5% in receiving SA group ($p = 0.006$). **Conclusion:** SA may be preferred over chemotherapy in advanced NET patients with Ki-67 ≤20%. **Keywords:** Somatostatin analogue, NET, Ki-67.

K5

Merkel Cell Carcinoma of the Knee Treated with Somatostatin Analogue and Radiotherapy: A Case Report

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Introduction: Merkel cell carcinoma (MCC) is a rare and aggressive primary cutaneous neuroendocrine malignancy. Chemotherapy with cisplatin (CDDP) and etoposide (VP16) is an effective treatment for metastatic MCC. **Aim(s):** To describe a case of MCC located on the knee in advanced stage, not eligible for standard therapy with CDDP and VP16 and treated with somatostatin analogues plus radiotherapy (RT). **Materials and Methods:** A 76 year old man was referred to our center in March 2012 complaining a 8 cm symptomatic (painful and limitation of motion), vegetating and ulcerated lesion of the right knee. Biopsy of the lesion revealed MCC (ki 67 91%, CgA + NSE + CD 117 – TTF1 –); CT scan and Octreoscan showed lesion in the right knee and homolateral inguinal lymph-node metastases. Because of HCV+ cirrosis with thrombocytopenia (93.000/mm3), patient was ineligible to chemotherapy with CDDP and VP16, therefore he received somatostatin analogue plus RT. **Results:** Patient received Lanreotide 120 mg every 28 days and RT on the primary lesion (20 Gy) and on the right inguinal lymph-nodes (20 Gy). The following examinations showed regression till disappearance of the primary and secondary lesions after about 7 months with a complete response until today. **Conclusion:** In this case, somatostatin analogues plus RT have represented a valid alternative therapy for patients with MCC not suitable to chemotherapy. **Keywords:** Merkel cell carcinoma, Somatostatin analogues, Radiotherapy.

K6

Combination of Lanreotide Autogel and Temozolomide in Patients with Progressive Gastro-Entero-Pancreatic Neuroendocrine Tumours (GEP-NET) – A Pilot-Study

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Introduction: Therapeutic options for patients with advanced progressive GEP-NET are still limited. **Aim(s):** To evaluate the combination of Lanreotide and Temozolomide in progressive G1 or G2 GEP-NET. **Materials and Methods:** A total of 40 patients with advanced progressive G1 or G2 GEP-NET are to be treated with Lanreotide Autogel 120 mg + Temozolomide for 6 months (combination phase). In case of clinical benefit defined as complete or partial response (CR, PR) or stable disease (SD) after combination phase patients are randomized to either Lanreotide alone (maintenance phase) or observation without specific intervention. Disease control rate (CR, PR, SD) after 6 months of combination treatment is the primary endpoint. After 15 patients have been treated for at least 4 months safety assessment is prespecified and provided to Data Safety Monitoring Committee. **Results:** So far, 36 patients have received the combination therapy (cutoff date: Oct. 1st). Preliminary response data after 4 months of combination treatment (15 patients) showed no patients with disease progression, 9 patients with SD, 2 patients showed PR. Data of 4 patients not evaluable due to dropped out. 27 patients experienced an adverse event (AE) of grade 1 and 2, 11 patients developed AE of grade 3, one patient developed a serious related AE. **Conclusion:** These preliminary data suggest that the combination of Lanreotide and Temozolomide might be a potential treatment option for patients with progressive G1 or G2 GEP-NET.
Keywords: GEP-NET, Lanreotide, Temozolomide.

K7

Management of Controversial Gastroenteropancreatic (GEP) Neuroendocrine Tumour (NET) Clinical Situations (CS) with Somatostatin Analogues (SSAs): Results of a Delphi Questionnaire (Q) Panel from the NETPraxis Program

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Introduction: In NET CS where use of SSAs is controversial due to lack of evidence, clinical experience and expert opinion can help establish recommendations. **Aim(s):** The NETPraxis program aims to develop a common guidance for controversial CS with SSAs in clinical practice in Spain. **Materials and Methods:** 5 CS were defined with a common core (non-functioning NET, not susceptible of surgery/locoregional therapy, Ki67<10% [except CS5], ECOG ≤2), and tailored questions on the use of SSAs (CS1: enteropancreatic origin, nonprogressive <6 mo; observation or SSA? CS2: pancreatic origin; initial SSA, molecularly targeted therapy (MTT) or chemotherapy? CS3: GEP-NET progressing with SSA; maintain SSA? CS4: GEP-NET, negative octreoscan; initial SSA? CS5: GEP-NET, Ki67>10%, positive octreoscan; initial SSA?). Management of CS was discussed with Spanish oncologists, followed by a 48-item Delphi Q with a 9-point rating scale (9=full agreement; consensus >2/3 of responses in the same tertile). **Results:** 65 Qs were retrieved. Consensus was attained in 23 items (48%) and near consensus in 12. Experts agreed on CS1) use of SSA (89%); CS2) use of SSA either as monotherapy or in combination with MTT (94%); CS3) maintaining the SSA at the time of progression (85%); CS4) use of SSA in low-risk patients (72%); CS5) use of SSA in patients with comorbidities (86%). **Conclusion:** Experts agreed on the use of SSAs in different controversial NET CS. A second Delphi round is in progress to achieve a common guidance in 25/48 items; results to be presented.
Keywords: SSA, Delphi, NETpraxis.

K8

Safety and Efficacy of Pasireotide LAR (PAS) in Patients with Advanced Neuroendocrine Tumors (NET): Findings of a Phase I, Multi-Center, Open-Label, Dose-Escalation Study

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Introduction: PAS, a next generation SSA, is investigated to determine the maximum tolerated dose (MTD) in pts with advanced NET. **Aim(s):** This phase I dose escalation and expansion (DE/DX) study evaluated the MTD of PAS in patients with advanced NET. Results of a planned interim analysis are presented. **Materials and Methods:** Pts were enrolled in 2 phases: DE phase (to determine the MTD after minimum of 2 treatment cycles) at starting a dose of 80 mg PAS i.m. followed by a dose expansion phase. **Results:** As of July-2015, 29 pts (15, DE; 14, DX) were treated with 80 mg (13 pts) and 120 mg (16 pts) doses. No protocol defined dose-limiting toxicities were observed in the study; however in a post hoc analysis a higher incidence of bradycardia (<40 BPM) was seen with 120 mg (31.3%) vs. 80 mg (0%) in the DX phase. At data cut-off, 92.3% vs. 75% pts in 80 mg vs. 120 mg (median treatment duration, 6.7 mos vs. 10.1 mos) had discontinued treatment; primarily due to disease progression (44.8%) or adverse events (AEs; 27.6%). Disease control rate (CR+PR+SD) was 76.9% (95% CI [46.2, 95.0]) in 80 mg and 93.8% (69.8, 99.8) in 120 mg arm. The most common AEs in the 80 mg vs. 120 mg were hyperglycemia (76.9% vs. 81.3%), fatigue (53.8% vs. 50%) and nausea (53.8% vs. 31.3%). Grade 3/4 AEs suspected to be drug-related were seen in 15.4% of the pts for the 80 mg vs. 31.3% for the 120 mg dose. **Conclusion:** MTD was defined at 120 mg for PAS in pts with advanced NET. This study is ongoing; PK parameters are to be further investigated to gain insights into safety. **Keywords:** Pasireotide, MTD.

K9

Expression of Somatostatin Receptors in Gastroenteropancreatic Neuroendocrine Neoplasm and Multicenter Retrospective Clinical Study of Octreotide LAR in the Treatment of Advanced GEP-NET

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Introduction: Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are known to overexpress somatostatin receptors (SSTRs), which forms the basis for octreotide long-acting repeatable (LAR) treatment in NEN. **Aim(s):** To detect the expression of SSTR subtypes 2 and 5 in GEP-NEN and investigate the efficacy and safety of octreotide LAR in the treatment of well-differentiated advanced GEP-NET in China. **Materials and Methods:** We conducted a multicenter retrospective study including four centers from across China. SSTR2 and SSTR5 expression were examined in 165 specimens by immunohistochemistry. The clinical data of 54 patients who received octreotide LAR were analyzed. **Results:** The overall expression rates of SSTR2 and SSTR5 were 67.3% and 55.2%, respectively. SSTR2 and SSTR5 positive expression was much higher in pancreatic and well-differentiated tumors ($P < 0.05$), and predicted better survival ($P = 0.001$, $P = 0.009$). Among the 54 patients who received octreotide LAR, the median OS was not reached, the median TTP was 20.2 months, with the ORR being 1.9%, and the SD rate being 79.6%. Fifteen (27.8%) of the patients experienced adverse drug reactions, no one experienced a serious adverse event. **Conclusion:** SSTR2 and SSTR5 are highly expressed in GEP-NEN with different tumor sites and differentiation. Both could serve as prognostic factors. Octreotide LAR is effective in Chinese patients with well-differentiated advanced GEP-NET, with a low incidence of adverse reactions. **Keywords:** Gastroenteropancreatic neuroendocrine neoplasm, somatostatin receptor, octreotide, treatment.

Medical Treatment – Targeted Therapies

L1

Sequential Everolimus and Sunitinib Treatment in Pancreatic Metastatic Well-Differentiated Neuroendocrine Tumors Resistant to Prior Treatments

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Introduction: Alternating treatment with sunitinib and everolimus, has been shown to be efficacious in renal cell carcinoma. **Aim(s):** To determine the efficacy of the above alternate sequence therapy in well and moderate-differentiated pancreatic neuroendocrine tumors (pNENs). **Materials and Methods:** Thirty-one patients were administered one compound and upon progression were changed to the other. All patients had grade 1 or 2 tumors, stage IV disease with similar metastatic pattern and had been exposed to similar therapies. Progression-free survival (PFS), estimate overall survival (OS) and the development of adverse events (AEs) were the primary end points. **Results:** Median PFS after first line everolimus was longer (16.3 months) compared to sunitinib (9 months) but not statistically significant (p = 0.15). Upon progression, sequential second line treatment with both agents showed no difference in the PFS (15.5 months for everolimus vs. 10.3 months for sunitinib, p = 0.3). No difference in OS between the two groups was observed. Discontinuation of treatment because of serious adverse events was less frequent with everolimus either as a first (10%) or second line treatment (9%) compared to sunitinib (36% and 15% respectively). **Conclusion:** Sequential agents exhibited a clinical important PFS during the first and second challenge. Everolimus was associated with less AEs and seemed to exert a longer PFS either as first or second line treatment compared with sunitinib, albeit without statistical significance. **Keywords:** Everolimus, Sunitinib, Pancreatic NETs.

L2

Everolimus Cumulative Dose and Dose Intensity in Pancreatic Neuroendocrine Tumors

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Introduction: Everolimus represents a new treatment option for advanced pancreatic neuroendocrine tumors (pNETs). **Aim(s):** The aim of this work is to assess if cumulative dose and dose intensity of everolimus may affect survival of advanced pNETs patients (pts). **Materials and Methods:** 111 pts (M/F = 62/49, median age 54 years) were treated with everolimus for ≥3 months. Cumulative dose (CD) was defined as the total amount of everolimus taken by the pts despite delay or dose reductions; Dose Intensity (DI) was defined as everolimus dose delivered per time unit (mg/day) taken by the pts in a given period of time. According to a ROC analysis, pts were stratified into two groups, with CD <1500 mg (Group A) and CD ≥1500 mg (Group B). **Results:** Response rate and toxicity were comparable in the two groups. However, pts in group A experienced more dose modifications than pts in group B. Median OS was 14 months in Group A (range 4–22 months), whilst in Group B it was not reached (HR: 26.9;95% CI: 4.0–176.7;p = 0.0006). Furthermore, analysis of data showed that pts who maintained a DI higher than 9 mg/day experienced a significantly longer OS and experienced a trend to higher response rate. **Conclusion:** Overall present data seem to suggest that CD and DI potentially play a prognostic role for pts with advanced PNETs treated with everolimus. This should prompt efforts to continue everolimus administration in responsive pts up to at least 1500 mg despite delays or temporary interruptions. **Keywords:** PNET, Dose intensity, Targeted therapy, Everolimus, Cumulative dose.

L3

Netazepide, a Gastrin/CCK2 Receptor Antagonist, Can Eradicate Gastric Neuroendocrine Tumours in Patients with Autoimmune Chronic Atrophic Gastritis

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Introduction: In a two-centre, 12-week, open trial in 16 patients with chronic atrophic gastritis, hypergastrinaemia, multiple gastric NETs, and raised circulating CgA, the gastrin/CCK2 receptor antagonist, netazepide, reduced the tumour number and size, and normalised CgA. **Aim(s):** To treat those patients with netazepide for longer, and to identify new biomarkers. **Materials and Methods:** After mean 14 months off netazepide, 13 patients took it for another 52 weeks. Assessments: gastroscopy; gene transcript expression in corpus biopsies and gastrin-treated CCK2R expressing gastric epithelial (AGSGR) cells in vitro using microarrays and qPCR; and blood CgA and gastrin ($p < 0.01$). **Results:** While off treatment, the number and size of tumours, and CgA all increased again. Netazepide for 52 weeks eradicated all tumours in 5 patients and reduced further the number and size of tumours in the others, and normalised CgA. Gastrin was unaffected. Netazepide was safe and well tolerated. Netazepide reduced mRNA abundances of CgA, histidine decarboxylase, pappalysin 2 (PAPPA2) and glycoprotein hormones alpha polypeptide in biopsies. Gastrin increased PAPPA2 expression in AGSGR cells, and PAPPA2 siRNA reversed the gastrin-induced cellular responses. **Conclusion:** A gastrin/CCK2 receptor antagonist is a potential medical and targeted treatment for gastric NETs type 1, and an alternative to endoscopic resection or surgery. Treatment can be monitored by CgA in blood or biomarkers in biopsies. A multicentre placebo-controlled trial is justified. **Keywords:** Netazepide.

L4

The Proteasome Inhibitor Bortezomib Is a Highly Effective Treatment Option for Gastroenteropancreatic Neuroendocrine Neoplasms and Sensitizes to DNA Damaging Therapy in vitro

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Introduction: Gastroenteropancreatic neuroendocrine neoplasms are fairly rare tumors with very heterogeneous behavior and molecular characteristics. Their generally slow proliferation render them virtually resistant to many DNA damaging therapeutic approaches. Bortezomib has been shown to be effective in GEP-NENs in vitro but has been withdrawn from clinical assessment due to a small phase II study on bortezomib monotherapy in 2004. **Aim(s):** The molecular and cell biological mechanisms of bortezomib activity was studied in vitro to assess the chemosensitizing effect in GEP-NENs. **Materials and Methods:** GEP-NEN cell lines of pancreatic and gastrointestinal offspring were treated with bortezomib, cisplatin or a combination of both treatments. The efficacy and molecular effects were studied by proliferation analyses, western blot, flow cytometry, HTCA and multiplexed gene expression analysis (Nanostring technologies). **Results:** Bortezomib was highly effective in 3/4 cell lines and synergistically sensitized to DNA damaging therapy. The clonogenic potential was strongly reduced by Bortezomib. It further suppressed the DNA damage response that was induced by cisplatin alone. Here, it induced G2/M arrest and extrinsic apoptotic signaling. **Conclusion:** Bortezomib has been shown to prevent DNA repair mechanism and induces DNA damaging stress and apoptosis in GEP-NENs in vitro. This effect should be further assessed for radiosensitizing approaches where it might have the potential to be combined with PRRT. **Keywords:** GEP-NEN, Targeted therapy, DNA repair, Chemotherapy.

L5

The CDK4/6 Inhibitor Palbociclib Induces Anti-Proliferative Mechanisms in Gastroenteropancreatic Neuroendocrine Neoplasms in vitro

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Introduction: Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are rare tumors with heterogeneous molecular backgrounds and mostly unknown druggable driver mutations.

Especially for the midgut NENs effective treatment options are limited. The retinoblastoma pathway is often inactive due to CDK4/6 overexpression in pancreatic NENs. Palbociclib is a FDA approved (ER-positive and HER2-negative breast cancer) cyclin-dependent kinases 4 and 6 inhibitor and might impair cell cycle progression and proliferation. **Aim(s):** The molecular and cell biological mechanisms of palbociclib were analyzed to assess the anti-proliferative therapeutic potential in GEP-NENs in vitro. **Materials and Methods:** GEP-NEN cell lines of pancreatic and gastrointestinal offspring (BON, QGP-1, KRJ-I, LCC-18) were treated with palbociclib (kindly provided by Pfizer Inc.) and analyzed by western blotting, flow cytometry and proliferation assay. **Results:** In this preliminary study we could show that palbociclib reduced the cellular proliferation of all tested cell lines. The cell cycle was arrested in G0/G1 Phase with a strong reduction of cell populations in the synthesis or mitotic phase. BON, KRJ-I and LCC-18 cells further induced apoptosis. These effects were associated with typical G0/G1 arrest protein expression/modification changes such as decrease of Rb phosphorylation and E2F1 expression. **Conclusion:** Palbociclib has therapeutic potential in GEP-NEN cells in vitro and should be further preclinically assessed. **Keywords:** GEP-NEN, targeted therapy, cyclin-dependent kinases 4/6.

L6

Impact of Prior Somatostatin Analogue (SSA) Use on Progression-Free Survival (PFS) in Patients with Advanced Nonfunctional Neuroendocrine Tumors (NET) of Lung or Gastrointestinal (GI) Origin: A Secondary Analysis from the RADIANT-4 Study

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Introduction: In the RADIANT-4 study, everolimus (EVE) reduced the risk of disease progression or death by 52% vs. placebo (PBO; $P < 0.00001$) in patients (pts) with advanced, well-differentiated, progressive, nonfunctional NET of lung/GI tract. **Aim(s):** To assess the impact of prior SSA on PFS in the RADIANT-4 study. **Materials and Methods:** Pts were randomized (2:1) to receive EVE 10 mg/day or PBO. This analysis reports baseline characteristics, PFS, and safety by prior SSA use. **Results:** Of 302 pts randomized, 163 (54%) had any prior SSA use (mostly for tumor control; EVE vs. PBO: 53% vs. 56%). Baseline characteristics were similar in pts with or without prior SSA. Primary tumor sites in prior SSA group: GI (65%), Lung (23%), and NET of unknown primary (12%). Pts received ≥1 type of SSA, which included octreotide LAR (77%), octreotide SC (14%), lanreotide (14%). Median duration of exposure to prior SSA was 15 mo (range, <0.1–103.5). Median PFS (central review; EVE vs. PBO) in prior SSA group was 11.1 (95% CI, 9.2–13.3) mo vs. 4.5 (3.6–7.9) mo (HR 0.56; 95% CI, 0.37–0.85); in SSA naïve pts, 9.5 (8.2–16.7) mo vs. 3.7 (2.4–8.1) mo (HR 0.57; 95% CI, 0.36–0.89). The most common drug-related adverse events (AEs) in EVE arm (prior SSA vs. SSA naive) included stomatitis (60% vs. 50%), diarrhea (34% vs. 28%), and peripheral edema (28% vs. 23%). **Conclusion:** EVE improves PFS in pts with advanced, progressive, nonfunctional NET of lung/GI tract regardless of prior SSA use. AEs were manageable and consistent with the overall population. **Keywords:** Everolimus, SSA, Nonfunctional NET.

L7

Everolimus (EVE) Safety Profile in Patients (pts) with Advanced G1-G2 Neuroendocrine Tumours (NETs) from Daily Clinical Practice

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Introduction: EVE has shown an overall favourable and well-characterized safety profile in randomized studies including advanced G1-G2 NETs. However, few data outside regulatory trials are available. **Aim(s):** Evaluation of EVE tolerability according to prior therapies for pts with advanced NETs in the community setting. **Materials and Methods:** Retrospective analysis on pts with advanced G1-G2 NETs treated with EVE in 10 Spanish University hospitals between June-2009 and June-2015. **Results:** We evaluated 124 pts, 52.4% with pancreatic and 47.6% with non-pancreatic NETs. Previous therapies included somatostatin analogs (71%), angiogenesis inhibitors

(33.1%), chemotherapy (27.4%) and others (8.1%). A total of 119 (95.9%) pts experienced EVE-related adverse events (AEs), which were grade (gr) 3-4 in 38 (30.6%) pts. Most common AEs of any gr included stomatitis (67.7%), hyperglycemia (67.7%), asthenia (56.4%), diarrhea (54%) and pneumonitis (23.4%). Most frequent gr 3-4 toxicities were hyperglycemia (7.3%), pneumonitis (5.7%), stomatitis (4.8%) and diarrhea (4.8%). No significant differences in any gr or gr 3-4 AEs were found in relation to prior therapies. Fifty-one (41.1%) pts required temporary EVE discontinuation due to toxicity and 38 (30.6%) dose reductions. EVE-related AEs led to definitive treatment discontinuation in 8.8% pts. **Conclusion:** Our findings in NET patients from clinical practice are consistent with EVE known safety profile and most AEs were gr 1-2. EVE tolerability is not influenced by previous therapies. **Keywords:** Everolimus, Tolerability.

L8

Everolimus (EVE) Treatment for Advanced G1-G2 Neuroendocrine Tumours (NETs) in the Community Setting: Clinical Benefit Irrespective of Previous Therapies

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Introduction: Randomized studies have shown EVE has antitumour activity in advanced G1-G2 NETs. However, data outside regulatory trials are limited. **Aim(s):** To assess EVE efficacy according to prior therapies in patients (pts) with advanced NETs from daily clinical practice. **Materials and Methods:** Retrospective analysis on pts with advanced G1-G2 NETs treated with EVE in 10 Spanish University hospitals between June-2009 and June-2015. **Results:** We evaluated 124 pts (61.3% males) with median age of 60 years (20-84). Most common primary sites were pancreas (52.4%), small intestine (22.6%) and lung (14.5%). Twenty-three (18.5%) pts were treated with EVE in first line, 53 (42.7%) in second line and 48 (38.7%) in third and successive lines. Previous treatments included somatostatin analogs (SSAs) (71%), angiogenesis inhibitors (AI) (33.1%), chemotherapy (CT) (27.4%) and others (8.1%). Objective response was reported in 15.3% and stable disease in 72.6% pts. Median progression-free survival (PFS) was 14.2 months (ms) (95% CI, 9.9–18.1) and median overall survival 42.3 ms (95% CI, 36.6–47.9). Median PFS was significantly better for pts treated in first line (27.1 ms; 95% CI, 7.8–48.2) than for those treated in second (19 ms; 95% CI, 13.4–24.6) or third and successive lines (10 ms; 95% CI, 5.4–14.6) ($p = 0.008$). No significant differences were found in relation to prior treatment with SSAs, AI or CT. **Conclusion:** EVE is an effective treatment for NET patients from daily clinical practice irrespective of previous therapies. **Keywords:** Everolimus, Previous therapies.

L9

Retrospective Review of Single Centre's Experience of the Side Effects Reported by Patients Receiving Everolimus and the Potential Implications Relating to Patient Monitoring and Education

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Introduction: Everolimus, an mTOR inhibitor, is a recommended therapy for patients with pancreatic neuroendocrine tumours. It has recognised toxicity profile. **Aim(s):** To identify side-effects reported in clinic which would guide both patient management and teaching. **Materials and Methods:** A retrospective review of patients receiving Everolimus between 2011 to 2015. **Results:** 25 patients were identified treated with Everolimus, all pancreatic NETs. Period of treatment 11 days to 2.3 years. The following side effects were reported: Stomatitis 68%, Fatigue 64%, Rash 36%, Diarrhoea 36%, Nausea 32%, PPS 32%, pneumonitis 28%, hyperglycaemia 28%, high cholesterol 12%, taste changes 12%, low mood 12%, epistaxis 4%, thrombocytopenia 4%, low phosphate 4%. Toxicities were reported by patients as early as two weeks from commencement to over two years. 79% of side effects occurred within the first month and 94% of stomatitis occurred in the first 6 weeks. Some side effects appear to be interrelated as all patients who reported low mood also experienced stomatitis and fatigue. Taste changes were reported by three of the patients who experienced stomatitis. **Conclusion:** The review highlights that the monitoring of patients regularly within the first six weeks could potentially have the greatest impact in helping to manage toxicities. Ongoing assessment of those patients taking Everolimus is essential alongside continuing engagement and education of them as side effects may occur throughout the treatment pathway. **Keywords:** Everolimus, Patient education, Side effects.

L10

The Efficiency of Sunitinib in Chinese Patients with Advanced Well-Differentiated Pancreatic Neuroendocrine Tumor

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Introduction: Systemic therapies for advanced Pancreatic neuroendocrine tumors (pNETs) are various. Sunitinib has shown its efficiency in pNET in clinical trials. While the efficiency of sunitinib in Chinese pNETs has not reported yet. **Aim(s):** To describe clinical outcomes of Chinese advanced pNETs patients (pts) treating with sunitinb, and compare the efficiency of sunitinb in first-line therapy and post-second line therapy in pNETs. **Materials and Methods:** Advanced pNET pts who accepted sunitinib treatment after disease progression were collected from April 2009 to May 2015. pts received sunitinib 37.5 mg/day or 25 mg/d if intolerable, on a continuous daily dosing schedule. Data examined included clinicopathological characteristics and outcomes. **Results:** Eighteen pNET pts were collected. Nine pts received sunitinib as the first-line therapy and 9 in the post-second line. mPFS is 12 month for both line therapy. The 1y-PFS%, ORR and DCR of first-line therapy and post-second line therapy are 44.4%, 22.2%, 88.9% and 43.7%, 33.3%, 77.8%, respectively; there is no difference between two groups. Commonly reported treatment associated any grade adverse events included diarrhea (8/15), proteinuria (8/15), hypertension (5/15) and rash (6/15). Four death due to disease progression and the mOS is not reached. **Conclusion:** First-line or post-second line Sunitinib in Chinese advanced progressive pNETs showed similar antitumor activity. And commonly reported adverse events were consistent with the known safety of sunitinib. **Keywords:** Sunitinib, Chinese, pNET, Efficiency.

L11

Efficacy of Lutetium-177 DOTA Octreotate Peptide Receptor Radionuclide Therapy in Patients with Advanced Neuroendocrine Tumours and Carcinoid Syndrome Refractory to Somatostatin Analogues

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Introduction: Somatostatin Analogues (SSAs) are considered the gold standard treatment in Neuroendocrine Tumours (NETs) and carcinoid syndrome. **Aim(s):** To assess the effect of Peptide Receptor Radionuclide Therapy (PRRT) on refractory carcinoid syndrome. **Materials and Methods:** A retrospective analysis included 35 patients with advanced NETs and refractory carcinoid syndrome despite maximum doses of SSAs, who had Lutetium177 DOTA Octreotate PRRT. Pre- and post-PRRT assessment of flushing, bowel frequency and 24 h urine 5-Hydroxyindoleacetic Acid (5-HIAA) was performed. **Results:** 26 patients had midgut, 4 pancreatic, 1 bronchial and 4 NETs of unknown primary. All 35 patients had refractory flushing; 22(62.8%) had significant improvement post treatment. In 2 the response was non-significant, 7 did not notice any change and one reported deterioration. Increased bowel frequency pre-treatment was noted in 17 in whom complete data was available; 12/17 (70.5%) reported significant reduction in bowel frequency with an average from 4.2 to 1.5 times per day. 2/17 had moderate reduction and in 3/17 it was non-significant. Data on 5-HIAA was available in 7 patients; in one and 2 patients 5-HIAA decreased significantly and moderately respectively, in one the fall was non-significant and in 3 it increased despite symptomatic improvement. **Conclusion:** In refractory carcinoid syndrome, PRRT seems very beneficial for symptom control. Prospective studies and comparison to new agents such as Telotristat Etiprate are needed. **Keywords:** PRRT, Carcinoid syndrome.

L12

Efficacy of Peptide Receptor Radionuclide Therapy in Patients with Advanced Bronchial Neuroendocrine Tumours

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Introduction: There is not established treatment pathway in advanced bronchial neuroendocrine tumours (bNETs). **Aim(s):** To assess efficacy of Peptide Receptor Radionuclide Therapy (PRRT) on bNETs. **Materials and Methods:** A retrospective analysis included 22 patients with bNETs, progressing despite previous treatment, who received PRRT. Symptomatic improvement, biochemical improvement [>50% decrease in Chromogranin A levels], time to disease progression (TTP) and renal and bone marrow toxicity (WHO criteria) were assessed. **Results:** 10 had a typical bronchial NET and 12 atypical; 14 had Yttrium 90 and 8 Lutetium 177 DOTATATE. Before PRRT, 12/22 patients had their primary resected,15/22 had platinum-based chemotherapy and 14/22 were on Somatostatin analogues (SSAs). Symptomatic improvement was noted in 10/12 patients (83.3%) who had respiratory and/or carcinoid syndrome symptoms. Biochemical improvement was noted in only 28%. Mean TTP was 14.1 months; 2/22 had no evidence of disease progression (median follow up was 66 months). Three patients had grade (G) 1 WHO bone marrow toxicity, two had WHO G2 and one WHO G3 and none had renal toxicity. For overall survival data was available in 14 patients; 6/14 are still alive (median follow-up 39.5 months) and 8 deceased with a mean survival of 26 months. **Conclusion:** PRRT appears beneficial for symptoms' control and temporary control of tumour growth in progressive bNETs despite other systemic treatments. Randomized trials are needed to identify further its efficacy in comparison to molecular targeted agents. **Keywords:** PRRT, Bronchial NETs.

L13

Is mTOR Pathway Activity a Good Predictor for Everolimus Therapy? A Pilot Study to Build Up a Phase II Trial in Pancreatic Neuroendocrine Neoplasias (pNENs)

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Introduction: Everolimus (EVE) is an approved treatment for progressive well-differentiated pNENs and usually induces stable disease. Until now, there is no reliable biomarker for the response to EVE. **Aim(s):** To study mTOR pathway activation as a new discriminator for EVE therapy. **Materials and Methods:** FFPE tumor material of 60 pNEN patients from 4 centers was macrodissected and RNA was extracted. Upregulation of 12 mTOR pathway signaling members was studied by TaqMan based RT-qPCR assays. Relative gene expression was determined according to the 40-DCT method using CALM2 as housekeeping gene. **Results:** Members of the mTOR pathway displayed a broad dynamic range of mRNA expression. mTOR levels ranged from 31,7 to 39,6 resembling an up to 250 fold difference in relative target gene expression and a median expression level of 37,7. MTOR expression correlated positively with AKT1 mRNA expression, but not with negative signaling members such as IGFBP3. Cluster analysis revealed tumor subtypes with very low mTOR pathway expression (47.5% of tumors) and upregulated mTOR pathway activity, while the latter exhibited either intact repression of IGFBP3 (21.7% of tumors) or dysregulated IGFBP3 expression (29.5% of tumors). **Conclusion:** Preliminary results indicate that a significant number of pNENs have impaired or downregulated mTOR pathway mediators. As a next step, a phase II clinical trial confining EVE treatment to patients with an activated mTOR pathway is planned. **Keywords:** Predict-study, Everolimus, pNEN, Gene signature, Predictive marker.

L14

Early Evaluation of Sunitinib in Treatment of Advanced Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NENs) by CT Imaging: RECIST or Choi Criteria?

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Introduction: There is no study to assess RECIST and Choi criteria in evaluating response of advanced GEP-NENs treated with sunitinb. **Aim(s):** To assess and compare Response Evaluation Criteria in Solid Tumors (RECIST) and Choi criteria in evaluating early response of advanced GEP-NENs treated with sunitinib. **Materials and Methods:** Eighteen patients with pathologically proven advanced GEP-NENs treated with sunitinib were enrolled in the study. Pre- and post-treatment enhanced CT scans were performed on all patients. Changes in target tumor size and density from pre-treatment to 1.4-3.0 months after treatment were measured and recorded for each patient. Tumor responses were identified by RECIST and Choi criteria. Time to tumor progression (TTP) for each patient was measured and compared between groups by Kaplan-Meier method. **Results:** Among the 18 patients, 4 (22%) exhibited a partial response (PR), 9 (50%) had stable disease (SD), and 5 (28%) experienced progressive disease (PD) according to RECIST. Based on Choi criteria, 8 (44%) patients exhibited PR, 4 (22%) had SD, and 6 (33%) experienced PD. By RECIST, TTP of PR group was significantly longer than that of PD group ($P = 0.007$), but not SD group ($P = 0.131$). By Choi criteria, TTP of PR group was significantly longer than SD group ($P = 0.026$) and PD group ($P < 0.001$). **Conclusion:** Choi criteria appear to be more precise than RECIST in assessing early response of advanced GEP-NENs treated with sunitinib. **Keywords:** Gastroenteropancreatic neuroendocrine neoplasm, Sunitinib, Time to progression, Computed tomography.

L15

Everolimus (EV) Plus Somatostatin Analog (SSA) Administered before or after Chemotherapy (CT) or PRRT in Advanced G1-G2 Neuroendocrine Tumor (NET): A Single Center Experience

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Introduction: In metastatic NET G1-G2 progressed after SSA, many treatment are appropriated including EV, CT and PRRT. However, there are no studies guiding the appropriate sequence of treatments. **Aim(s):** We evaluate our experience to compare EV plus SSA treatment administered before or after CT or PRRT, to evaluate differences in the sequences. **Materials and Methods:** 39 patients (pts) with G1-2 NET progressed after SSA were treated with EV 10 mg orally daily combined with octreotide LAR 30 mg every 28 days or with CT (included fluoropyrimidines, temozolamide, oxaliplatine based on phisician decision) or with PRRT untill progression or unexaptable toxicities in different sequences: 20 pts received EV + SSA upfront and then CT, 11 received CT and then EVE + SSA, 8 received PRRT, CT and then EVE + SSA Mean age was 59 years (28–78), there were 24 male,15 female. Primary tumor originated from pancreas (20 pts), gastrointestinal tract (11 pts), lung (4 pts) and was unknown in 4 pts. **Results:** In the group of 20 pts that received EV + SSA upfront 7 pts are still in treatment without progression and didn't received CT or PRRT yet. Median PFS of EV + SSA treatment was 20, 53 months in pts treated with EV+SSA upfront, 7, 35 months in pts treated with CT before EV + SSA, 9.2 in pts treated even with PRRT before EV+SSA (p value = 0.0014). Median PFS of all sequence treatment was 63,0. **Conclusion:** In metastatic NET

G1-G2 progressed after SSA, EV+SSA has a significant longer PFS when used upfront before CT or PRRT, may giving a more efficient sequence. **Keywords:** Everolimus SSA.

L16

Long Term Renal and Haematological Side Effects in NET Patients Treated with Lu-177-DOTATATE

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Introduction: Long term renal and bone marrow side effects may be a problem after PRRT. **Aim(s):** Evaluation of kidney and BM dosimetry, and other risk parameters in predicting long term side effects. **Materials and Methods:** 83 NET-patients initiating Lu-177-DOTATATE therapy (2–4 cycles of 7.4 GBq) were included. Kidney function was monitored by GFR measurements. Kidney dosimetry, based on SPECT/CT was performed after every cycle. BM dosimetry was based on time-activity curves. **Results:** GFR decreased at a yearly rate of 4.8 ml/min ($p < 0.001$) after PRRT. Cumulated mean (range) absorbed kidney dose was 15 (2–34) Gy. No correlation between kidney dose and GFR change was found. Neither high age, low baseline GFR nor clinical renal risk factors (hypertension/diabetes/previous PRRT/chemotherapy) was predictive of renal deterioration. B-hemoglobin (Hb), -white blood cells and -platelets (PLT) decreased during PRRT treatment ($p < 0.001$). Hb and PLT remained decreased during 3-9 months follow up ($p < 0.001$). BM absorbed dose was 0.5 (0.1–1.1) Gy. High BM dose was associated with a more severe decrease in PLT ($p = 0.01$). Older patients decreased more extensively in Hb and PLT after PRRT compared to younger patients ($p < 0.05$). Neither previous PRRT/chemotherapy nor bone metastases did predict the degree of BM affection. **Conclusion:** Bone marrow dosimetry predicts to a limited degree the severity of bone marrow affection after PRRT. Neither kidney dosimetry nor clinical risk factors predict the degree of GFR decrease. **Keywords:** PRRT, Dosimetry.

L17

Everolimus in Pancreatic Neuroendocrine Carcinomas G3

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Introduction: Neuroendocrine Carcinomas (NEC) G3 are heterogeneous diseases with different behaviors, basing on tumor morphology and Ki67 value. Platinum-based chemotherapy is considered the standard treatment in these pts. However, tumors with well-moderately differentiated morphology (NET G3), with Ki67 <55% may be considered a separate entity in terms of prognosis and therapeutic options. **Aim(s):** To investigate everolimus efficacy in pancreatic NET (pNET) G3. **Materials and Methods:** Retrospective analysis of pts with pNET G3 and Ki67 20–55% treated with everolimus. **Results:** 15 pts with stage IV pNET G3 (median age 55 yr), median Ki67 30% (range 22–55%) and ECOG PS 0-1 were evaluated. Of these, 4 pts received everolimus as first line treatment, whereas 11 had been pre-treated with chemotherapy (7 pts) or PRRT (4 pts). Everolimus was given in combination with somatostatin analogs in 14/15 pts. Median PFS was 6 months, and median OS was 28 months. 11 pts acheived disease stabilization (SD) at 3 months f-up. 6 pts (40%) maintained SD for at least 12 months. 3 out of 4 pts who received everolimus as first line therapy had sustained SD (PFS: 12, 17, and 22 months). Safety profile was consistent with those reported by RCTs, adverse events occurring in 9 pts (66.7%) (grade 3-4 in 4 pts, 26.7%). **Conclusion:** This study suggests that everolimus is active in pancreatic NEC G3 with well/moderately differentiated morphology and Ki67<55%, in which more toxic platinum based therapy is, to date, the only available treatment. **Keywords:** Neuroendocrine carcinoma, Everolimus.

L18

Impact of Prior Chemotherapy (Chemo) on Progression-Free Survival (PFS) in Patients (Pts) with Advanced, Nonfunctional Lung or Gastrointestinal (GI) Neuroendocrine Tumors (NET): A Secondary Analysis from the Phase 3 RADIANT-4 Study

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Introduction: In the phase 3 RADIANT-4 study, everolimus (EVE) improved PFS by 7.1 months (mo) compared to placebo (PBO; $P < 0.00001$) in pts with advanced, progressive, nonfunctional NET of lung or GI tract. **Aim(s):** To evaluate impact of prior chemo use on PFS in RADIANT-4. **Materials and Methods:** In RADIANT-4, pts were randomized (2:1) to EVE 10 mg/d or PBO, both with best supportive care. A subgroup analysis of the RADIANT-4 study by prior chemo use is presented. **Results:** Of 302 pts, 77 (25%) had received chemo (EVE, n = 54 & PBO, n = 23) and 225 (75%) were chemo-naïve (EVE, n = 151 & PBO, n = 74) prior to study entry. Baseline characteristics were comparable between subgroups. Primary tumor sites (prior chemo vs. chemo-naïve): Lung (49% vs. 23%), GI (38% vs. 65%), NET of unknown primary (13% vs. 12%). Median PFS (95% CI) in prior chemo group (EVE vs. PBO) was 9.2 (5.6–11.7) mo vs. 2.1 (1.9–3.7) mo (HR 0.35; 95% CI 0.19–0.64). In chemo-naïve group (EVE vs. PBO), median PFS (95% CI) was 11.2 (9.2–16.6) mo vs. 5.4 (3.7–9.0) mo (HR 0.60; 95% CI 0.42–0.86). Most frequent drug-related G3/4 AEs (EVE vs. PBO) in prior chemo group: stomatitis (9% vs. 0), anemia (8% vs. 4%) & diarrhea (6% vs. 0); chemo-naïve group: diarrhea (8% vs. 3%) & stomatitis (7% vs. 0). **Conclusion:** EVE improved PFS in pts with advanced, well-differentiated, progressive, nonfunctional NET of lung or GI origin irrespective of prior chemo use. EVE safety profile was similar to overall RADIANT-4 population. **Keywords:** Everolimus, Nonfunctional NET, Prior chemotherapy.

L19

Sunitinib (SU) in Patients with Advanced, Progressive Pancreatic Neuroendocrine Tumors (pNET): Final Overall Survival (OS) Results from a Phase III Randomized Study Including Adjustment for Crossover

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Introduction: This pivotal, Phase 3, double-blind study of SU in patients (pts) with advanced, progressive pNETs met its primary endpoint with median progression-free survival of 11.4 months (mo) for SU vs. 5.5 mo for placebo (PBO; HR = 0.42; 95% CI 0.26–0.66; $p < 0.001$). OS difference favored SU (HR = 0.41; 95% CI 0.19–0.89; $p = 0.02$). At 2 years after study closure, median OS was 33.0 mo for SU vs. 26.7 mo for PBO (HR = 0.71; 95% CI 0.47–1.09; $p = 0.115$). **Aim(s):** To report final OS at 5 years follow-up since study closure. **Materials and Methods:** Pts were randomly assigned (1:1) to SU 37.5 mg/d (n = 86) or PBO (n = 85). Pts receiving PBO could crossover to SU at disease progression or study closure. OS was analyzed using the Kaplan-Meier method and Cox proportional hazards model in the intent-to-treat population. Also, OS data were analyzed using 3 different methods to adjust for the crossover effect. **Results:** At 5 years follow-up, median OS was 38.6 mo for SU vs. 29.1 mo for PBO (HR = 0.73, 95% CI 0.50–1.06; $p = 0.094$) with 59 (69%) pts randomized to PBO crossed over to SU. After censoring PBO-arm data at crossover, median OS was 16.3 mo for PBO (HR = 0.40; 95% CI 0.23–0.71). The time-dependent Cox model yielded HR = 0.46 (95% CI 0.27–0.78). Using the rank-preserving structural failure time model, median OS was 13.2 mo for PBO (HR = 0.34; 95% CI 0.14–1.28). **Conclusion:** The 5-year OS difference (9.5 mo) between SU and PBO is confirmed. Correction for crossover yielded a stronger OS advantage with SU, confirming that crossover likely confounded the OS results. **Keywords:** Sutent, OS.

L20

Everolimus for Advanced, Progressive, Nonfunctional Neuroendocrine Tumors (NET) of the Gastrointestinal (GI) Tract: Efficacy and Safety from a RADIANT-4 Subgroup Analysis

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Introduction: Everolimus (EVE) demonstrated progression-free survival (PFS) benefit of 7.1 months compared to placebo in the phase 3 RADIANT-4 study in patients (pts) with advanced, well-differentiated, progressive, nonfunctional NET. **Aim(s):** To evaluate the efficacy and safety of EVE in GI NET subset of RADIANT-4. **Materials and Methods:** In RADIANT-4, pts were randomized (2:1) to EVE (10 mg/d) or PBO. The present analysis included pts with GI NET (stomach, colon, rectum, appendix, caecum, ileum, duodenum, jejunum, or small intestine). **Results:** Of 302 pts, 175 had GI NET (EVE [n = 118], PBO [n = 57]). Median age was 63 y; females: 55%; G1/G2: 75%/25%; WHO PS0/PS1: 78% or 22%; Caucasian: 73%. Ileum (41%), rectum (23%) and jejunum (13%) were the most common locations. Prior therapies (EVE vs. PBO) included: surgery (70% vs. 84%), somatostatin analogues (59% vs. 63%), and chemotherapy (19% vs. 12%). Median PFS (95% CI) by central review (EVE vs. PBO) was 13.1 (9.2–17.3) mo vs. 5.4 (3.6–9.3) mo with an estimated 44% risk-reduction in favor of EVE (HR, 0.56; 95% CI, 0.37–0.84). The most frequent G3/4 adverse events irrespective of drug-relationship reported in ≥5% pts (EVE vs. PBO) included diarrhea, hypertension, and stomatitis. **Conclusion:** EVE demonstrated improvement in PFS for pts with GI NET with an estimated 44% reduction of risk in disease progression or death in favor of EVE vs. PBO. Safety profile for EVE was consistent with that previously reported. **Keywords:** Everolimus, progression-free survival, gastrointestinal NET.

L21

Efficacy and Safety of Targeted Agents for Treatment of Gastroenteropancreatic (GEP) Neuroendocrine Tumor (NET): Single Center Experience

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Introduction: As clinical features of NET are heterogeneous, the evaluation of real-world outcomes with everolimus and sunitinib are necessary. **Aim(s):** We retrospectively analyze the treatment outcomes of these agents for patients (pts) with GEP-NET. **Materials and Methods:** Between March 2007 and October 2014, a total of 44 GEP-NET pts treated with everolimus or sunitinib were identified. Considering distinct characteristics between pancreatic (Pan) and non-Pan NETs, efficacy analysis was performed separately, while safety analysis included all pts. **Results:** PanNET was most common type (n = 28, 64%) and followed by hindgut NET (n = 11, 25%) and foregut NET (n = 5, 11%). Sunitinib and everolimus were given in 27 (61%) and 17 (39%) pts. In pts with PanNET, median progression-free survival (PFS) with everolimus and sunitinib was 16.6 mo (95% CI, 8.0–25.1) and 8.0 mo (95% CI, 0.0–17.4; p = 0.51). For non-PanNET pts, median PFS was 14.7 months (95% CI, 2.4–27.0) with everolimus and 1.7 months (95% CI, 0.5–3.0; p = 0.001) with sunitinib. Most common grade 3-4 toxicities were neutropenia (n = 9, 33%), and anemia (5, 19%) in sunitinib group, and pneumonitis (2, 12%) in everolimus group. **Conclusion:** Both everolimus and sunitinib were well tolerable and effective in GEP-NET pts. The activity of everolimus was seen across all GEP-NETs and consistent with previous trials. For non-PanNET, sunitnib showed only modest activity in our study cohort, but this might be due to the discrepancies in the patient characteristics. **Keywords:** Everolimus, sunitinib, gastroenteropancreatic NET.

L22

Sunitinib in the Treatment of Unresectable or Metastatic Gastroenteropancreatic Neuroendocrine Neoplasm: A Multicenter Retrospective Study in China

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Introduction: Sunitinib has shown activity against pancreatic neuroendocrine tumors (NEN) in a global phase III clinical trial. **Aim(s):** To determine the efficacy and safety of sunitinib in the treatment of advanced gastroenteropancreatic NEN (GEP-NEN), and the clinical significance of steady-state sunitinib serum concentrations in China. **Materials and Methods:** We conducted a multicenter retrospective study including six centers from across China. A total of 50 patients with advanced GEP-NENs treated with sunitinib were evaluated. Steady-state serum concentrations of sunitinib were measured. **Results:** The median TTP was 15.1 months, with the ORR being 4.0%, the SD rate being 80.0%.47.7% of patients required a dosage decrease from 37.5 mg/d to 25 mg/d due to adverse events, which in most cases were alleviated or disappeared with the dosage reduction. In 16 patients who experienced sunitinib-related hypertension,2 achieved PR and 13 had SD. Steady-state serum concentrations of sunitinib were similar between the 2 dosage groups (P = 0.836), and between patients whose best overall response were PR, SD or PD (P = 0.087). **Conclusion:** Sunitinib had similar treatment efficacy to patients who received the drug in a global phase III clinical trial. A 25 mg/d dosage was better tolerated than 37.5 mg/d in Chinese patients, and there were no significant differences in steady-state sunitinib serum concentration between the 2 dosage groups. Sunitinib-related hypertension may be a predictor of a better treatment effect. **Keywords:** Gastroenteropancreatic neuroendocrine neoplasm, Sunitinib, Treatment.

L23

Everolimus in the Treatment of Advanced Gastroenteropancreatic Neuroendocrine Neoplasm: A Single-Center Retrospective Study in China

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Introduction: Everolimus showed antitumor activity in patients with advanced pancreatic neuroendocrine tumors in a phase III clinical trial, but data in Chinese patients was limited. **Aim(s):** To determine the safety and efficacy of everolimus in Chinese patients with advanced gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs). **Materials and Methods:** A total of 15 patients who were treated with everolimus between November 2013 and December 2015 were evaluated for adverse events and tumor responses retrospectively. **Results:** The median follow-up duration was 24.7 months. 86.7% of patients required a dosage decrease from 10 to 7.5 or 5 mg/day due to adverse events, which included stomatitis, non-infectious pneumonitis, aspartate and alanine transaminase increased, dyspnea, abdominal and musculoskeletal pain. 26.7% of patients experienced musculoskeletal pain, which was rarely reported in western patients. Of the 11 patients who received imaging evaluation, one patient achieved partial responses (PR) and 4 had stable disease (SD). The median time to progressive (TTP) was 3.9 months. **Conclusion:** A 5 or 7.5 mg/day dosage of everolimus was better tolerated than 10 mg/day in Chinese patients, and Chinese patients experienced a higher ratio of drug-related musculoskeletal pain than western patients. The short TTP may be related to the dosage reduction. **Keywords:** Gastroenteropancreatic neuroendocrine neoplasm, Everolimus, Treatment.

Medical Treatment – Others

M1

CDK-Inhibitors as New Therapeutic Treatment for Human Bronchial Carcinoids

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Introduction: Bronchial Carcinoids (BC) are still orphan of medical therapy. We previously demonstrated that 70% of primary BC cultures are sensitive to Everolimus (E), an mTOR inhibitor, while 30% are not. We also observed that in 2 human BC cell lines,

the NCI-H720 (sensitive to E) and NCI-H727 (resistant to E), mTOR resistance may be linked to a differential cell cycle protein expression (CyclinD1/E, CDK2/4, p27kip1/p27kip1phospho-Ser10), which is higher in BC resistant to E as compared to sensitive ones, suggesting an impaired p27 function. **Aim(s):** Evaluate the response of BC immortalized cell lines and primary culture to Dinaciclib (D), a novel and potent CDK inhibitor. **Materials and Methods:** We have assessed cell viability and apoptosis activation assay on BC primary cultures and immortalized cell lines, resistant or sensitive to mTOR inhibitor. **Results:** D is effective in reducing cell viability and in activating apoptosis in human BC primary cultures and cell lines that display resistance to mTOR inhibitors, displaying a Cyclin-CDK basal over-expression. On the contrary, D is not effective in E-sensitive BC tissues and cell lines. Moreover, the combination of D with E can overcome the resistance previously shown in NCI-H727 cells, with a more potent effect as compared to single treatments. **Conclusion:** D could represent a putative medical therapy for those patients showing resistance to mTOR inhibitors, which, in turn, may be linked to a deranged protein cell cycle profile. **Keywords:** Bronchial carcinoid, medical therapy, mTOR resistance, CDK inhibitors.

M2

Systemic Treatments and Prognostic Factors in Chinese Patients with Progressive Advanced Well-Differentiated Pancreatic Neuroendocrine Tumors

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Introduction: Patients with well-differentiated pancreatic neuroendocrine tumors (pNETs) often present with metastatic disease at the time of diagnosis when curative surgery is not feasible. A variety of systemic therapeutic options exist, but the best strategy is still unknown. **Aim(s):** To investigate the prognostic factors in Chinese patients with advanced pNETs and compare progression free survival (PFS) of patients treated with somatostatin analogues (Arm S), targeted therapy (Arm T) and chemotherapy (Arm C) in 1st line as well as in tumors with ki67 index <10% or ≥10%. **Materials and Methods:** We retrospectively analyzed the data of 55 patients with progressive advanced well-differentiated pNETs receiving medical treatments at Peking Union Medical College Hospital from April 2009 to May 2015. **Results:** The 5- and 10-year overall survival rates were 67% and 58%, respectively. In 1st line setting, mPFS were 7 m, 12 m and 16 m in patients of Arm S, T and C, respectively (P = 0.9990). For patients with ki67 index < 10%, mPFS were 8 m, 11 m and 8 m in Arm S, T and C, respectively (P = 0.8617). For patients with ki67 ≥10%, mPFS were 5 m, 8 m and 12 m in Arm S, T and C, respectively (P = 0.6158). Primary tumor resection and ki67 index ≤5% were independent prognostic factor evaluated by multivariate analysis. **Conclusion:** Patients with progressive advanced pNETs treated with chemotherapy had longer PFS. Primary tumor resection should be considered for patients with metastatic diseases. **Keywords:** Advanced pancreatic neuroendocrine tumors, Systemic treatment, Prognostic factor.

M3

Systemic Treatment Sequences Across Europe for Patients (pts) with Advanced Non-Functional (NF) Well-Differentiated Pancreatic Neuroendocrine Tumours (WD pNETs)

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Introduction: Different systemic therapies (ST) are available for pts with advanced WD pNETs; however, the best treatment modalities and optimal sequencing are currently unknown. **Aim(s):** To explore therapy sequences used in European centres for treatment of NF WD pNETs in relation to pts and tumour characteristics. **Materials and Methods:** Retrospective analysis of pts diagnosed with advanced NF WD pNETs from January 2003 to January 2014 who received ST at 8 European University hospitals. **Results:** We evaluated 210 pts (51.9% males) with median age of 58 years (19-88). Most pts had grade (G) 1 (20%) or 2 (73.3%) tumours and positive SRS status (84.1%). Median number of lines of therapy was 2 (1-12). Most common first-line treatments were somatostatin analogs (SSAs) (36.7%) and chemotherapy (CT) (27.6%), followed by PRRT (11.9%), sunitinib (11%) and everolimus (10%). Median PFS for the whole cohort was 16.4 months (m) (95% CI, 15.3–17.6). Better PFS was observed for pts receiving PRRT (28.2 m; 95% CI, 12.1–44.2) than for those treated with SSAs (15.8 m; 95% CI, 14.2–17.5), CT (12.1 m; 95% CI, 8.6–15.6) or targeted agents (TA) (17.5 m; 95% CI, 14.7–20.3) ($p < 0.001$). First-line SSAs were more commonly used in pts with G1 tumours and positive SRS, whereas PRRT, CT or TA were preferred in pts with G2-3 ($p = 0.041$) and CT or TA in those with negative SRS ($p = 0.027$). **Conclusion:** Different therapeutic strategies have shown efficacy for advanced NF WD pNETs. Tumour grade and SRS status may play a role in guiding treatment selection. **Keywords:** pNET, Treatment sequences.

M4

The Role of Hepatic Intra-Arterial Therapies in Metastatic Neuroendocrine Tumours (NETs): A Specialist Center Experience

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Introduction: Liver metastases are relatively common in patients with NETs, having a negative impact on prognosis. The options for selective liver metastases therapy are limited to catheter guided procedures: TACE, TAE or SIRT. Data regarding the effectiveness & safety of these procedures in different types of NETs is limited. **Aim(s):** To explore the clinical outcome, survival and safety profile of catheter-guided therapies for liver metastases in a group of NETs patients of different origin. **Materials and Methods:** Retrospective case series of consecutive patients treated at a single tertiary university medical center from 2005 to 2015. **Results:** 45 patients with G1, G2 and low G3 NETs of different origins with liver metastases were investigated. Clinical improvement & tumor response were observed in 43/45 patients (96%). The median TTP following the first treatment was 12.3 ± 1.2 months. The median OS for the entire group was 23.33 ± 6.5 months, and it was more pronounced in the MTC subgroup. There was a trend for a better survival time in patients without extrahepatic metastasis. Noteworthy, primary tumor resection had a beneficial effect on the survival. **Conclusion:** Hepatic intra-arterial therapies are well tolerated and associated with both clinical improvement and tumor stabilization for prolonged periods of time in the majority of patients with NETs and liver metastases of varying origin. These therapies should be always considered, irrespective of the presence of extrahepatic metastasis. **Keywords:** Hepatic chemoembolization, SIRT, NETs, MTC.

M5

Efficacy and Safety of Telotristat Etiprate in Patients with Carcinoid Syndrome Not Adequately Controlled by Somatostatin Analog Therapy: Analysis of the Ongoing TELESTAR Extension Period

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Introduction: TELESTAR was a pivotal, randomized phase 3 study evaluating telotristat etiprate (TE), a tryptophan hydroxylase inhibitor, among patients (pts) with carcinoid syndrome (CS). When added to somatostatin analogues (SSA), 250 mg tid and 500 mg tid TE each produced significantly greater bowel movement (BM) frequency reduction averaged over 12 weeks (wks) than placebo (PBO) plus SSA ($p < 0.001$). Pts crossed over to open-label (OL) treatment with TE 500 mg tid after Wk 12. The extension phase (Wk 13 to Wk 48) is still ongoing. **Aim(s):** Examine initial efficacy and safety in the crossover (CO) to OL TE. **Materials and Methods:** Changes from baseline (CFB) in BMs/day were examined at Wks 12, 24, and 36, and safety was reviewed. **Results:** Among 135 randomized pts, baseline BMs/day (prior to Wk 1) were 5.2, 6.3, and 6.0 respectively on PBO, 250 mg and 500 mg tid. At Wk 12, CFB were –0.9 (PBO), –1.7 (TE 250 mg), and –2.1 (TE 500 mg) (n = 108 pts with BM data). 115 pts entered the extension, and at Wk 24, CFB were –1.8, –2.1, and –2.1 (n = 98), and at Wk 36 CFB were –1.8, –2.2, and –1.9 (n = 73), respectively, in pts originally assigned to PBO, 250 mg tid, and 500 mg tid TE. The Wk 12 CO to 500 mg tid TE was well tolerated. No safety signals were observed with the CO. **Conclusion:** Decreases in BM frequency were observed in pts who received TE 500 mg tid after crossing over from either PBO or 250 mg and were sustained in those on 500 mg. BM reduction and favorable safety were observed in pts treated beyond Wk 12. **Keywords:** Telotristat, Carcinoid syndrome, Tryptophan.

M6

Therapeutic Strategies in Patients with Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NEN): Results from the National Neuroendocrine Cancer Registry of Spain (R-GETNE)

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Introduction: The Spanish National Neuroendocrine Cancer Registry is a hospital-based registry of GEP-NENs launched by GETNE in 2001. **Aim(s):** We present therapeutic strategies and patterns of care. **Materials and Methods:** Data from this national registry that covers 57 academic and community Spanish sites was provided online. **Results:** The study cohort comprised 2487 patients. 68% underwent surgery, most with curative intent (85%), but also with palliative purposes (12%). Surgical resection of the primary tumor was performed in 92%, and 22% underwent resection of metastatic disease. Local–regional therapies (embolization, chemoembolization, radiofrequency) were performed in only 5% and PRRT in 2%. 41% received systemic therapy: 40% somatostatin analogues (SSA), 28% chemotherapy, 14% targeted therapies and 7% interferon and 4% palliative radiotherapy. Responses in advanced disease were reported in: 6% of patients treated with SSA, 15% of those treated with other systemic therapies. At November 2015, 563 patients had died (23%) and 4% had developed other tumor. The main causes of death were tumor progression (85%) and treatment related (9%). RR and OS by grade, stage and therapeutic strategy will be provided at the meeting. **Conclusion:** There was an extensive use of surgery and systemic therapies and a low use of local–regional ablative approaches and PRRT, reflecting barriers of referrals to expert centres and the lack of availability of radionuclide therapy in Spain. **Keywords:** Net, Surgery, Somatostatin analogues, Chemotherapy, Targeted therapy, Survival.

M7

Patient Interviews in TELESTAR, a Phase 3 Study of Telotristat Etiprate, Report Meaningful Improvement in Carcinoid Syndrome

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Introduction: Telotristat etiprate (TE) reduces serotonin production. In TELESTAR, a phase 3 study in patients (pts) with carcinoid syndrome (CS) on somatostatin analogues with ≥4 bowel movements (BM) per day, TE significantly reduced BM frequency (freq). Overall (n = 135), durable response (DR, ≥30% reduction in BMs/day for ≥50% of the study period) was observed in 44% (250 mg tid) and 42% (500 mg tid), vs. 20% on placebo (PBO); p ≤0.02 for each TE vs. PBO. A subset with similar demographics to the overall trial was interviewed. **Aim(s):** To assess pt reported impact of treatment (tx) on CS and whether symptom changes were meaningful. **Materials and Methods:** Participating sites were asked to invite (prior to randomization) all eligible pts to phone interviews scheduled at the end of the double-blind tx period. Pts and interviewers were blinded to tx. **Results:** Among the 33 pts who answered the tx satisfaction interview questions, DR was seen in 1/9, 3/9, and 5/15 pts on PBO, 250 mg tid, and 500 mg tid TE, respectively. Reductions in BM freq were considered meaningful by 3/9, 7/9, and 10/15 pts on PBO, 250 mg tid, and 500 mg tid TE. All 8 TE pts with DR reported being 'very satisfied', and reported a meaningful reduction in BM freq. Reports of 'very satisfied' were 0/9, 5/9, and 7/15 pts on PBO, 250 mg tid, and 500 mg tid TE. **Conclusion:** Among the subset interviewed in the study, pts with DR on TE reported the highest level of CS tx satisfaction and meaningful improvement in BM freq. **Keywords:** Serotonin, Bowel movement, Durable response, Treatment satisfaction.

M8

Telotristat Etiprate Appears to Halt Carcinoid Heart Disease

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Introduction: Carcinoid Heart Disease (CHD) is a serious complication of the Carcinoid Syndrome (in as many as 50% of patients during the course of their disease). 46% of cases operated with bioprosthetic valves develop recurrent carcinoid valvulopathy on the newly implanted tissue valves. Until now, only mechanical prosthetic valves avoid recurrent fibrosis. **Aim(s):** To demonstrate the effects of telotristat etiprate, a tryptophan hydroxylase inhibitor, on serotonin levels and its effect upon the course of CHD. **Materials and Methods:** 2 patients with CHD were among those entered in the TELESTAR phase III trial. One demonstrated recurrent carcinoid valve disease on the tricuspid and pulmonic bioprosthetic (tissue) replaced valves; the other demonstrated carcinoid valve disease on the native tricuspid and pulmonic valves, suggesting the likelihood that valve surgery might be imminent. **Results:** Both patients demonstrated no further fibrosis of valves on serial echocardiographic studies since enrollment in the TELESTAR trial and continued treatment with telotristat etiprate. **Conclusion:** Carcinoid Heart Disease is a frequent complication of the Carcinoid Syndrome. Telotristat etiprate reduces serotonin to levels which appear subthreshhold to that which stimulates the fibrosis associated with CHD. This drug might prevent the need for valve surgery in many cases, or enable the use of bioprosthetic valves in others, without recurrent fibrosis. **Keywords:** Carcinoid heart disease, Valve, Heart failure, Carcinoid syndrome, Prosthetic valves, Telotristat etiprate.

PRRT-Ablative Therapies-Endoscopic Treatment

N1

Peptide Receptor Radionuclide Therapy Prolongs Survival in Neuroendocrine Neoplasms: A Single Centre Study in 1,048 Patients Over 10 Years

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Introduction: Peptide receptor radionuclide therapy (PRRT) of somatostatin receptor (SSTR) expressing neuroendocrine neoplasms (NEN) has shown promising results about progression free survival (PFS) and overall survival (OS) in numerous phase II trials, and also in a recently published randomized controlled prospective phase III study (NETTER-1). **Aim(s):** To assess the OS and PFS in NEN patients (pts) undergoing PRRT. **Materials and Methods:** Of the 2294 pts screened by Ga-68 SSTR PET/CT, 1048 pts received ≥1 cycle of Y-90 or Lu-177 based PRRT and were included in the intention to treat analysis. PFS determined by Ga-68 SSTR PET/CT was analyzed. **Results:** OS (median) of all pts was 51 months (mo). Pts with age ≤40 y (70 mo), those treated with a combination of Y-90 and Lu-177 PRRT (64 mo), with G1 tumours (88 mo) and tumours of small intestinal origin (69 mo) had improved survival. Pts with G3 tumours (23 mo), those treated with exclusive Y-90 based PRRT (24 mo) had a shorter survival. PFS of all pts was 19 mo, significantly worse in pts treated with exclusive Y-90 based PRRT (13 mo), in G3 tumours (7 mo), lung carcinoids (11 mo) and tumours of unknown origin (13 mo). PFS after the first and second reinstallation of PRRT for progression after 6-month therapy-free intervals were 11 mo and 8 mo, respectively. **Conclusion:** PRRT prolongs OS in NEN depending on the radionuclide used, grade and origin of tumour, which is not exactly mirrored in the PFS estimated by molecular response assessment using Ga-68 SSTR PET/CT. **Keywords:** PRRT, Survival, PET/CT.

N2

Nephrotoxicity after PRRT with 177Lu-DOTA-Octreotate

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Introduction: Renal toxicity may occur after Peptide Receptor Radionuclide Therapy (PRRT). Risk factors have been identified for renal toxicity after 90Y based PRRT. **Aim(s):** We investigated the renal function over time, the incidence of nephrotoxicity and associated risk factors after PRRT with 177Lu-DOTA0-Tyr3-Octreotate. Kidney dose was evaluated and compared to the accepted dose limits in external beam radiotherapy (EBRT) and 90Y-based PRRT. **Materials and Methods:** The incidence of renal toxicity (CTCAE v4.0) was evaluated in 323 patients and analysis of the annual loss of creatinine clearance (CLR) was done in 209 patients. Risk factors, including absorbed kidney dose, were analyzed with a non-linear mixed effect regression model. **Results:** Three (1%) out of 323 patients developed grade 2 (sub)acute renal toxicity, no grade 3-4 was observed. The average baseline CLR (and SD) was 108 ±5 ml/min and the yearly decrease of CLR (and SD) was 3.4 ±0.4%. Annual CLR loss of >20% per year was not observed. No significant higher annual loss of CLR was observed in patients with hypertension, diabetes, high cumulative injected activity, radiation dose to the kidneys and CTCAE grade at baseline. The mean absorbed kidney dose in 228 patients was 20.1 ± 4.9 Gy. **Conclusion:** None of our patients had (sub)acute grade 3-4 or long-term renal toxicity. No risk factors for renal toxicity could be identified. Radiation dose threshold, adopted from EBRT and 90Y-based PRRT does not seem valid for PRRT with 177Lu-DOTA0-Tyr3-Octreotate. **Keywords:** PRRT, Kidneys, Toxicity, Dosimetry.

N3

A Blood-Based Multi-Transcript Test, the NETest, Predicts and Defines PRRT Efficacy in Neuroendocrine Tumors

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Introduction: Peptide receptor radionuclide therapy (PRRT) is an effective NET treatment. Predicting response is based on somatostatin receptor expression and efficacy evaluated by RECIST criteria. Both have limited accuracy. The NETest measures tumor activity in blood and correlates cell signaling and metabolism directly with tumor activity. **Aim(s):** Assess the effectiveness of the NETest as a PRRT predictive marker. **Materials and Methods:** 177Lu-octreotate treated NETs (n = 54) followed for 33 months. Histological grade, somatostatin receptor imaging (SRI), CgA (ELISA, normal <108 ng/ml) and NETest (qPCR with multianalyte algorithmic analyses) were evaluated. A mathematical response index comprising NETest genes regulating metabolism and growth factor signaling and grade was developed as a Predictive Quotient Index (PQI). Response was assessed by RECIST. **Results:** The PQI (NETest [metabolism/signaling]/grade) accurately predicted responders (97%) and non-responders (91%). This was significantly better than elevated SRI uptake (94% vs. 38% accuracy: $\chi^2 = 31.8$, $p < 0.0001$). PRRT disease control was 72%; median PFS not achieved (median follow-up 16 months). NETest accurately (89%, $\chi^2 = 27.4$; $p = 1.2\times10{-}7$) correlated with response. Baseline SRI ($p = 0.58$), CgA ($p = 0.53$) and grade ($p = 0.12$) did not predict treatment efficacy. **Conclusion:** The NETest is a predictive multi-molecular biomarker for PRRT efficacy. Alterations in levels correlated with treatment responses. The NETest accurately (94%) predicted PRRT efficacy significantly outperforming SRI. **Keywords:** NETest, PRRT.

N4

Endoscopic Ultrasound-Guided Radiofrequency Ablation for Pancreatic Neoplasms

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Introduction: Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) is a recognised therapeutic option for a range of neoplasms. **Aim(s):** To ascertain the feasibility, safety and early results of EUS-RFA for pancreatic neoplasms with a novel probe. **Materials and Methods:** Prospective, multi-centre pilot trial examining the Habib TM EUS-RFA catheter – a novel probe comprising a 1Fr wire of 190 cm working length which can be inserted via the biopsy channel of an echoendoscope. **Results:** Nine patients (8 female, 1 male) were recruited: 6 had pancreatic cystic neoplasms, 3 had pancreatic neuroendocrine tumours (NET). Mean sizes (± standard deviation) of cystic neoplasms and NET were 36.5 mm (±17.9 mm) and 27.5 mm (±17.7 mm), respectively. EUS-RFA was successfully executed in all patients. In the 6 patients with cystic neoplasms, responses at 3-6 months ranged from 48.4% reduction in lesion size to complete resolution of cysts. Patients with NET underwent 1 or 2 sessions of EUS-RFA with no adverse events. Herein, changes in tumour vascularity and central tumour necrosis were observed. Overall, there were no major complications 48 hrs post-procedure. Two patients experienced mild abdominal pain which resolved within 72 hrs. **Conclusion:** Preliminary data show EUS-RFA with the Habib TM probe is well tolerated, technically straightforward and safe. Efficacy has been demonstrated in both pancreatic cystic neoplasms and NET. Further clinical studies are required, and indeed are underway at Imperial College London. **Keywords:** Ablation, Pancreas, Neuroendocrine.

N5

Personalized 177Lu-Octreotate Peptide Receptor Radionuclide Therapy (PRRT) Allows a Safe and Significant Increase of Radiation Dose to Neuroendocrine Tumors (NETs)

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Introduction: 177Lu-octreotate PRRT is commonly administered at fixed/empiric activity per cycle, which results in highly variable radiation doses to critical organs and undertreatment of the majority of patients. **Aim(s):** To assess the potential of personalized PRRT to safely increase absorbed radiation dose rate to tumors. **Materials and Methods:** Twelve NET patients underwent four 177Lu-octreotate induction cycles followed by quantitative SPECT dosimetry. The median activity per cycle was 7.4 (5.6–8.1) GBq. We simulated a personalized PRRT protocol where activity per cycle was adjusted to reach, over 4 cycles, cumulative doses of 23 Gy to the kidney or 2 Gy to the bone marrow (BM), the generally recognized safe dose thresholds. **Results:** A total activity of 29.7 ± 2.3 GBq was administered over 4 cycles, resulting in radiation doses of 16.1 ± 5.0 Gy to kidney, 0.67 ± 0.28 Gy to BM and 113 ± 57 Gy to tumor. In a personalized regime, we could have significantly increased administered activity to 46.3 ± 15.1 GBq over 4 cycles, which would have increased tumor dose to 168 ± 76 Gy, i.e. an average 1.56-fold increase vs. empiric regime (ranging from 0.99 to 2.50 fold; $P = 0.0025$). In all cases, the dose-limiting organ was the kidney, which would have received the maximum dose (23 Gy), while the BM would have received 0.96 ± 0.33 Gy. **Conclusion:** Personalized PRRT allows significantly increasing tumor radiation dose and dose rate, hence maximizing the likelihood of response, while limiting the risk of toxicity. **Keywords:** Personalized, PRRT, Neuroendocrine tumors.

N6

Somatostatin Analogs and mTOR Inhibitors as Radioprotectors or Radiosensitizers in Neuroendocrine Tumor Cells

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Introduction: PRRT can deliver radiation doses of up to 250 Gy to the tumors. Nevertheless, complete remission is extremely rare, compared to similar radiotherapies for thyroid cancer and non-Hodgkin lymphoma. **Aim(s):** One hypothesis potentially explaining the discrepancies between expected result and observed outcome of PRRT might be that somatostatin analogs induce a G1 arrest in NET cells, thereby rendering them radioresistant. Other medical therapeutics like mTOR inhibitors may also contribute to radiosensitivity towards PRRT. **Materials and Methods:** To investigate this, NET cell lines were incubated with or without agonists and exposed to different radiation doses from a 137Cs source between 0 and 50 Gy. Cells were harvested at distinct timepoints, stained with propidium iodide and the cell cycle distribution was assessed by FACS analysis. Proliferation, vitality and mitochondrial activity were assessed using cell counting, clonogenic assay and Alamar Blue assay, respectively. **Results:** Experiments in five tested NET cell lines showed a radiation-induced decline in G1 cells as well as a G2/M arrest. Also, the percentage of apoptotic cells in sub-G1 phase increased time- and dose-dependently. Pretreatment with a potential G1 inhibitor did not only result in a G1 arrest and a decrease of radiation-induced G2/M arrest, but also in a reduced metabolic activity and cell proliferation. In this particular case, a G1 arrest seems to sensitize NET cells to radiation. **Conclusion:** Further experiments are needed to delineate radiosensitizers. **Keywords:** PRRT.

N7

Ultrasound-Guided Radiofrequency Ablation of Liver Metastasis in Two Cases with Neuroendocrine Tumors

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Introduction: Theraputic modalities in patients with metastatic neuroendocrine tumors (NET), ineligible for radical surgery include somatostatin analogues, chemotherapy, biological therapy and local ablation or embolization of liver metastasis. **Aim(s):** We report two cases with carcinoid syndrome and multiple neuroendocrine liver metastasis, treated with ultrasound-guided ablative therapy. **Materials and Methods:** Case 1 was a female, 61-years old, with lung NET and case 2 a female, aged of 47 years, with pancreatic NET. **Results:** After surgical resection and histological diagnosis of NET, there was appearance of carcinoid syndrome in both cases. Contrasted enhanced ultrasound, CT and somatostatin-receptor scintigraphy and SPECT-CT showed the presence of multiple liver metastases, confirmed by liver biopsy with histological and immunohistochemical investigations. Combined therapy included octreotide LAR and multiple sessions of ultrasound guided-radiofrequency ablation (case 1 and case 2), as well as chemotherapy and Denosumab (Xgeva) in case 2, with good effect. **Conclusion:** Radiofrequency ablation is a safe and effective method for patients with nonresectable neuroendocrine liver metastasis. In our cases the combination with octreotide LAR it leads to significant improvement of severe carcinoid syndrome and prolongation of survival. **Keywords:** NET, Liver metastasis, Ultrasound-guided ablative therapy.

N8

Favourable responses in Patients with Bulky Neuroendocrine Tumours (NET) – A Personalised Approach Using 90Y-DOTA-Octreotate Sequenced with 177Lu-DOTA-Octreotate Induction Peptide Receptor Chemoradionuclide Therapy (PRCRT)

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Introduction: Bulky disease from NET is an adverse prognostic factor for response to 177Lu-DOTA-octreotate (LuTate) PRCRT. 90Y-DOTA-octreotate (YTate) has more penetrating particulate emissions. **Aim(s):** We assessed the efficacy and toxicity of YTate sequenced with LuTate induction in this setting. **Materials and Methods:** 26 patients (pts) (17 male; 27-74 y.o) completed PRRT using 1-2 YTate cycles sequenced with 2-3 LuTate cycles (median cumulative activity YTate 6.5GBq, LuTate 21GBq) were reviewed. All had at least one lesion >4 cm transaxial diameter. 58% had ENETS Grade 2/3, and 73% FDG-avid disease. 7 pts were treated for uncontrolled symptoms, 19 for progressive disease. **Results:** All pts with uncontrolled symptoms improved during PRCRT; 4 reported complete control at 3 months. Pts with previous progression had stabilisation (37%) or regression (42% partial, 21% minor response) on CT, 74% had biochemical response. Median overall survival was not reached, median follow-up was 35 mnths. Median progression free survival 33 months. 8 pts had Grade 3/4 lymphopaenia, 2 pts Grade 3/4 thrombocytopaenia, no significant hepatic or renal toxicity. **Conclusion:** YTate sequenced with LuTate PRCRT achieved high responses in pts with bulky NET, more favourable than results with either agent used alone or other approved therapies, particularly with adverse prognostic features of this cohort. Results support personalisation limiting YTate to 1-2 cycles to increase efficacy whilst preventing potential toxicity from using it exclusively for induction. **Keywords:** PRRT, y-90

N9

PRRT for Malignant Pheochromocytomas and Paragangliomas: The Singapore General Hospital Experience

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Introduction: In recent years, the use of 177Lu-DOTATATE radioisotope therapy has been expanded to patients with metastatic pheochromocytomas and paragangliomas (PCC/PGL). Although this is not the standard of care, treatment options are limited for those with MIBG negative disease. Our centre has treated over 40 patients with NETS with PRRT since 2012. **Aim(s):** We share our clinical experience of PRRT in 4 patients with functional metastatic PCC/PGL. **Materials and Methods:** Three PGL patients and 1 PCC patient have undergone PRRT since 2014. **Results:** The patient with PCC showed progressive disease despite 3 cycles of PRRT. He also developed new onset cushing's syndrome from the tumour. Two of our PGL patients showed progressive disease following their first cycle. One had mixed response on imaging and increased catecholamine secretion while the other developed haematuria due to invasion of the bladder by the recurrent primary tumour 2 months following treatment. These 2 patients are currently still undergoing active therapy. The last patient presented with bilateral inoperable glomus tumours. She underwent a single session intraarterial PRRT under general anaesthesia with post-procedural monitoring in the intensive care unit. **Conclusion:** All our patients underwent PRRT under alpha and beta blockade. None experienced hormonal crises nor required prolonged hospitalisation for blood pressure control. More experience is required before PRRT can be established as standard treatment for metastatic PCC/PGL. **Keywords:** PRRT, Pheochromocytoma, Paraganglioma.

N10

Theragnostic Approach of Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET) – The Role of Nuclear Medicine (NM) in a Multidisciplinary Team

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Introduction: NET pts are a clinical challenge requiring intervention of multiple medical specialties. **Aim(s):** Our work focuses on diagnostic and therapeutic role of NM in multidisciplinary team using functional features of NETs. **Materials and Methods:** GEP-NET cases were examined focusing on those who did NM diagnostic (somatostatin receptor scintigraphy-SRS/positron emission tomography-PET for evaluation of receptor status/disease extent, evaluation of response to therapy; 18F-FDG PET for evaluation of undifferentiated component) and therapeutic (177Lu-DOTATATE peptide radionuclide radiotherapy-PRRT) procedures. **Results:** 40 GEP-NETs were diagnosed (Apr012-Sep015); 20 Male; 23–87 y; gastric (7), duodenal (3), small bowel (6), pancreatic (12), appendiceal (2), large bowel (3), rectal (3) and unknown primary (4) tumors; 25% G1, 53% G2, 22% G3. 48% pts had metastasis at diagnosis, all G3 pts were in this group. Pancreatic tumors were most prevalent in both groups; all appendiceal and rectal tumors were non metastatic. Majority (62%) did NM procedures (48% SRS, 20% 68Ga-DOTA PET/CT, 15% 18F-FDG PET/CT). 3 pts did PRRT: 2 pancreatic (1G1/1 G2), 1 jejunal (G2); liver and lymphatic metastasis (also bone in jejunal). G2 pancreas NET did 2 cycles and died without apparent progression; G2 jejunal NET did 4 cycles with disease stability; G1 pancreas NET did 3 cycles with clinical and imaging remission. **Conclusion:** NM has

an important diagnostic and therapeutic role in GEP-NET pts; multidisciplinary approach is decisive for successful clinical management. **Keywords:** PRRT, GEP-NET.

N11

Retreatment with Peptide-Receptor Radionuclide Therapy: Effects on Long-Term Survival, Renal and Bone Marrow Toxicity Using Yttrium-90 vs. Lutetium-177

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Introduction: PRRT is an effective treatment for metastatic NETs. The effect of PRRT retreatment is unknown. **Aim(s):** To determine efficacy & toxicity of retreatment with PRRT. **Materials and Methods:** We reviewed patients retreated with PRRT. Patients included: 2 or more cycles of PRRT and retreated >12 mths later. We evaluated PFS and toxicity (renal and BM) after initial and retreatment PRRT. Treatment activities were 3.2GBq/cycle for 90Y- and 7.4GBq/cycle for 177Lu-DOTATATE. **Results:** 48 patients included, 37.5% midgut NETs, 33% pancreatic NETs. Tumour grade was available in 33 patients: 42% G1, 45% G2, and 12% G3. First course of PRRT (mean 3 cycles), 46/48 were treated with 90Y-DOTATATE. Median PFS: 28.8 mths. Median time to retreatment: 26.9 mths. Renal impairment: 3 (6.25%), all stage 3. BM toxicity: 5 (10%). In PRRT retreatment (mean 2 cycles), 30/48 had 90Y-, 18/48 had 177Lu-DOTATATE. Retreatment response in 38/48 patients: 13% PR, 63% SD & 23% PD. Median PFS: 20.6 mths (90Y 22.1 mths; 177Lu 15.8 mths). Renal dysfunction seen in 15/48 (31%): stage 2/3 (13), stage 4 (1) and stage 5 (1). BM toxicity: 10 (21%) patients, 7/10 having prolonged suppression. In 40/48 patients with further follow up data, 16 have SD, 18 are no longer alive and 6 were retreated with further PRRT. **Conclusion:** Patients retreated with PRRT had median PFS of 20.6 mths, with slightly higher renal and BM toxicity. Only 2 patients had stage 4/5 renal toxicity. In patients with PD the benefit of PRRT outweighs the risk of permanent renal or BM dysfunction. **Keywords:** PRRT, Retreatment.

N12

Induction and Maintenance Regimen with Peptide Receptor Radionuclide Therapy (PRRT) Lu-177-DOTA-TATE (Lu-177) in Patients with Advanced Neuroendocrine Tumours (NET)

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Introduction: PRRT using Lu-177 is a treatment option for advanced NETs. **Aim(s):** We hypothesize long-term and ongoing therapy with Lu-177 improves outcomes, is effective and safe for these patients. We evaluated toxicities of a Lu-177 regimen of induction (4 cycles of 5.6 GBq every 10 weeks) and maintenance (up to 8 cycles of 3.7 GBq given ≈6 monthly). **Materials and Methods:** Of 184 NET patients treated with Lu-177, 126 had <6 cycles (9 withdrawn; 117 ongoing), 58 had ≥6 cycles (6-7 cycles; n = 27; 8–9; n = 18; 10-11; n = 13). In 58, the primary included: PNET (n = 21), GNET (n = 27), likely GNET (n = 3), other (n = 7). Cumulative mean administered dose was 28.8 ± 4.5 GBq for 6-7 cycles, 35.7 ± 3.6 GBq for 8-9 and 44.5 ± 6.4 GBq for 10–11. **Results:** 43 patients remain on treatment. 15 patients have stopped treatment: 1 is disease free (after 6 cycles); 11 discontinued due to biochemical, anatomic or symptomatic progression between cycles (after 6 cycles; n = 7, after 7; n = 1, after 8; n = 1, after 10; n = 2); 4 died (after 7 cycles; n = 1, after 8; n = 2, after 9; n = 1). Lymphopenia (≥ Grade 3 [CTCAE v.4] n = 10) was the most common measurable adverse event (AE). Other Grade 3 AEs occurred in platelets (n = 1), creatinine and eGFR (n = 2), and creatinine (n = 2). No myelodysplasia was seen. **Conclusion:** Induction and maintenance therapy with Lu-177 is a safe regimen for NET patients. This regimen is potentially more effective than literature reported treatment regimens; in the cohort presented, median survival has not been reached at 54 months. **Keywords:** Neuroendocrine, Lu-177-DOTA-TATE.

N13

Long-Term Follow-Up of Peptide Receptor Radionuclide Therapy with 177Lu-DOTATATE in Advanced Well-Differentiated Pancreatic Neuroendocrine Tumors

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Introduction: 177Lu-dotatate (Lu-PRRT) is a valid therapeutic option in advanced G1-G2 pancreatic neuroendocrine tumors (P-NETs). **Aim(s):** We evaluated long-term efficacy and toxicity in 65 consecutive patients (pts) with P-NETs treated with a personal-

ized activity of Lu-PRRT. We also evaluated the role of FDG PET as an independent prognostic factor in P-NET pts. **Materials and Methods:** 65 consecutive pts with P-NETs were enrolled in a prospective study. Pts were treated with two different total activities (18.5GBq or 27.8 GBq) in 5 cycles on the basis of kidney function and bone marrow parameters. 59 pts underwent FDG PET before Lu-PRRT. **Results:** Median follow-up was 59 months. 30 pts received a mean full activity (FA) of 25.5 GBq and 35 a mean reduced activity (RA) of 17.8 GBq. The DCR in the FA group was 87%; in the RA group was 85% ($p = 0.83$). Median PFS was 53.4 months in the FA arm and 24.4 months in the RA arm ($p = 0.42$). Median OS was not reached in FA pts and was 63.8 months in RA group ($p = 0.013$). There were no cases of grade 3 or 4 hematological toxicity. Median PFS in the FDG PET-positive group was 21.2 months, compared to 68.7 months in FDG PET-negative pts ($p < 0.0003$), regardless of the total activity administered. Median OS was not reached in the negative FDG PET group and was 63.8 months in the positive FDG PET group ($p = 0.005$). **Conclusion:** Lu-PRRT showed antitumor activity in P-NET pts and was well tolerated when used with a personalized schedule. FDG PET was confirmed to be a valid prognostic factor in P-NETs. **Keywords:** PRRT, FDG-PET, P-NET.

N14

Gastric Type I Neuroendocrine Tumors Endoscopic Treatment Options

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Introduction: From 1998 till 2014 in our institution we have identified 72 patients with type I gastric neuroendocrine tumors (NET), 42 of them, without regional or distant metastases, undergone different types of endoscopic treatment. **Aim(s):** In patients (21) with type I flat G1 lesions 0.5 cm and smaller, located within mucosa, we have used argon-plasma coagulation (APC). Mean tumor amount, destructed with APC was 14, mean size – 0.4 cm. We have not observed any tumor recurrence at treatment sites, but in 28.5% patients new G1 NETs were developed within 1 year after treatment in different mucosal areas. **Materials and Methods:** Mean amount of de novo tumors was 4,4, mean size – 0.2 cm. In all cases second phase APC was implemented. Patients (18) with gastric type 1 G1 NETs sized 0.5–1 cm undergone endoscopic mucosal resection (EMR). In 72.2% of them we have diagnosed simultaneously small (less than 0.5 cm) and bigger (0.5–1 cm) tumors, so EMR was performed in parallel with APC. **Results:** In all cases for EMR we used endoscopic snares, prior to EMR the submucosal saline injection was performed. We have not registered tumor relapse in all EMR group patients. In 3 patients with type I G2 gastric NETs invading submucosa (SM1), endoscopic submucosal dissection (ESD) was performed. For ESD we have used hydroxiethyl starch solution submucosal injection and resected tumors completely (R0) with DualKnife. **Conclusion:** No serious adverse effects were noted, all patients are under surveillance. **Keywords:** Gastric, NET, Endoscopic, EMR, ESD, APC.

N15

NETTER-1 Phase III in Patients with Midgut Neuroendocrine Tumors Treated with 177Lu-DOTATATE: Efficacy and Safety Results

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Introduction: There are limited therapeutic options for patients with advanced midgut NETs progressing on first-line somatostatin analog therapy. **Aim(s):** Evaluate the activity and safety of 177Lu-DOTA0-Tyr3-Octreotate (Lutathera®) in patients with advanced, progressive sstr positive midgut NETs. **Materials and Methods:** 230 patients grade 1-2 metastatic midgut NETs were randomized to Lutathera 7.4 GBq every 8 weeks (x4 administrations) vs. Octreotide LAR 60 mg every 4 weeks. Primary endpoint was PFS (RECIST 1.1) with tumor assessment every 12 weeks. Secondary objectives included ORR, OS, toxicity and QoL. **Results:** Median PFS was not reached for Lutathera and was 8.4 months with control ($p < 0.0001$, HR 0.21). There were 23 centrally confirmed disease progressions or deaths in the Lutathera arm and 67 in the Octreotide LAR 60 mg arm. The objective radiographic response rate was 18% with Lutathera and 3% with control ($p = 0.0008$). Interim OS analysis (13 deaths in Lutathera group and 22 in control group; $p = 0.019$) strongly suggests an improvement in OS. Only 5% (6 patients) experienced Lutathera dose modifying toxicity. Adverse events grade 3 or 4 neutropenia, thrombocytopenia and lymphopenia occurred in 1%, 2% and 9% of patients in Lutathera arm vs. none in controls. **Conclusion:** NETTER-1 trial provides evidence for a clinically meaningful and statistically significant increase in PFS and ORR, and suggests an OS benefit in patients with advanced midgut NETs treated with Lutathera. Lutathera safety profile was found to be very favorable. **Keywords:** Lutathera, PRRT, NET.

Surgical Treatment

O1

Uncinatectomy: Rethinking the Surgical Approach for Neuroendocrine and Intraductal Papillary Mucinous Neoplasms of the Pancreas

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Introduction: Pancreatic neuroendocrine tumors (pNETs) and intraductal papillary mucinous neoplasms (IPMN) are increasingly recognized pancreatic tumors due to advances in imaging. Standard of care is surgical resection for these tumors is via the appropriate procedure: pancreaticoduodenectomy or enucleation. **Aim(s):** We present a case series on three patients with these two types of tumors in the uncinate process of the pancreas who were treated via an uncinatectomy with roux-en-y anastomosis, a novel surgical technique. **Materials and Methods:** None. **Results:** All three patients successfully underwent the procedure with negative surgical margins and benign peri-pancreatic lymph nodes. Two patients developed post-operative pancreatic leaks, one which resolved spontaneously and another that required a prolonged ICU admission. Currently all three patients have recovered and are doing well. **Conclusion:** This parenchymal sparing procedure provides benefits over traditional therapy such as preservation of pancreatic endocrine and exocrine function, preservation of the biliary tree, ampulla and duodenum. Disadvantages of this procedure include Wirsung Duct injury, fistula formation and pancreatic leak. We minimized this risk by performing the uncinatectomy with a roux-en-y anastomosis. Our experience has demonstrated that this procedure can be safe, well tolerated and has benefits that warrant it's consideration in the management of patients with small pNETs and IPMN tumors. **Keywords:** Pancreatic neuroendocrine tumor, IPMN, Uncinatectomy.

O2

Resection of the Primary Tumor Prior to Peptide Receptor Radionuclide Therapy Improves Treatment Response and Progression-Free Survival in Pancreatic Neuroendocrine Tumors with Unresectable Liver Metastases

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Introduction: A low burden of disease represents an independent favorable prognostic factor of response to peptide receptor radionuclide therapy (PRRT) in patients affected by gastro-entero-pancreatic neuroendocrine tumors. However it is not clear whether this is due to a lower diffusion of the disease or thanks to debulking surgery. **Aim(s):** To ascertain whether resection of the primary tumor prior to PRRT could have an impact on response to PRRT and on progression-free survival in patients with G1-G2 metastatic pancreatic neuroendocrine tumors (PNETs). **Materials and Methods:** From 1996 to 2013 those patients diagnosed with G1-G2 pancreatic neuroendocrine tumor (PNET), and synchronous unresectable liver metastases who were eligible to receive upfront PRRT were included in the study. Two groups of comparison were identified: those submitted for primary tumor resection before PRRT and those who were not. **Results:** Of the 94 subjects 31 were previously submitted for primary tumor resection. Patients who underwent surgery before PRRT showed higher stabilization or objective responses after PRRT ($p = 0.006$) and this translated into a better median PFS (70 vs. 30 months, $p = 0.002$). At multivariate analysis, after propensity score adjustements, operated patients showed a statistically significantly improved PFS: HR5.11 (1.43– 18.3), $P = 0.012$. **Conclusion:** Primary tumor resection prior to PRRT can make the tumor burden at baseline a modifiable prognostic factor to enhance the response to PRRT and obtain an improved PFS. **Keywords:** PNET, PRRT, Debulking surgery, PFS.

O3

Resectable Primary Tumor in Patients with Pancreatic Neuroendocrine Tumors Located to the Body or Tail and Unresectable Liver Metastases: Does Distal Pancreatectomy Improve Survival?

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Introduction: The role of primary tumor surgery in pancreatic neuroendocrine tumor (PNET) with unresectable liver metastases is controversial and international guidelines do not recommend surgery in that setting of patients. **Aim(s):** To assess whether or not distal pancreatectomy performed at diagnosis is associated with improved

long-term survival for body or tail primary localizations with unresectable liver metastases. **Materials and Methods:** From two institutional databases of patients affected by PNET and unresectable liver metastases, 30 patients with a potentially resectable but not-resected primary tumor located in the body or tail were identified and compared with a group of 63 patients who underwent a left-pancreatectomy at diagnosis. The endpoint was overall survival (OS). **Results:** The two groups were homogeneous except for liver tumor burden, percentage of G3 patients, extrahepatic matastases and age. Postoperative mortality was nil. After the propensity score adjustments median OS for patients undergoing left-pancreatectomy was 111 months vs. 52 for the non-operated patients ($p = 0.004$). At multivariate analysis, no surgery HR = 6.05 (95% CI: 1.65–22.2), liver tumor burden >25% and higher Ki-67 index were associated with an increased risk of death during follow-up. **Conclusion:** In PNETs located in the body or tail, distal pancreatectomy is associated with longer survival and should be proposed at diagnosis in resectable patients. **Keywords:** PNET, Surgery, Liver metastases, Distal pancreatectomy, Survival.

O4

Prognostic Factors for Recurrence of Sporadic Pancreatic Neuroendocrine Tumors after Surgical Resection

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Introduction: Pancreatic neuroendocrine tumors (PNET) are rare neoplasms with heterogeneous presentation. The diagnosis of malignancy is often difficult, and then further studies may contribute to improve prognosis criteria. **Aim(s):** To evaluate prognostic factors of patients with sporadic PNET submitted to surgical treatment. **Materials and Methods:** We retrospectively evaluated 114 patients admitted to our Hospital. We evaluated tumor diagnosis, patients' surgical risk and comorbidities, surgery technique, postoperative complications, disease recurrence, and tumor caracteristics. **Results:** PNET diagnosis was nonfunctioning in 33 patients (PNET-NF), insulinomas in 70 (PNET-I) and other functional tumors in 11 (PNET-OF). PNET-NF group showed significantly higher age, lower weight and lower BMI than PNET-I. PNET-I group underwent significantly more pancreatic enucleations and less pancreatoduodenectomies than other groups. 30-day mortality was significantly higher in PNET-NF group. PNET-I group showed more tumors with grade I, smaller diameter and lower TNM staging and disease recurrence. Gender, weight, BMI, ASA, tumor diagnosis, tumor grade and diameter were indicators of disease recurrence. In multivariate analysis, diagnosis of PNET and BMI were independent prognostic factors for tumor recurrence. **Conclusion:** Patients with PNET-NF had higher incidence of death during postoperative period. PNET-I had less malignancy. PNET type and BMI were independent prognostic factors for disease recurrence. **Keywords:** Pancreas, Neuroendocrine tumor, Prognosis, Recurrence.

O5

Liver Transplantation for Gastroenteropancreatic Neuroendocrine Tumors

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Introduction: Neuroendocrine tumors (NET) are rare neoplasms and liver transplantation (LT) for hepatic metastases is indicated in selected cases where other therapies have failed. **Aim(s):** We aimed to present results of LT for two cases of gastroenteropancreatic (GEP) NETs. **Materials and Methods:** We performed 738 adult-LTs from January 2008 to December 2015, with only 2 patients transplanted for GEP-NETs that were reviewed. **Results:** Patients were female with 29 and 32 years at transplantation. In the first case, a grade 1 ileal NET with mesenteric lymph node and liver metastases associated to carcinoid syndrome was diagnosed in 2005, and submitted to ileal resection in 2005, resection of hepatic hilar lymph node metastases in 2008 and LT in 2015. The second case, presented grade 2-pancreatic insulinoma associated to hypoglycemia diagnosed in 1999. Patient was submitted to pancreatic enucleation in 1999 and 2004, pancreaticoduodenectomy and hepatectomy in 2005. In 2006 was started hepatic chemoembolization that was followed for LT in 2008. The interval between metastases diagnosis and LT was 10 and 3 years respectively. The LT perioperative period occurred uneventfully, and patients are alive with normal liver function, without tumor recurrence 3 months and 7 years after LT. **Conclusion:** LT can be considered for high selected cases of metastatic GEP-NETs. Longer intervals until LT may be associated with better outcomes; however further studies are needed to identify optimal criteria for transplantation in these cases. **Keywords:** Liver transplant, Metastasis.

O6

Outcomes of Cytoreductive Surgery for Well-Differentiated Metastatic Neuroendocrine Tumors in the Setting of Extra-Hepatic Metastases

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Introduction: Cytoreduction with extra-hepatic disease for neuroendocrine tumors (NET) remains controversial. **Aim(s):** To define the outcomes of cytoreduction for metastatic NETs in the setting of

extra-hepatic metastates. **Materials and Methods:** Patients undergoing cytoreductive surgery for G1 or G2 NETs with extra-hepatic metastases were identified from an institutional database (2003-2014). Primary outcomes were post-operative hormonal response, progression-free and overall survival (PFS, OS). **Results:** 55 patients were identified, with median age of 59.3 years old. 80% had small bowel primaries and 49.1% were G1. 13% had only extra-hepatic metastases. The others had combined intra/extra-hepatic metastases. Resection included liver (87%), small bowel (22%), mesenteric (25%) and retroperitoneal (11%) nodes, and peritoneum (7%). 30-day major morbidity (Clavien III-V) was 18%, with 3.6% mortality. Median length of stay was 7 days. Liver embolization was used in 31% at a median of 15 months after surgery. Post-operative hormonal response occurred in 70%. 41 (75%) patients received somatostatine analogs, more commonly with small bowel primaries, but without difference in grade, carcinoid syndrome or 5HIAA response to surgery. 5-year OS was 77% and 5-year PFS was 51%. **Conclusion:** Cytoreduction of metastatic well-differentiated NET with extra-hepatic metastatic disease provides significant tumoral and hormonal control, with favourable PFS and OS. Aggressive surgical management appears indicated even with extra-hepatic disease. **Keywords:** Cytoreduction, Surgery.

O7

Impact of Early Surgery on Prognosis in Advanced Gastro-Entero-Pancreatic Neuroendocrine Tumours (GEP-NET)

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Introduction: In gastro-entero-pancreatic neuroendocrine tumours (GEP-NET) the role of surgery remains to be determined. **Aim(s):** This retrospective analysis of GEP-NET patients using the new Austrian GEP-NET registry (ANETS) examines the impact of surgery versus conservative therapy as first line treatment in regard to progression free survival (PFS). **Materials and Methods:** Data of 39 patients with advanced GEP-NET were assessed in the ANETS registry between January 2014 and December 2015. Patients were analysed in two groups according to first line treatment. 13 patients were treated with surgery or with ablative procedures as TACE (transarterial chemoembolization), while 26 patients were treated with drug therapy including Somatostatin analogues and/or targeted therapy. **Results:** Patient characteristics did not differ significantly with regard to age, sex, primary tumour site and grading (G1, G2, G3). However, patients treated by surgery had significantly less tumour load at the time of diagnosis. PFS was significantly better in the group treated with surgery and/or TACE compared to a drug-based first line therapy (PFS 25 vs. 18 month; $p = 0.012$) This observation was independent of histological grading or primary tumour site. **Conclusion:** This first experience with a new GEP-NET registry in Austria suggests a benefit of early surgery and/or local-ablative treatments in advanced GEP-NETs. Despite several limitations it gives reason for further investigations. **Keywords:** GEP-NET surgery, Medical treatment, Prognosis, GEP-NET-registry.

O8

Well Differentiated, Non Functioning Neuroendocrine Tumours of the Pancreas: A Surgical Series with Clinical and Pathological Correlations

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Introduction: The only curative treatment for pancreatic neuroendocrine tumors (PNET) is surgery. **Aim(s):** Describe clinical and pathologic features of resected non-functioning (NF) G1 and G2 PNET. **Materials and Methods:** We retrospectively reviewed data of patients (P) who underwent surgery for PNET between 2011 and 2015 in our Center. G3 and functioning tumours were excluded. Clinical and pathologic features of G1 and G2 were compared. A subanalisys was performed considering the Ki67 cutoff of 5%, defining two groups: G1G2a and G2b. **Results:** Of 183 resected PNET, 149 were NF, 61 G1 and 74 G2. Radical surgery rate was 92%. No differences between G1 and G2 for gender, age and clinical onset (symptomatic or incidental). G2 resulted significantly larger then G1 (mean diameter: 37.8 vs. 19.3 mm, $p < 0.001$), with higher rate of distant metastases (18.9 vs. 1.6%, $p < 0.001$), vascular invasion (60.8 vs. 18%, $p < 0.001$) and peri-endoneural infiltration (41.9 vs. 14.7%, $p < 0.001$). The rate of nodal involvement was evaluable in 105 P who received limphadenectomy, resulting higher in G2 (56.5%) compared with G1 (32.5%) (p 0.03). The subanalysis shows that G2b presents larger diameters (mean diameter: 28.8 vs. 15.7 mm, $p < 0.001$) and a higher rate of vascular and peri-endoneural infiltration (p 0.001, p 0.01). **Conclusion:** In this large series of resected PNETs, we found significant associations between tumor grade and local invasion, nodal involvement and distant metastases. Similar results are evident in the subanalysis considering Ki67 5% cutoff. Follow up is ongoing. **Keywords:** Grade.

O9

Surgical Management of Nonfunctioning Pancreatic Neuroendocrine Tumors 2 cm or Less in Size: Results from a Multi-Institutional Clinical Analysis in China

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Introduction: There is a paucity of evidence regarding surgical management and survival in nonfunctioning PNETs 2 cm or less. **Aim(s):** To investigate the importance of surgical management through clinical analysis of NF-PNETs ≤2 cm in imaging size in China. **Materials and Methods:** We reviewed patients with NF-PNETs at three institutions in China from January 1, 2010 to August 30, 2015. Patients were included if the tumor was sporadic and ≤2 cm in image manifestations. **Results:** There were 49 patients. 38.8% had nonspecific symptoms and the others were diagnosed through health imaging examination. Through imaging diagnosis, the size of the tumors was 1.5 ± 0.4 cm and 8.2% had regional lymph nodes metastasis but no one had distant metastasis. 30.6% underwent pancreaticoduodenectomy, 44.9% distal pancreatectomy, 22.4% local resection and only one patient with multiple focuses in pancreas had total pancreatectomy. Postoperative pathological diagnosis showed that the proportion of G1 grade was 79.6%, G2 14.3%, and G3 6.1%. Pathological diagnosis reported that 14.3% had regional lymph nodes metastasis positive, 12.2% perineuronal invasion and 4.1% perineuronal invasion. Follow-up on November 30, 2015, 14.3% had metastasis and 6.1% died from tumor metastasis. Three-year progression-free survival rate rate was 82.3% and three-year overall survival was 91.6%. **Conclusion:** The minority of NF-PNETs 2 cm or less will metastasize. It suggests that they should receive surgical management and long-term follow-up. **Keywords:** NF-PNETs ≤2 cm, Surgical management, Clinical analysis.

O10

Evaluation of the Therapeutic Approaches Impacting on the Survival of Patients with an Advanced Pancreatic Neuroendocrine Tumor

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Introduction: The therapeutic approaches in metastatic pancreatic neuroendocrine tumors (pNET) are currently used as a palliative strategy to control symptoms and potentially improving patient survival. **Aim(s):** We evaluated the impact of different treatments on the survival of well-differentiated metastatic pNET patients (pts). **Materials and Methods:** Retrospective study of variables in a consecutive multicenter cohort (n = 312) of pathologically confirmed, sporadic, well-differentiated metastatic pNET pts diagnosed between 1993 to 2010. The minimum follow-up was set at 5 years. **Results:** 129 pts. underwent surgery, being the intent curative in 33 (10.6%) and palliative in 96 (30.8%). 140 pts (44.9%) did not undergo surgery. The median OS from the time of diagnosis was 18.5 years, 10.0 years, and 4.6 years, respectively. The statistical evaluation revealed a benefit of the curative intent surgery at 5 and 10 years with Odds ratio 2.1 (vs palliative) and 6.8 (vs conservative). Although 258 pts had liver metastases, only 47 (18.2%) underwent loco-regional treatment which resulted in a significant prolonged survival at 5 and 10 years (Odds ratio 1.61). 249 (79.8%) pts underwent systemic treatment without showing any significant improvement of the OS. **Conclusion:** These data show that an interventional approach improves the OS in pNETs. We believe that an appropriate multidisciplinary pNET patient selection can optimize the therapeutic strategies resulting in a significant impact on the survival. All authors equally contributed to this work. **Keywords:** pNET.

O11

Minimally Invasive vs. Open Pancreatic Surgery in Patients with Multiple Endocrine Neoplasia Type 1

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Introduction: The role of minimally invasive pancreatic surgery for pancreatic neuroendocrine neoplasms (pNENs) in patients with multiple endocrine neoplasia type 1 (MEN1) is not well defined. **Aim(s):** The aim of this study was to compare the outcome of minimally invasive versus open pancreatic resections in patients with MEN1. **Materials and Methods:** Prospectively collected data of MEN1 patients who underwent a primary distal pancreatic resection and/or enucleation for nonfunctioning pNENs or insulinoma were retrospectively analyzed regarding the outcome of minimally invasive or open pancreatic resections. **Results:** 33 patients underwent primary pancreatic resection for either organic hyperinsulinism (n = 9, 27%) or non-functioning pNENs >1 cm in size (n = 24, 73%). Twenty-one (64%) patients underwent an open surgical (group 1) and 12 patients (36%) a minimally invasive approach, either laparoscopic (n = 8) or robotic-assisted (n = 4) (group2). Group 2 had a significant shorter operative time (200 vs. 260 minutes; p = 0.036), less intraoperative blood loss (120 vs. 280 ml; p < 0.001) and a shorter hospital stay (11 vs. 15.5 days; p = 0.034). The rate of patients with postoperative complications, especially postoperative pancreatic fistulas, was not different between groups (62% group 1 vs. 67% group 2, p = 0.74). **Conclusion:** Minimally invasive distal pancreatic resections and enucleations are feasible and safe in MEN1 patients with insulinoma or non-functioning pNENs. **Keywords:** Pancreatic neuroendocrine neoplasm, Laparoscopic pancreatic resection, MEN1.

O12

Factors Affecting Recurrences of the Non-Functioning Pancreatic NET after Resection

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Introduction: In 2010, WHO classification has been modified. However, the usefulness of the criteria for surgeons has not been elucidated, because the criteria is defined by cell growth represented by Ki67 for overall survival and may not represent invasiveness of the tumor. **Aim(s):** The purpose of the study is to examine if the WHO 2010 classification correlates with the recurrence rate after tumor resection. **Materials and Methods:** From January 2000 to June 2014, we had 106 pancreatic NET patients who underwent resection without distant metastasis. We analyzed 45 non-functioning PNET patients for WHO 2010 classification and other pathological factors with survivals and recurrence rate for non-functioning PNET. **Results:** There were 29 G1 PNET patients, 14 G2 PNET patients and 2 PNEC patients. 1) WHO2010 predicted disease free survival (p = 0.041). 2) Pathological lymphatic invasion(ly), vein invasion (v) and lymphnode metastasis correlated with disease free survival (DFS, p = 0.003, p = 0.001 and p = 0.002 respectively) but tumor peripheral invasion did not. 3) Ly, v, peripheral invasion did not correlate with recurrence type. 4) WHO2010 status correlated with invasiveness such as ly and v. 5) Lymphnode metastasis was an independent relapsing factor. (p = 0.025, risk ratio: 10.8, 95% CI: 1.37-119). **Conclusion:** WHO2010 criteria represented tumor invasiveness as well as tumor growth. Of note, nodal status correlated with DFS independently, suggesting that examination of the nodal metastasis is essential whenever PNET is resected. **Keywords:** WHO2010, invasiveness.

O13

Curative Resection in Digestive Neuroendocrine Neoplasms: Recurrence-Free Survival Rate and Definition of a Risk Score for Recurrence

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Introduction: Surgery with radical intent is the only curative option for digestive neuroendocrine neoplasms (DNENs), but clinical practice shows disease-free pts recurring even after years. **Aim(s):** To determine in consecutive DNENs treated by radical surgery the recurrence-free survival (RFS), and define a risk score for recurrence. **Materials and Methods:** Retrospective analysis of sporadic pancreatic (pNENs) or small bowel NENs (SbNENs) who had R0/R1 surgery (1993-2014) followed by ≥12 month-observation. Pts were classified by ENETS TNM/grading system. Survival analysis was performed by Kaplan-Meier, risk factors by Cox-Regression, cut-off by ROC. **Results:** 157 pts (35.7% pNENs, 64.3% SbNENs) were analyzed, with 2.5% median ki67 (1%-20%); 17.8% stage IV at diagnosis. Median RFS was 53 months (5-yr rate 47.3%). 4 risk factors for recurrence were significant at multivariate analysis: ki67>5%, R1 status, lymphnodal involvement, primary tumor size (>30 mm in pNENs, >14 mm in SbNENs); primary site not significant. 3 risk categories were identified: low risk (0-1 factors), moderate risk (2 factors; HR vs. low risk 5.99, P < 0.01), high risk (3-4 factors; HR vs. moderate risk 2.28; HR vs. lor risk 12.46; P < 0.05). **Conclusion:** Almost 50% of DNENs treated by curative surgery recur, independently from primary site, in 5 years. Major risk factors are ki67, primary size, lymphnode involvement and R status (R0/R1). Definition

of risk categories might help in selecting patients who may benefit from adjuvant treatments. **Keywords:** Neuroendocrine, Curative surgery, Recurrence risk.

O14

Duodenum Preserving Pancreatic Head Resection for Neuroendocrine Pancreatic Tumors of the Head of the Pancreas

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Introduction: Duodenum Preserving Pancreatic Head Resection (DPPHR) is a surgical procedure uncommonly used in benign tumors of the head of the pancreas as alternative to pancreaticoduodenectomy. **Aim(s):** We reviewed our experience in Neuroendocrine Pancreatic Tumors of the head of the pancreas (NPThp) who had a DPPHR from 1991 to 2015, in order to evaluate the complications and long term clinical outcome. **Materials and Methods:** Among 110 patients with NPThp (17 MEN1), 80 underwent a surgical operation. Eight patients (10%) had a DPPHR. Follow-up was until December 2015. **Results:** 5 M/3 F, averaging 53 years, three insulinomas and five non-functioning tumors. Tumor size was 1.4 cm (range 0.8–2.0). One patient had a previous central pancreatectomy and one patient had a synchronous colonic cancer (T2N0). One patient had a chronic pancreatitis. All patients had complications: 5 pancreatic fistula (3 grade A, 2 grade B), 1 delayed gastric emptying, 1 bleeding and 1 patient had a duodenal ulcer. Hospital stay was 16.8 days (range 10–28) with one readmission for fistula infection. None required reoperation. Three patients died during the follow-up for unrelated reasons (121, 105, 3 mo. after surgery). After DPPHR only two patients showed pancreatic exocrine insufficiency (one chronic pancreatitis and the one with previous central pancreatectomy) and one had worsened previous diabetes. **Conclusion:** DPPHR for NPThp is associated to high rate of short-term complications but a better long term preservation of pancreatic function is achieved. **Keywords:** DPPHR.

O15

Cystic Pancreatic Neuroendocrine Tumors: A Clinicopathologic Study and Long-Term Follow-Up after Surgical Resection in a Single Institution

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Introduction: Cystic pancreatic endocrine tumors (CPETs) are rare lesions accounting for 2–17% of all endocrine pancreatic neoplasms. Their natural history and prognostic factors remain unclear. **Aim(s):** Describe the clinicopathologic features of CPETs and evaluate long-term outcome after surgical resection (SR). **Materials and Methods:** We retrospectively reviewed data of patients (P) who underwent SR for CPETs in our Institution between 1998 and 2015. Continuous variables were reported as median with SD. **Results:** Study population consisted in 46 P (21 M/25 F), with a median age of 54 y (± 15). 20 P (43.5%) presented symptomatic onset, 7 (15.2%) were functioning tumors and 2 (4.3%) were metastatic at the diagnosis. Regarding to the site, 9 (19.6%) were localized to the head, 12 (26.1%) to the body, 18 (7%) to the tail and 7 (15.2%) were multifocal. 4 P (8.7%) were MEN1. Surgery was radical in all cases. For what concern specimens, 38 (82.6%) were G1 and 8 (17.4%) were G2. Perineural, vascular and lymphatic microscopic local invasion was found in 5 (10.9%), 8 (17.4%) and 1 (2.2%) respectively. Nodal metastases were found in 11 (23.9%) among 35 who received lymphadenectomy. Main pancreatic duct enlargement was present in 6 P (13%). At a median follow-up of 59 months (± 38), 37 P are disease free and 5 P (10.8%) incur in disease progression (4 P were lost at FU). **Conclusion:** CPETs are characterized by a well-differentiated pattern and a good long-term outcome. More studies are needed to better define their biologic behavior. **Keywords:** Pancreas, Cystic.

O16

Number and Localization of Positive Lymph Nodes Correlate with Recurrence in Nonfunctioning Pancreatic Neuroendocrine Neoplasms: Implications for Surgery, Staging and Surveillance

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Introduction: Lymph Nodes involvement is a powerful prognostic factor for nonfunctioning pancreatic neuroendocrine neoplasms (NF-PNEN). **Aim(s):** To assess the prognostic value of the number and localization of positive lymph-nodes (PLN). **Materials and Methods:** Among 370 pts submitted to surgery for PNEN (2000-2014) we selected those who underwent radical (R0 or R1) pancreaticoduodenectomy (PD) for NF-PNEN with no distant metastases (M0) or inherited syndrome. **Results:** 53 patients were included. 31 patients (58.5%) had nodal metastases (N1). The median number of examined lymph nodes (ELN) and positive lymph nodes (PLN) were 20 (IQR 14-33) and 1 (IQR 0-2), respectively. ELN was significantly higher in N1 pts (23 vs. 17.5, P = 0.048). At a median follow-up of 46 months (IQR 28-68), 14 patients (26%) had recurrence and 4 (7.5%) deceased. N1 NF-PNEN had a significantly worse 3-year DFS compared with N0 NF-PNEN (69% vs. 94%, P = 0.013). Pts with PLN >1 had a worse DFS compared with those who had 0 or 1 PLN (62% vs. 90%, P = 0.005). On multivariate analysis, age >60 years, G3 NF-PNEN and PLN >1 were independent predictors of recurrence. PLN were always localized in stations 13 and 17. Involvement of station 12 was associated with a significant poorer DFS. **Conclusion:**

The number and the localization of PLN are associated with risk of recurrence after radical PD for NF-PNEN. An adequate lymphadenectomy (including station 12) should be routinely performed. This study suggests preliminary findings to support a revision of the current TNM-based staging systems. **Keywords:** PNEN, Nodes.

O17

Comparison of Radiological and Histological Tumor Size in Pancreatic Neuroendocrine Neoplasm

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Introduction: Radiological tumor size of pancreatic neuroendocrine neoplasms (PNEN) is crucial for management especially for asymptomatic, small lesions. **Aim(s):** Aim of this study was to compare radiological tumor size (RTS) and pathological tumor size (PTS) in patients with PNEN. **Materials and Methods:** 231 patients with sporadic PNEN who underwent pancreatic resection between 2000 and 2014 were included. RTS was defined as the largest tumor diameter at Ultra-Sound (US), Endoscopic Ultrasound (EUS), Computed Tomography (CT) or Magnetic Resonance (MR). PTS was defined as the largest tumor diameter at final pathological analysis. **Results:** The median RTS on US, CT, MR, and EUS were 10 mm (range 2–21 mm), 15 mm (range 11–25 mm), 17 mm (range 13–26 mm), and 23 mm (range 14–21 mm), respectively. The median PTS was 20 mm (range 13–30 mm). Difference between RTS and PTS was significant only for US RTS ($P = 0.009$). In the subgroup analysis of the T1 PNEN, the median RTS on US, EUS, CT, and MR were 14 mm (range 6–22 mm), 16 mm (range 3–24 mm), 11 mm (range 3–14 mm) and 13.5 mm (range 3–26 mm), respectively and was not significantly different from the median PFS. Among all patients, MR was the imaging technique that best correlated with PTS on linear regression analysis ($R = 0.8$, $P < 0.0001$). **Conclusion:** Among small PNEN <2 cm all the imaging techniques can identify the real tumor size of the lesion, although MR is the most accurate procedure. **Keywords:** Pancreatic neuroendocrine neoplasm, Size, Radiology, Pathology, Surgery.

O18

Neuroendocrine Liver Metastasis: A Novel Nomogram to Predict Patient's Prognosis after Liver Resection

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Introduction: Despite surgery remains the only potentially curative option for patients with neuroendocrine liver metastases (NELMs), the factors determining the prognosis of patients following hepatectomy are poorly understood. **Aim(s):** To developed a nomogram able to predict patient's prognosis. **Materials and Methods:** A multicentric database including 7 tertiary referral hepato-biliary-pancreatic centers was used to identify patients who underwent hepatectomy for NELMs between January, 1990 and December, 2014. **Results:** The median age of the 238 patients included in the study was 61.9 years (IQR: 51.5–70.1) and 132 (55.5%) patients were male. The median number of NELMs was 3 (IQR: 2–7) with a median size of 45 mm (IQR: 24–75) and median Ki-67 of 9% (IQR: 2–15). The 5- and 10-year overall survival (OS) were 67.1% and 50.8%, respectively. Number of NELMs ($HR = 1.06$, $p = 0.007$), metastasis size ($HR = 1.01$, $p < 0.001$), and Ki-67 ($HR = 1.06$, $p < 0.001$) resulted predictors of OS in multivariable analysis and were included in the nomogram predicting patient's prognosis. The stratification into 3 risk classes based on the predictions of our nomogram demonstrated a good prognostic discrimination (c-index = 0.72). The 5-year OS resulted 97.0% for patients in low-risk class, 71.0% in medium-risk class, and 41.1% for patients in high-risk class ($p < 0.001$). **Conclusion:** The classification based on the prediction of our nomogram demonstrated a good ability to discriminate patients with favorable and poor prognosis. **Keywords:** Neuroendocrine liver metastasis, Surgery, Nomogram.

O19

How Long Should We Look Up for Recurrence after Resection of Pancreatic Neuroendocrine Tumors?

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Introduction: There remains several unsolved issues to be settled about the management of pancreatic neuroendocrine tumors (PNETs) after resection. One of these problems are the follow up period after a complete resection of the tumor. **Aim(s):** We aimed to reveal the proper follow-up period after resection of PNETs. **Materials and Methods:** We retrospectively reviewed patients with PNETs who were operated in Kyoto University Hospital during 1992-2013. Duration for recurrence were compared according to the grades of initial tumor resected in the primary operation. Pathological grading were determined according to the 2010 WHO criteria. **Results:** There were 95 patients who underwent complete resection of PNETs (G1:G2:G3:unknown = 54:19:2:20). Twenty patients (21%; G1:G2:G3: unknown = 5:9:2:4, 9%:47%:100%:20%, respectively) had recurrences. Mean duration for recurrence after primary resection was 31.2 ± 22.0 months (G1:G2:G3: Unknown = 65.6:17.6:7.5:34.2, p = 0.02 between G1-G3). All G3 patients had recurrence within 1 year after the operation whereas the duration for recurrence scattered from 1.5 months to 11.3 years. Patients with recurrent disease were all operated by conventional radical resection, whereas no one who were treated with enucleation had recurrence. **Conclusion:** Duration for recurrence varies according to the WHO grading. Although G1 is considered to be relatively benign, we have to follow the patients for more than 10 years. **Keywords:** Pancreatic neuroendocrine tumor, Enucleation, Follow-up period.

O20

Appropriate Indication of Organ Preserving Surgery for Pancreatic Neuroendocrine Neoplasm

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Introduction: Organ preserving surgery (OPS) has been accepted for pancreatic neuroendocrine neoplasm (PNEN), particularly in a small and low malignant tumors. **Aim(s):** The aim of this study was to analyze the surgical outcome after these OPS in our institute, especially focusing on the lymph-node metastasis and post operative locoregional recurrence. **Materials and Methods:** 48 consecutive patients with PNEN underwent operation between 2003 and 2015. Patients were retrospectively classified into one of two groups: Organ Preserving group (OPG) and Standard operation group (SOG). We have applied OPS based on size criteria with tumor size less than 1.5 cm in non-functional PNEN and less than 2 cm in insulinoma with no evident bulky lymph-node swelling on preoperative imaging. **Results:** The median follow up periods was 30 months. OPS included enucleation in 2 patients, duodenum preserving pancreas head resection in 4 patients, central pancreatectomy in 2 and laparoscopic spleen preserving distal pancreatectomy in 5. The other 35 patients underwent standard pancreatectomy with regional lymph-node dissection. There were no statistically significant difference between these 2 groups in terms for operation time, bleeding amount and in-hospital stay. The OS was 80% at 5 years (median follow-up time 30 months). The lymph-node metastasis was recognized only in SOG with 12 patients (25%). There were no locoregional recurrent case in OPG. **Conclusion:** In selected patients, organ preserving surgery might be applicable for PNEN. **Keywords:** Organ preserving surgery, DPPHR.

O21

Intra-Operative Portal Vein Insulin Assay Combined with Occlusion of the Pancreas for Complicated Pancreatogenous Hypoglycemia

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Introduction: Pancreatogenous hypoglycemia is a rare endocrine disorder. The precise localization of hypersecreting tissue and determination of complete resection are two main challenges for complicated pancreatogenous hypoglycemia, such as multiple endocrine neoplasia syndromes type-1 (MEN-1) and nesidioblastosis. **Aim(s):** To assess the significance of intraoperative portal vein insulin assay for complicated pancreatogenous hypoglycemia. **Materials and Methods:** Two patients with Whipple's triad syndrome were diagnosed with MEN-1 and nesidioblastosis, respectively. Rapid portal vein insulin assay combined with temporary occlusion of the pancreas were applied in both patients. **Results:** Both patients were successfully cured by the operation without recurrence of hypoglycemia in the follow-up. For MEN-1 patient, the portal vein insulin decreased to the normal level after resection of tumors in the pancreatic body and tail. Complete resection of hypersecreting tissue was determined and the total pancreatectomy was avoided with certain of nonfunctional tumors in the head of pancreas. Based on the results of intraoperative portal vein insulin assay after occlusion of the pancreas, complete resection was also decided after the resection of pancreatic body and tail for patient with nesidioblastosis. **Conclusion:** The intraoperative portal vein insulin assay is an accurate method to determine complete resection of hypersecreting tissue for complicated pancreatogenous hypoglycemia. **Keywords:** Insulin assay, Pancreatogenous hypoglycemia, Nesidioblastosis, MEN1, Portal vein.

Non Digestive NETs (Bronchial, MTC, Pheochromocytoma)

P1

Efficacy and Safety of Everolimus in Advanced, Progressive, Nonfunctional Neuroendocrine Tumors (NET) of the Lung: A Subgroup Analysis of the Phase 3 RADIANT-4 Study

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Introduction: In the phase 3, RADIANT-4 study, everolimus (EVE) improved median progression-free survival (PFS) by 7.1 months in patients (pts) with advanced, progressive, nonfunctional NET of lung or GI tract compared to placebo (PBO); HR, 0.48; 95% CI, 0.35–0.67; P < 0.00001. **Aim(s):** To evaluate efficacy and safety of EVE in pts with lung NET from RADIANT-4. **Materials and Methods:** In RADIANT-4 study, pts were randomized (2:1) to EVE 10 mg/d or PBO, both with best supportive care. The present analysis reports subgroup of lung NET. **Results:** Of 302 pts, 90 had lung NET (EVE, n = 63 and PBO, n = 27). Median age, 65 years; males: 52%; most pts (99%) had well-differentiated disease; WHO PS 0/1/2: 71%/28%/1%; Caucasian: 86%. Prior therapies (EVE vs. PBO) included: somatostatin analogues (mostly for tumor growth control; 43% vs. 41%), surgery (52% vs. 67%), and chemotherapy (40% vs. 48%). Median PFS (95% CI) by central review (EVE vs. PBO) was 9.2 (6.8–10.9) vs. 3.6 (1.9–5.1) months with tumor progression risk-reduction by 50% in EVE (HR, 0.50; 95% CI, 0.28–0.88). Most frequent (≥5%) G3/4 adverse events irrespective of drug-relationship (EVE vs. PBO) were stomatitis (11% vs. 0), hyperglycemia (10% vs. 0), diarrhea (7% vs. 0), hypophosphatemia (7% vs. 0), dyspnea (5% vs. 7%), and hypertension (0 vs. 7%). **Conclusion:** EVE treatment improved PFS by 6 months and reduced tumor progression risk by 50% in pts with advanced, progressive, nonfunctional lung NET compared to PBO. EVE safety profile was similar to overall RADIANT-4 population. **Keywords:** PFS, Everolimus, Lung carcinoid.

P2

Pathomorphology of Sporadic Medullary Thyroid Carcinoma – A Retrospective Analysis for a Period of 10 Years

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Introduction: Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor, often difficult for diagnosis both clinically and histologically. **Aim(s):** We analyzed the pathomorphology of all patients with MTC, consecutively operated during the last ten years. **Materials and Methods:** Twenty four patients (12-m, 12-f, mean age 53.67 ± 13.27 y) with final histological diagnosis of MTC were included. **Results:** The proportion of MTC was 2.8% of all malignant thyroid tumors, surgically removed for the study period (n = 846). The size of MTC showed variations (from 1 to 12 cm, mean-3.27 ± 2.59 cm) and most of the cases (62%) were categorized as T3 tumor stage (T1-2, T2-7 and T3-15 cases). All MTC were infiltrative tumors, with various growth pattern, composed of neuroendocrine cells with cellular and nuclear pleomorphism. Lymph node (LN) metastasis were found in 17 patients (71%) and there were also variations in the size (0.5 to 3 cm) and number (1 to 10)/per case. Immunohistochemistry showed different degrees of calcitonin expression in tumor cells and amyloid stroma. During the follow up, reoperations for appearance of new LN metastasis were done in 8 of the patients and in 1 case there were also data for distant metastasis (pulmo, bones). **Conclusion:** The patients with MTC are presented often with advanced tumor stage and lymph node metastasis. The recognition of its specific cytomorphologic features is essential for the differential diagnosis with other types of malignant thyroid nodules. **Keywords:** Medullary thyroid carcinoma, Surgery, Pathology.

P3

Merkel Cell Carcinoma of Lymph Node Without Skin Primary Can – and Should – Be Distinguished from Others Metastatic Neuroendocrine Carcinoma

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Introduction: Merkel cell carcinoma of lymph node without primary tumour (MCCNWP) is a rare tumour which can be misinterpreted as lymph node metastasis (LNM) from a high-grade neuroendocrine carcinoma (NEC) on histological examination. However, this distinction is crucial for therapeutic management. **Aim(s):** Establish relevant tools for MCCNWP diagnosis. **Materials and Methods:** In this retrospective monocentric study, 17 MCCNWP were compared with 17 superficial LNM from other NEC (LNMNEC) (lung = 5, thyroid = 7, digestive tract = 3, other = 2). Clinical, morphological and immunohistochemical data (expression of Cytokeratin 7, 19, 20, chromogranin A, TTF1 and Cdx2) were available for all cases. The presence of Merkel cell Polyomavirus (MCPyV) was evaluated in all tumours by immunohistochemistry (CM2B4 antibody directed against MCPyV large t antigen) and PCR. **Results:** MCCNWP occurred almost exclusively in the groin area (15 cases) and always presented at a localized stage at time of diagnosis. On the contrary, only one LNM from a non-Merkel NEC presented in the groin area and 9 patients already had a generalized disease. Cytokeratin 20, CM2B4 and TTF1 expressions were observed respectively in 17, 8 and 0 MCCNWP and in 0, 0, 14 LNMNEC. MCPyV was identified by PCR in 15 MCCNWP and no LNMNEC. Death occurred in 5 MCCNWP and in 9 LNMNEC (median follow-up respectively 19 and 21 months). **Conclusion:** Site, tumour extension, CK20 and TTF1 expressions and MCPyV identification are major clues for MCCNWP diagnosis. **Keywords:** Merkel cell carcinoma, Lymph node, MCPyV.

P4

Thymic Neuroendocrine Neoplasia: Therapy with Everolimus

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Introduction: Due to the low incidence of 0.02/100 000 no established medical therapy for thymic neuroendocrine neoplasia (t-NEN) exists. **Aim(s):** This is the first report on the effect of everolimus on t-NEN. **Materials and Methods:** 4 patients (37; 38; 54; 55 yrs, 2 male, 2 female, all nonsmokers) with t-NEN (Ki-67 10; 20; 20; 5% respectively) received everolimus 10 mg/d after failure of at least 1 previous medical therapy (2,3,6,1 resp.). Everolimus was applied after a median of 32.4 months after first diagnosis (range 5–56 months). In 3 patients thoracic pain led to the diagnosis, whereas in 1 patient the t-NEN was an incidental finding. The tumor size at first diagnosis was 22;13;11; 9 cm resp. Thymectomy was performed in 3 cases. All patients developed metastasis, in 3 cases after thymectomy. No hormonal hypersecretion was observed, 1 patient had multiple endocrine neoplasia type 1. **Results:** We observed stable disease for a median of 20,8 months (7–42). Longer sustained response was associated with lower Ki-67 index and lower number of previous medical therapies. No severe side effects occured. **Conclusion:** This first series on everolimus in t-NEN shows promising results, especially in patients with lower proliferation index. Everolimus was well tolerated. **Keywords:** Thymus neuroendocrine neoplasia, Thymic carcinoid, Everolimus, Targeted therapy, mTOR inhibitor, Men1.

P5

A Case Series of 27 Primary Ovarian Neuroendocrine Tumors

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Introduction: Primary neuroendocrine tumors of the ovary are rare and often found incidentally. **Aim(s):** We examined 27 primary ovarian carcinoids treated at a single institution over the course of 21 years, one of the largest series in literature. **Materials and Methods:** All patients with ovarian neuroendocrine tumors between 1994 and 2015 were retrospectively reviewed in this IRB approved analysis. Of 99 patients identified, pathology confirmed 27 primary ovarian carcinoids. Clinical outcomes, surgical and pathological findings were reviewed. A Kaplan Meier curve was constructed using this data. **Results:** The mean age of our cohort was 48.7 years (range 23-75 years). All tumors were associated with ovarian teratoma. The majority of tumors were benign. 19 patients (70.4%) had carcinoids associated with dermoid cysts, of which 9 were associated with thyroid tissue (strumal carcinoid). 7 patients (25.9%) had ovarian mucinous tumors, of which 3 were benign and 4 were malignant. Bilateral disease was found in 2 patients. All patients with benign tumors had no evidence of carcinoid disease at time of review. Of the 4 malignant tumors, one patient is alive with disease, two have died of disease, and one was lost to follow-up. **Conclusion:** Our case series is one of the largest reported. The majority of tumors were found to have a benign outcome with a good prognosis. The average age of these patients was younger than expected in malignant ovarian tumors. All of the malignant tumors were of the mucinous carcinoid variant. **Keywords:** Ovarian carcinoid, Neuroendocrine.

Clinical Cases / Reports

Q1

Pseudotumor of Thymus Occuring after Hypercortisolism Recovery: Case Report

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Introduction: Cushing syndrome is due to an ectopic secreting adrenocorticotropic hormone (ACTH) in 10% to 20% of cases. Among them, thymic tumors represent almost half of cases. It has been described that patients sometimes develop benign hyperplasia after hypercortisolism correction. **Aim(s):** We represent a case of a thymic tumor to enhance the awareness of this entity in order to avert diagnostic thoracotomy. **Materials and Methods:** Case report. **Results:** A 45 y.o man was admitted in our department to manage a severe cushing's syndrome. The results of endocrine work-up were consistent with an ectopic cushing syndrome. Morphologic investigations, a computed tomography body scan and an octreoscan, has shown a 1/1.5 cm pulmonary tumor. the patient underwent a thoracic surgery. the histology revealed a carcinoid tumor with positive immunostaining for ACTH. this surgery led to a rapid remission of the hypercortisolism. However, 6 months later, a follow-up CT scan showed a triangular nodular mediastinal enlargement. Based on the fact that the cortisol and ACTH levels were normal, we have decided to not operate the patient and follow the thymic tumor progression by CT scan months later, the CT scan has shown a significant reduction in the thymic enlargement. **Conclusion:** The mechanisms of thymic hyperplasia is thought to be thymic depletion resulting for high plasmatic cortisol concentrations followed by the thymic enlargement. **Keywords:** Thymic tumor, Cushing's syndrome, Ectopic secretion.

Q2

Very Early Response to Sunitinib in VHL Patient with Pancreatic Neuroendocrine Tumor

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Introduction: Pancreatic neuroendocrine tumors (pNET) arise in 8-17% of Von Hippel Lindau (VHL) patients and surgery plays a key role for resectable lesions. Alternative medical therapy, such as target therapy (TT), can be used when surgery is unfeasible. **Aim(s):** Case report. **Materials and Methods:** A 32 years old female affected by pNET in the spectrum of VHL presented a major nodule in the pancreatic body (62x71x45 mm) and similar lesions in the head (max 27 mm). **Results:** Pancreatic lesions were judged unresectable, so medical therapy with sunitinib, a multiple thyrosine kinase receptors inhibitors, was started (37.5 mg/day, 4 weeks on+2 off). After only 12 days of treatment, patient was hospitalized due to abdominal pain and nausea. Surveillance CT confirmed the same size of pancreatic lesions, but displayed an increased hypodensity, suggesting a colliquative area. Tumor density (TD) measured 85 HU versus 133 HU in the prior treatment CT, with a reduction of 36%. According to RECIST criteria this is a stable disease (SD), while with CHOI criteria this is considered a partial response (PR). After six months of therapy, TD measured 83 HU and we observed a PR even according to RECIST criteria: 38 mm versus 71 mm, with size reduction of 53%. After one year the patient was in SD. **Conclusion:** TT may often modify TD. Moreover, as in our case, a TD modification may anticipate a dimensional response and can be used as response therapy criterion. According to literature, this is the first case of documented early (<8 weeks) response to sunitinib. **Keywords:** VHL therapy.

Q3

The Application of Octreotide in a SINET Patient with Carcinoid Syndrome, Carcinoid Heart Disease and Carcinoid Crisis: A Case Report

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Introduction: In Chinese population, small intestinal neuroendocrine tumor (SINET) only accounts for 2.2% of gastroenteropancreatic NET, while carcinoid syndrome, carcinoid heart disease (CHD) and carcinoid crisis are rarer. **Aim(s):** To report a case of SINET with carcinoid syndrome, CHD and carcinoid crisis happening sequentially and the usage of Octreotide in this patient. **Materials and Methods:** In August 2012 a 57-year-old male patient presented with diarrhea, flushing and weight loss due to SINET (G2, Stage IV). Octreotide LAR 30 mg was applied every 4 weeks since August 2012. **Results:** Symptoms alleviated and serum CgA declined from 1568 ng/ml to 704 ng/ml and CT showed stable disease. However, in October 2013, the patient manifested CHD with chest distress and gasp. Echocardiogram showed severe tricuspid insufficiency and right atrial enlargement. Besides diuretic therapy, we increased the frequency of Octreotide LAR (30 mg) to every 3 weeks, and symptoms remitted again. 8 months later, carcinoid crisis happened in the patient with hypotension, tachypnea, cyanosis, and severe hypoxemia. High dosage of short-acting Octreotide (1.2 mg–1.4 mg iv drip/d) was used. After the symptoms were controlled, Octreotide LAR was maximized to 60 mg every 3 weeks. **Conclusion:** This case shows Octreotide LAR can help control carcinoid syndrome and CHD in SINET, while high dosage of short-acting Octreotide is vital when carcinoid crisis occurs. **Keywords:** Octreotide, Small intestinal neuroendocrine tumor, Carcinoid syndrome, Carcinoid heart disease, Carcinoid crisis.

Q4

Non-Secreting Pancreatic Neuroendocrine Tumors Co-Esistenting with ACTH-Dependent Cushing Disease

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Introduction: Pancreatic neuroendocrine tumors (pNET) occur occasionally as cause of ectopic ACTH-dependent Cushing disease (ECD). **Materials and Methods:** We reviewed 4 patients (pts) with occult ACTH-dependent Cushing disease (OACD) and coexistent non secreting pNET. **Results:** 1rst pt was a 68yrs male underwent bilateral adrenectomy for OACD, because he was resistant to pharmacological treatment (ketoconazole and mitotane). Histological samples showed bilateral macronodular adrenal hyperplasia (BMAH). Pt started treatment with SSA. After 5 yrs disease free survival, a octreoscan and a total-body TC documented liver and lung metastatic pNET. Despite radiometabolic treatment, pt died for progression disease. 2nd pt was a 58yrs male, 3rt pt was a 31yrs male and 4th pz was a 68yrs female. All pts were diagnosed for ECD. In all cases, presurgery TC and 68Ga-PET/TC showed a pancreatic nodule, suggestive for pNET. Biopsy confirmed the diagnosis but immunoistomemistry (IIC) for ACTH and CRH was negative. All pts started treatment with SSA and ketoconazole. Only a pt was responder to medical treatment, with a good clinical and biochemical response. As two pts were resistant to pharmacological treatment, they underwent bilateral adrenectomy. Histological samples showed BMAH. **Conclusion:** Our small case-series suggest that in ECD/OACD a coexistent pNET should be considered. A careful clinical, morphological and histological with ACTH and CRH IIC evaluations are suggested for distinguishing not-secreting pNET in the clinical contest of ECD. **Keywords:** NET.

Q5

Multivisceral Transplantation and Vascularised Sentinel Forearm Flap for a Metastatic Gut-Derived Neuroendocrine Tumour: Follow-Up

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Introduction: We previously reported the first documented case of a novel approach in a patient with extensive mesenteric metastases from a small bowel (SB) NET: this combined multivisceral transplantation (MVT) and a vascularised sentinel forearm flap (VSFF) from the same donor. **Aim(s):** We re-present this case after prolonged follow-up. **Materials and Methods:** A male patient was diagnosed with a well-differentiated Grade 1 (Ki67<1%) NET when aged 44. Initial biochemistry was: chromogranin A 395 pmol/L (normal <60), chromogranin B 349 pmol/L (normal <150), 24 hr urinary 5-HIAA 643 μmol/L (normal <40). Pre-operative 68-Ga DOTATATE PET/CT demonstrated uptake in an aorto-caval lymph node and bulky mesenteric disease, which was confirmed at laparotomy as stage IV disease encasing the mesenteric root. Numerous lymph nodes and multifocal primary tumour (7 sub-centimetre lesions) were also found at surgery. **Results:** Following 4 cycles of neoadjuvant 177-Lu PRRT, he simultaneously received modified MVT (stomach, pancreas, spleen, small bowel, right hemi-colon), VSFF and resection of the aorto-caval lymph node. Disease stage was pT3 N1 M0 L1 V0 R0. **Conclusion:** The patient is currently well and fully physically active 30-months post-MVT/VSFF with no evidence of disease recurrence on follow-up imaging or biochemistry. There was never any rejection in the visceral graft, with one mild, easily treated reaction in the VSFF. **Keywords:** Neuroendocrine, Transplantation, Multivisceral, Forearm flap.

Q6

Cystic Neuroendocrine Tumors of the Pancreas (c-pNETs): A Single-Center Experience

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Introduction: c-pNETs are rare and may be less aggressive than their solid counterparts. **Aim(s):** To report on the clinical manifestations and outcomes of patients (pts) treated for c-pNETs. **Materials and Methods:** We identified all pts diagnosed with a c-pNET at Mayo Clinic from 1990 to 2014. Data on patient characteristics and outcomes of therapy were analyzed. **Results:** 46 pts were identified, (65% were males). Median age at diagnosis (dx) was 59.5 years (31–78 years). 26 (57%) pts had no symptoms at dx. Abdominal pain was the most common symptom. Five pts (12%) had symptoms due to hormonal secretion and 4 (9%) had metastases at dx. 10 pts (22%) had MEN1. The dx was made on a resection specimen in 63%, on FNA in 26%, a core needle biopsy in 9% and an open biopsy in 2%. 15 NETs (33%) were of WHO grade 1, five (11%) of grade 2 and 26 (56%) were ungraded. The majority of pts (66%) had unifocal tumors. Most pts (93%) underwent resection, most often distal pancreatectomy (81%). Most NETs were located in the tail (52%) followed by body and head (15% each). The ENETS T-stage was: T1: 30%; T2: 39%; T3: 28%; T4: 2%. Only 4 pts (9%) had nodal involvement. Among resected pts, recurrences occurred in 9 with a median time to recurrence being 68.9 months (range: 6 to 220 months). T-stage did not predict recurrences ($p = 0.31$). **Conclusion:** c-pNETs are often diagnosed incidentally, and are usually unifocal, nonfunctional and in the tail. The prognosis after resection is good with majority of pts cured but late recurrences may occur. **Keywords:** Pancreatic NETs, Cystic, Prognosis.

Q7

Type 1 Gastric Neuroendocrine Tumor with SAPHO Syndrome Effectively Treated by Octreotide: A Case Report

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Introduction: Type 1 gastric neuroendocrine tumor (gNET) which is associated with chronic atrophic gastritis type A can be treated with SSA for the recurrence. SAPHO syndrome characterized by synovitis, acne, pustulosis, hyperostosis and osteitis is a kind of rare aseptic inflammation, which is thought to be related with abnormal autoimmune. Presently, there is no satisfied treatment for this illness. **Aim(s):** To present a case with type 1 g-NET and SAPHO syndrome effectively treated with long-acting octreotide. **Materials and Methods:** A 54-year-old female with type 1 gNET who had recurrence disease after ESD therapy was treated with SSA for 22 months. Interestingly, the skin lesions of palmoplantar pustulosis and arthralgia before was disappeared during the treatment and was recurred after the treatment was terminate for 4 months. The diagnosis of palmoplantar pustulosis was confirmed by clinical manifestation and histopathological findings and hyperostosis and osteitis was confirmed by X-ray, so the diagnosis of SAPHO syndrome was made. **Results:** The treatment with SSA was given for another 6 months. The skin lesions presented notable improvement after first injection and the arthralgia was alleviated after the second injection, and all the symptoms of SAPHO syndrome were disappeared during the treatment. No tumor was found in the follow-up of gastroscopy. **Conclusion:** This rare case reminds us to notice SAPHO syndrome as a possible complication of type 1 g-NET and SSA may be an effective therapy for this condition. **Keywords:** gNET, SAPHO syndrome, SSA.

Q8

Heterotopic Pancreas Mimicking a Gastrointestinal Neuroendocrine Tumor: A Case Report

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Introduction: Heterotopic pancreas, defined as an atypical presence of pancreatic tissue with no anatomic or vascular continuity with the pancreas, is relatively rare. In most cases it is diagnosed during autopsy or incidentally, since it becomes symptomatic only in few cases, causing bleeding, pain or obstruction. **Aim(s):** To report a case of heterotopic pancreas mimicking an intestinal neuroendocrine tumor at 68Ga PET/CT scan. **Materials and Methods:** A 50-year-old woman was evaluated at the Department of Gastroenterology and Endoscopy Unit because of an incidental detection of a hypervascular nodule close to the Treitz at computed tomography (CT), performed as a part of chronic liver disease follow-up. A neuroendocrine tumor was supposed. Her past medical history was unremarkable. The patient did not present any symptom suggestive for neuroendocrine syndrome and her blood exams including general and specific circulating neuroendocrine markers were normal, except for mild liver function test impairment. A 68Gallium DOTATOC positron emission tomography/computed tomography (68Ga PET/CT) showed a high affinity for somatostatin receptor. **Results:** Enucleation of the lesion was performed and a heterotopic pancreatic tissue was finally proved at histology. **Conclusion:** The present case suggests that heterotopic pancreas should be considered in the differential diagnosis of gastrointestinal lesions positive on 68Ga PET/CT scan and it should be taken into account as a false positive result. **Keywords:** 68GA PET/CT, Heterotopic pancreas, Neuroendocrine neoplasms.

Q9

Carcinoid Tumors Presenting as Appendicitis

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Introduction: Many conditions related to appendix present as appendicitis. These conditions can range from fecolith obstruction to tumors. Carcinoid tumors are most common tumors to present in appendix. Most of the carcinoid tumors in appendix present as appendicitis. Majority of the cases are diagnosed after histopathological examination. Tumors with the size of 2 cm are treated with right hemicolectomy. **Aim(s):** To determine the frequency of carcinoid tumors in appendectomies using histopathological data. **Materials and Methods:** A retrospective study was conducted at Sir Ganga Ram Hospital, Lahore for a time period of 7 years from June 2005 to November 2012. 2,231 appendectomies were analyzed, out of which 13 appendectomy specimens were diagnosed as carcinoid tumors. Incidental and negative appendectomies were excluded from this study. **Results:** 0.60% of the appendectomy specimens were diagnosed as carcinoid tumors (n = 13), male to female ratio was (5.5:1), 77% (n = 10) of the tumors were up to 1 cm in size and 23% (n = 3) of the tumors were of 1.5 cm in size. Majority of the tumors (n = 9) had well differentiated cell types. 77% of the tumors were localized to the tip of the appendix, 15% of the tumors spread locally to the distal half of the appendix and 8% spread to the mesentery. **Conclusion:** Carcinoid tumors of the appendix, mostly present as appendicitis in early stage. While 90% of the cases show excellent prognosis with appendectomy, 10% of the cases might need further management. **Keywords:** Carcinoid tumors, Appendicitis, Appendectomy.

Q10

Non-Functioning Adrenal Composite Pheochromocytoma-Ganglioneuroma Simultaneous with Subclinical Cushing's Syndrome Due to Contralateral Adrenal Hyperplasia – An Unusual Presentation

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Introduction: 'Composite' pheochromocytoma is a rare tumor, consisting of pheochromocytoma and neuroblastic tumors. The definite diagnosis is histological. Subclinical Cushing's syndrome refers to autonomous glucocorticoid production without specific signs and symptoms of Cushing's syndrome. **Aim(s):** To present an unusual case of composite pheochromocytoma-ganglioneuroma, simultaneous with subclinical Cushing's syndrome. **Materials and Methods:** A 53-year old Caucasian female presented with central obesity and hypertension, and no other clinical signs of hypercorticism or of catecholamine excess. Hormonal evaluation was suggestive of subclinical Cushing's syndrome. Urinary metanephrines were within the normal range. Imaging revealed a right adrenal mass suspicious of malignancy, as well as a left adrenal adenoma. Right adrenalectomy and surgical removal of the left adrenal tumor were performed. **Results:** Histopathological examination led to the diagnosis of right composite pheochromocytoma-ganglioneuroma and contralateral adrenocortical hyperplasia. **Conclusion:** Pheochromocytoma is usually characterized by a cathecolaminergic effect; however the signs and symptoms can be variable or even absent. The presence of ganglioneuroma in composites might interfere with the effects of cathecolamines. To the best of our knowledge, the co-occurrence of subclinical Cushing's syndrome and non-functioning contralateral composite pheochromocytoma-ganglioneuroma has not been reported before. **Keywords:** Adrenal, Composite, Pheochromocytoma, Ganglioneuroma, Hypercorticism.

Q11

The Difficulties of Response Assessment after Peptide Receptor Radionucleotide Therapy (PRRT): An Unusual Case of Symptomatic Pseudoprogression

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Introduction: In previous studies patient symptoms, biochemistry (including chromogranin A) and imaging using RECIST criteria have been used to assess tumour response to PRRT. **Aim(s):** The optimal methods to assess tumour response to PRRT remains unclear. **Materials and Methods:** We present the case of a forty-nine year old male with a grade 2 (KI-67 4.7%) well-differentiated metastatic rectal neuroendocrine carcinoma with liver, lymph node and bone metastases. All tumours were gallium DOTATATE avid but had previously enlarged on somatostatin analogue therapy. **Results:** Eight weeks after the fourth cycle of PRRT with lutetium-177 DOTATATE, the patient complained of increasing abdominal pain and a CT scan showed a 20% enlargement of liver metastases, consistent with progressive disease by RECIST 1.1 criteria compared to baseline. There were no new lesions present. Four weeks later, a gallium-68 DOTATATE PET revealed an 89% reduction in standard uptake value (SUV) max of the liver metastasie, consistent with a response to the therapy. The pain subsided with conservative management over 3 weeks. Chromogranin A was never elevated above the normal range. **Conclusion:** This case highlights the pitfalls in assessing response to PRRT and the importance of using multiple imaging modalities, including functional imaging, to determine treatment efficacy. **Keywords:** Peptide receptor radionucleotide therapy, Pseudoprogression, Neuroendocrine carcinoma.

Q12

A Single Centres Experience of Cardiac Metastasis from Neuroendocrine Tumours (NET)

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Introduction: Cardiac metastasis from NET are rare with little information to guide management strategies. Previous case reports discuss varying strategies including observation, somatostatin analogues (SSA), chemotherapy, radiotherapy and resection. **Aim(s):** We present a single institution experience of managing such cardiac metastases. **Materials and Methods:** We retrospectively searched the NET multidisciplinary database at a single centre in Queensland, Australia over the period of 2007 to 2015. **Results:** Out of 194 patients we found 4 with intra-cardiac metastases and 8 others with para-cardiac metastases. Of the intra-cardiac metastasis, all patients had a grade 1 small bowel primary NET with multiple sites of metastases. Cardiac metastasis was always diagnosed on routine imaging with gallium-68 DOTATATE PET imaging. Of the four patients, one patient did not receive SSA and was managed with observation alone. One patient, who had progressive peritoneal metastases on SSA, received four cycles of Peptide Receptor Radionucleotide Therapy (PRRT) with lutetium-177 DOTATATE without cardiac complications. No patients underwent resection of the cardiac metastases. With a median duration of 2 years post diagnosis of cardiac metastasis, all patients are alive with stable disease and no cardiac complications. **Conclusion:** With better diagnostic techniques cardiac metastases from NET are more likely to be diagnosed incidentally. Our experience suggests they can be managed with observation, SSA or PRRT without cardiac sequelae. **Keywords:** Cardiac metastasis, NET.

Q13

MEN1 Syndrome with Pancreatic Involvement and Synchronous Lung Adenocarcinoma: A Case Report

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Introduction: Lung lesions in MEN1 patients makes us consider firstly a neuroendocrine tumor (NET) as carcinoids are part of MEN1 syndrome. **Aim(s):** To report the clinical and pathological features of a patient with synchronous MEN1 syndrome with both pulmonary carcinoid and adenocarcinoma. **Materials and Methods:** A 66 years old male, belonging a MEN 1 family and with previous antrectomy for duodenal ulcer, was observed for persistent epigastric pain. Laboratory findings were consistent with Zollinger-Ellison syndrome and hyperparathyroidism. CEA was slightly elevated. Abdominal CT-scan showed a 6 cm hypervascular mass in the body of the pancreas positive to Octreoscan scintigraphy, while FDG-PET demonstrated hypermetabolism in the pancreas and the right lung in an area of 2.6 cm confirmed by thoracic MRI, with mediastinal pleura involvement. The patient underwent a right superior lobectomy. Histology reported acinar adenocarcinoma (T3N1G3) coexisting with 1 cm carcinoid with one positive lymphnode. Three months later he underwent a spleen-distal pancreatectomy, subtotal parathyroidectomy and duodenal tumor excision. **Results:** Histology confirmed a duodenal gastrinoma (< 2 mm) and a pancreatic NET with Ki67 =7%. One year later mediastinal lymphnode recurrence occurred, treated with radiotherapy with lymphnode shrinkage. Eight years after observation no evidence of disease is shown and Dotatoc-PET is negative. Slight hypergastrinism is controlled with low dose PPI. **Conclusion:** Non-NET have to be taken in consideration in MEN1 patients. **Keywords:** MEN1.

Q14

Ectopic Malignant Insulinoma with Multiple Liver Metastases: A Case Report

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Introduction: Malignant insulinoma arising from ectopic pancreas is very rare. **Aim(s):** To report the diagnosis and treatment of a case with ectopic malignant insulinoma. **Materials and Methods:** A 31-year-old woman was detected a lesion (size 1.7 cm) in the liver by ultrasound in 2008(misdiagnosed as hemangioma). Since 2012 she complained of confusion, hand trembling, palpitation and sweating, and these symptoms occurred more frequently over the time. On May 2014 she was found to be hypoglycemic, elevated serum insulin and C-P, Abdomen CT with contrast showed multiple lesions in liver (largest 4.3 cm), enlarged lymph nodes around the pancreas, a lesion (3.5 cm) at proximal jejunum. Liver biopsy showed NET G1, Ki-67 (+2%). Octreoscan showed high expression of SSR in jejunum area, multiple liver masses and mesenteric lymph nodes. 68Ga-exendin-4 PET/CT confirmed the lesion located at jejunum section, below the body of pancreas, where expressed GLP-1R was most hypercaptant (SUV 21.7), supposed to jejunum origin. The diagnosis of ectopic malignant insulinoma was made. **Results:** The patient received everolimus plus long acting octreotide since Jun 2014. Hypoglycemia did not recur one week after treatment, and had PR after treatment of 4 months. She stopped everolimus on March 2015 and received SSA alone as maintenance treatment until now. **Conclusion:** 68Ga-exendin-4 PET/CT is very useful to locate ectopic insulinoma. Everolimus and SSA are effective for advanced malignant insulinoma. **Keywords:** Ectopic malignant insulinoma, Octreotide, Everolimus, 68GA-exendin-4 PET/CT.

Q15

MEN1-Related Glucagonomatosis Incidentally Revealed during Management of Recurrent Intestinal Obstruction Following Surgery for Crohn's Disease

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Introduction: Glucagonomas may present with varied intestinal symptoms, weight loss, diabetes and a typical rash. MEN1 related glucagonomas are extremely rare. **Aim(s):** We present a case of MEN1-associated glucagonomas. **Materials and Methods:** Our case is a 64 year old lady with Crohn's disease treated with multiple bowel resections 30 years ago, pelvic surgery and percutaneous radiation for a dysgerminoma, radiation for hyperthyroidism and surgery for a meningioma. She developed recurrent episodic intestinal obstruction following her last abdominal surgery, as well as a skin rash. Abdominal CT incidentally identified a 1.4 cm lesion in the pancreatic neck investigated with EUS and FNA. Findings were suggestive for a NET.68-Ga DOTATATE PET/CT showed multiple tracer uptake foci in the pancreatic body and tail. Blood results included: gastrin 133 pmol/L (≤60), glucagon 523 pmol/L (≤50), chromogranin B 156 pmol/L (<150), prolactin 3900 ng/mL (<25). Serum calcium and PTH were normal. She underwent sub-total pancreatectomy with regional lymphadenectomy, splenectomy, cholecystectomy and adhesiolysis. **Results:** Histology revealed >50 pancreatic tumours between < 2 mm to 15 mm (G2) with strong positivity on staining for glucagon in all lesions (pT1-2mult, pN0, M0). 4 weeks post-surgery she developed gastric perforation with a gastro-cutaneous fistula. Gastrin was 289 pmol/L at the time of perforation. **Conclusion:** We hypothesize this was a rebound effect following normalisation of glucagon after pancreatic surgery. Gene screening results for MEN1 are pending. **Keywords:** MEN1, Glucagonoma.

Q16

Is Screening of Young Asymptomatic MEN1 Patients Necessary?

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Introduction: Recent clinical practice guidelines recommend that routine screening of MEN1 mutation carriers should start at the age of 5 years to detect MEN1-associated tumors which is controversial in the scientific community. **Aim(s):** Evaluation of the occurrence of clinically relevant MEN1 organ manifestations in children (<18 years). **Materials and Methods:** A prospective and retrospective collected data base of MEN1 patients who undergo an annual screening program was retrospectively analyzed for organ manifestations of MEN1 patients <18 years. The annual costs of a screening visit were calculated based on the German Diagnosis Related Groups. **Results:** Eleven of 84 MEN1 patients were diagnosed with at least one organ manifestation below the age of 18 years. Seven (63%) young patients had pNENs (3 NF-PNENs, 4 insulinomas). None of the pNENs was malignant. All 4 insulinomas were diagnosed based on hypoglycemic symptoms, only one patient was younger than 16 years when symptoms occurred. The other organ manifestations were mild asymptomatic pHPT (4 patients, 36%) and asymptomatic pituitary adenomas (3 patients, 27%). No bronchial or thymic carcinoids occurred before the age of 18 years. Surgery was indicated in 10 patients (91%). The costs for the annual routine screening visit was calculated with 2.200€. **Conclusion:** Symptomatic or severe manifestations rarely occur in MEN1 below the age of 16 years. With regard to cost effectiveness routine screening in asymptomatic MEN1 patients should postponed until the age of 16 years. **Keywords:** Screening, MEN1.

Q17

An Unusual Phenotype of Multiple Endocrine Neoplasia Type 1 with a Small Intestine Neuroendocrine Tumor Associated with Large Deletion of the MEN1 Gene

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Introduction: Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant inherited tumor syndrome that is caused by germline mutations in the Menin suppressor gene on chromosome 11q13. Small intestine neuroendocrine neoplasias (SI-NEN) are currently not considered to be part of the phenotype of the MEN1-syndrome. **Aim(s):** Investigating a connection between an unusual and aggressive phenotype of the MEN1 syndrome with SI-NEN and

the occurence of large deletion of the MEN1 gene. **Materials and Methods:** Besides conventional mutation analysis of MEN1 patients modern techniques as Multiplex-ligation-dependent probe amplification (MLPA) were used for the search for larger gene deletions. Ga68-Dotatoc PET/CT was used as an imaging method to detect SI-NENs. **Results:** Presenting a female patient with a rare and aggressive phenotype of MEN1 that is associated with a large germline deletion of the MEN1 gene. The organ manifestations of the reported young female patient included so far pHPT, malignant NF-pNENs, NF-duodenal NEN, pituitary adenoma, non-functioning adrenal adenoma and a malignant jejunal NET (SI-NEN). **Conclusion:** In our patient the SI-NENs was detected during follow-up imaging on Ga68-Dotatoc PET/CT and could be completely resected. Although SI-NENs are extremely rare, these tumors should also be considered in MEN1 patients. Whether an aggressive phenotype or the occurrence of SI-NENs in MEN1 are more likely associated with large deletions of the gene warrants further investigation. **Keywords:** MEN1, Deletion mutation, SI-NEN.

Q18

A Case of Multiple Pancreatic Insulinoma Laparoscopically Resected through Precise Spatial Diagnosis by SACI Test

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Introduction: Case: A 58-year-old man representing cold sweat, palpitation and nausea was admitted to our hospital and was pointed out parathyroid, pancreatic and superior mediastinal masses with CT. **Aim(s):** The pancreatic and mediastinal masses were diagnosed as neuroendocrine tumor by EUS-FNA. Because of the high serum intact PTH, we suspected multiple endocrine neoplasia type 1 and he gradually showed frequent symptom of hypoglycemia. **Materials and Methods:** Dynamic CT scan showed five masses spreading from body to tail of the pancreas and EUS showed suspicious lesions in the pancreatic head. FDG-PET and DOTATOC-PET studies showed multiple hot spots all through the pancreas with no evidence of liver metastases. To identify the localization of lesions secreting insulin, we performed the selective arterial calcium injection (SACI) test. SACI test showed increased insulin secretion at the proximal and distal site of splenic artery, indicating that the responsible lesions resided in the pancreas body and tail, but not in the pancreas head. **Results:** We performed laparoscopic distal pancreatectomy. The serum insulin level got normalized right after the operation, and he never showed hypoglycemic symptoms. The histological examination showed multiple small endocrine tumors other than those detected before the operation, suggesting that the image diagnosis is not enough for the detection of the PNET. **Conclusion:** This case suggests that SACI test is indispensable when we plan the resection of PNET especially of MEN1 patients. **Keywords:** Insulinoma, SACI test, MEN1.

Q19

Bizarre Neuroendocrine Tumour Presentations

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Introduction: Herein we present two cases of neuroendocrine tumours (NET) with atypical presentations. **Materials and Methods:** Case 1: A 87 year-old woman with a growing hypervascular cutaneous lesion in the left scapula was evaluated by Dermatology. The lesion was excised, and histopathology showed a NET metastasis. The patient had no carcinoid syndrome. An abdominal CT scan showed a nodular lesion in the proximal small intestine with exuberant desmoplastic reaction. Somatostatin receptor scintigraphy confirmed overexpression in this lesion and no evidence of distant metastasis. The patient underwent palliative surgery. The surgical specimen confirmed a low-grade (G1) NET (Ki67 1%). **Results:** Case 2: A 53 year-old male was admitted in the emergency department with upper GI bleeding and hypotension. He was on acetilsalicilic acid and clopidogrel due to recent coronary revascularization. Blood tests showed a hemoglobin value of 5 g/dL. Upper endoscopy and colonoscopy were inconclusive. Abdominal CT scan findings were unremarkable. The patient maintained GI bleeding with the need for transfusion. A capsule endoscopy revealed a subepitelial lesion in the small intestine with superficial erosion. Segmental small intestinal resection was performed. The surgical specimen showed a G2 NET (Ki67 3–20%, T2N0). **Conclusion:** The authors report two cases of NET with an unusual presentation: cutaneous metastasis and obscure upper GI bleeding. We highlight the radiological, endoscopic and histological documentation of cases. **Keywords:** Cutaneous metastasis, GI bleeding.

Q20

Collision Tumor of the Appendix: Mucinous Cystadenoma and Carcinoid. A Case Report

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Introduction: Mucinous cystadenoma is the most common of benign neoplasms of the appendix and carcinoid is the most common type of primary malignant lesions of the appendix. **Aim(s):** We report a rare case of a 39-year-old female with combined mucinous cystadenoma and carcinoid tumor of the appendix. **Materials and Methods:** A 39-year-old white woman presented after incidentally palpating an abdominal mass. She refered abdominal pain on her right iliac fossa. No relevant personal history. Abdominal ultrasound and computed tomography (CT-scan) revealed a cystic tumor in the right iliac fossa, originating from the appendix. **Results:** She underwent laparoscopic surgical exploration and an appendiceal

tumor were found, so laparoscopic appendectomy were performed. Histopathological examination showed cystic neoplasia, tumor size 3 cms. The specimen had features of mucinous cystoadenoma. An small area of the appendiceal wall, was involved by a well differentiated neuroendocrine neoplasm WHO grade I, a carcinoid tumor. The neoplastic cells infiltrated the entire thickness of the appendiceal wall, but the mesoappendix were not compromised. Tumor size was 1,2 cms. **Conclusion:** Rare cases of mucinous cystadenomas of the appendix coexisting with carcinoid tumors. We reported a collision tumor with no transitional zone between. The clinical presentation of our patient and the differential diagnosis of ovarian lesions, also globet cell adenocarcinoids from appendiceal tumors have to be highlighted. **Keywords:** Collision tumor, Appendix tumor.

Q21

Neuroendocrine Tumours of the Thymus: A Report of Four Cases

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Introduction: Neuroendocrine tumours of the thymus (thymic carcinoids) are a rare group of malignancies with a reported incidence of about 1 in 5 million. Over a ten year period in our institution, covering a population of 3.5 million, there had only been two confirmed cases. **Aim(s):** Within the past 12 months four cases have presented and have demonstrated many of the classical features associated with these rare neoplasms. In the presentation of our case series we will explore differences in the presenting features of thymic carcinoid and illustrate some of the difficulties surrounding diagnosis and management along with an up-to-date review of the literature.

Q22

Second Primary Malignancies Incidence in Patients with Neuroendocrine Tumours – Retrospective Review of 454 Neuroendocrine Tumour Cases

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Introduction: Increased incidence of second primary malignancies (SPM) in patients (pts) with neuroendocrine tumors (NET) has been reported. **Aim(s):** Assessment of SPM incidence in NET pts. Analysis of its associations with pts gender, primary NET site and NET TNM stage. **Materials and Methods:** A review data of 454 pts diagnosed with NET, who were followed-up from 1995 to 2015. NET pts who developed SPM were identified. Pts with MEN1/2 were excluded. **Results:** 52 NET pts from 454 reviewed NET cases (11.5%) were found to have developed 54 SPM. SPM occurred most frequently in pts with pancreatic NET (16%) and ileocaecal valve NET (15.4%). In females (n = 36) the most common SPM were breast (n = 7), uterine (n = 7) and renal cancers (n = 4) and in males (n = 16) prostate (n = 4) and thyroid cancers (n = 3). There was a significantly increased incidence of SPM in overall NET pts (SIR = 1.38;95% CI: 1,03–1,81) and in female NET pts (SIR = 1.61;95% CI: 1.13–2.23) compared to a general Polish population. In overall NET pts the incidence of thyroid cancer (SIR = 6,94;95% CI: 2.25–16.21) and renal cancer (SIR = 4.39; 95% CI: 1.42–10.24) was increased. In female pts there was significantly increased incidence of uterine cancer (SIR = 2.93; 95% CI: 1.18–6.03) and renal cancer (SIR = 7.14; 95% CI: 1.95–18.29) and in male pts thyroid cancer (SIR = 33.13; 95% CI: 6.87–97.41). No significant associations of SPM incidence and primary NET site or NET TNM stage were found. **Conclusion:** Due to increased risk of SPM NET pts' follow up should include regular anti cancer screening schemes. **Keywords:** Neuroendocrine, Cancer.

Q23

Ectopic Cushing Syndrome in a Patient with Metastatic Medullary Thyroid Carcinoma

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Introduction: Ectopic Cushing syndrome was reported in 0.6% of patients with medullary thyroid carcinoma; it usually occurred in metastatic cases and significantly increases mortality. **Aim(s):** To present a case with ectopic Cushing syndrome. **Materials and Methods:** Calcitonin was measured by chemiluminescence, plasma cortisol and ACTH by electrochemiluminescence, chromogranin A (CgA) and neuron specific enolase (NSE) by ELISA. **Results:** A 68 years old man with sporadic metastatic medullary carcinoma presented with hypertension, muscle weakness, without diarrhoea. Biochemical work-up revealed hypokalemia (K = 2.5 mmol/l), hyperglycaemia (163 mg/dl), increased calcitonin (42890 pg/ml), CgA (539 ng/ml), NSE (40.9 ng/ml) and ACTH-dependent Cushing: elevated free-urinary cortisol (1096 mcg/24 h, normal range: 21–111), loss of diurnal cortisol rhythm (8 a.m. plasma cortisol = 45.7 mcg/dl, 11 p.m. plasma cortisol = 38.2 mcg/dl), failure to suppress to DXM (43.7 mcg/dl), increased ACTH levels (167.2 pg/ml). Computed tomography imaging was negative for pituitary adenoma. Screening for RET germline mutations (direct sequencing of PCR products of exons 10, 11, 13, 14, 15) was negative. Metyrapone 750 mg/day failed to control hypercortisolism. Bilateral adrenalectomy was performed with normalization of kalemia. Thereafter, diarrhoea occurred and somatostatin analogues were administered. **Conclusion:** Bilateral adrenalectomy may be required when inhibitors of steroidogenesis failed to control hypercortisolism. **Keywords:** Ectopic cushing syndrome, Medullary thyroid carcinoma.

Q24

MEN1 Associated Thymic Neuroendocrine Tumors in Oulu University Hospital Finland

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Introduction: Thymic neuroendocrine tumors (TNET) are rare and account 2–5% of all thymic tumors. TNET can occur either sporadically or as a manifestation of an inherited tumor syndrome such as multiple endocrine neoplasia type 1 (MEN1). The prognosis is severe. **Aim(s):** To evaluate the prognosis of MEN1-related TNET. **Materials and Methods:** We present a series of 6 patients with MEN1 and TNET diagnosed in our hospital between 1985 and 2015. **Results:** They were all men, mean age at the time of diagnosis was 44.3 years. Half of the patients were asymptomatic and TNET was found in a routine imaging. Two patients had chest pain and one cough and bronchorrea. One patient had a history of smoking. Histological analysis of all the TNETs presented staining to kromogranin A and synaptophysin. Proliferation index was relatively low (1–5%) when analyzed. Two patients received post-operative radiation and interferon, and 3 patients had somatostatin analog therapy. One patient also received chemotherapy and one lutetium treatment, two had tumor recurrence. During the follow-up (mean 61 months, range 9–101 months) 3 patients were diagnosed with metastasis of TNET. Three patients are still alive and under regular follow-ups. One patient died of a renal clear-cell carcinoma, one of a cardiac cause and one of TNET itself. **Conclusion:** Due to the aggressive and often asymptomatic nature of TNET, patients with MEN1, especially male, should be screened regularly during the follow-up after the age of 40. **Keywords:** Thymic neuroendocrine tumor, Thymic carcinoid tumor, MEN1.

Q25

Subtype Classification and Clinicopathological Features of Gastric Neuroendocrine Neoplasms: Experiences in 116 Chinese Patients

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Introduction: Gastric NEN are a heterogeneous group of tumors. **Aim(s):** To investigate subtype classification and clinicopathological features of gNEN in Chinese pts. **Materials and Methods:** A total of 116 pts with gNEN were referred to our hospital from Jun 2012 to Oct 2015. They were subclassified into 4 types using the criteria: Well-differentiated gastric NET are classified into three types: type 1 (hypergastrinemia and achlorhydria, related to autoimmune chronic atrophic gastritis), type 2 (hypergastrinemia and ZES, related to gastrinoma or MEN1, type 3 (sporadic disease with normal serum gastrin level). Poorly differentiated NEC and MANEC belong to type 4. The clinicopathological features were analyzed. **Results:** There were 54 (46.6%), 5(4.3%), 37 (31.9%), and 20 (17.2%) pts with type 1, 2, 3, and 4 gNEN, respectively. Of 54 pts with type 1 gNET, one received surgery, 44 treated with endoscopic resection, 9 with endoscopy plus SSA, no mets or death was documented in the follow-up period. Five type 2 pts had significantly elevated serum gastrin level, including 3 gastrinoma and 2 MEN1. Of 37 pts with type 3, 20(54.1%) treated with endoscopic or surgical resection, 13(35%) treated with SSA, and 4(10.8%) with NET G3 received SSA plus chemo. Of 20 pts with type 4 gNEN, 16(80%) had distant mets at diagnosis, 20(100%) received chemo, 13(65%) died during the follow-up period. **Conclusion:** Different types of gNEN have different treatment strategies and prognosis, subtype diagnosis of gNEN is critical and feasible in practice. **Keywords:** Gastric NEN, type 1.

… None of the Above

R1

Pancreatic Neuroendocrine Tumors: Experience from a Single Institute

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Introduction: A dedicated multidisciplinary team is necessary in the management of pancreatic neuroendocrine tumor (pNET). **Aim(s):** To evaluate in patients affected by pNET prognostic factors related to persistent/recurrent disease and mortality, in our single institute experience during the last 5 years. **Materials and Methods:** We analyzed clinical (age, sex) and pathological factors (tumor size, lymphnodes, Ki 67 index) for predicting disease free survival and overall survival through Cox proportional Hazard Model. **Results:** The study included 20 patients (9 Females, 11 Males; Mean age 56.4 + 10.5) who referred to our institute for pNET between 2010 and 2015. 16 patients underwent surgery although 4 patients were judged unresectable due to systemic involvement. In these cases liver biopsy confirmed diagnosis. According to 2010 WHO pathological classification our patients were subdivided in: G1 3 patients, G2 13 patients, G3 4 patients. 12 patients started medical treatment after first progression disease. Among these 8 patients were enrolled to somatostatin analogs (SSA) and 4 patients initiated chemotherapy as first line strategy. Everolimus was reserved only as second line option for 3 patients and Peptide receptor radionuclide therapy (PRRT) for 2 patients. Ki-67 index was the only factor associated with poorer disease free survival (HR 1.03; 95% CI: 1.01–1.06). **Conclusion:**

In patients with pNETs intensity of follow up and therapeutic management should be assessed according to Ki 67 index. **Keywords:** Pancreatic, Ki-67.

R2

Current Trials in Neuroendocrine Tumours: A Systematic Review

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Introduction: Trials in neuroendocrine tumours (NETs) have increased markedly in number over the last 10 years. Researchers do not have ready access to a summary of open trials to identify research gaps. **Aim(s):** To systematically identify currently open, registered trials in NET to describe the current research landscape and direct future trials. **Materials and Methods:** 9 international databases and conference abstracts were searched. Open NET trials were included and classified into randomised (RCTs), single-arm interventional and non-interventional trials. Unreported trials recently closed to accrual were also identified. **Results:** 74 currently open interventional trials (17 RCTs, 57 single-arm) were identified. These investigated the modalities of somatostatin analogues (4), antiangiogenic agents (16), mTOR inhibitors (6), PRRT (5), novel therapies/combinations (37) and others (6). 48 trials had recently closed to accrual and await full reporting, with 169 further observational trials. Only three trials investigated liver-directed therapies (one RCT, two single-arm). No currently open trials investigated surgical therapies, nor used symptom control or quality of life as primary endpoints (although TELESTAR and TELECAST recently completed accrual). **Conclusion:** Current trials in neuroendocrine tumours investigate a wide range of systemic therapies, but few address the role of surgery, the effect of liver-directed therapies or using symptom control as the primary endpoint. These areas should be prioritised in future research. **Keywords:** Trials, Review.

R3

Promoting High Quality Care in Clinical Trials for Patients with Neuroendocrine Tumors (NETs)

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Introduction: The European Institute of Oncology is an ENETS Center of Excellence. Many patients (pts) are treated in clinical trials. The clinical research nurse (CRN) is a key figure in care delivery. Optimising staff resources means some trial activities are delivered by nursing staff with limited research experience. To provide high quality care & accurate trial results, all nursing staff caring for NET pts should have appropriate trial related support and training. **Aim(s):** To involve nursing staff, develop knowledge, ensure pt safety and high quality research in NET studies. **Materials and Methods:** We used the Plan-Do-Check-Act (PDCA) quality improvement tool, to problem solve and implement potential solutions – a methodology applied in various healthcare settings. **Results:** P: We analysed the problem, reviewed literature and met with peers to develop a strategy of 1-to-1 training and development of a Nursing Summary. D: Strategies were implemented in in- & out-patient settings. C: Efficacy was evaluated. Issues remained in relation to key activities (eg PK sampling, document completion). A: Study specific nursing tools (checklist) were developed with the NET multidisciplinary team (MDT) indicating examinations, timing, sampling and documentation required. This has been implemented and is ongoing. **Conclusion:** Through the PDCA process, with MDT working and open discussion, we developed practical solutions aimed to promote involvement of nursing staff and develop knowledge in relation to specific NET studies. **Keywords:** Neuroendocrine, Trials, Nursing.

R4

miR-196a Is Specifically Regulated in FDG-PET Positive and Negative Small Intestinal Neuroendocrine Tumor Patients at Late Stage of Disease

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Introduction: This collaborative research plan aims at elucidating the glycolytic metabolism in advanced FDG-PET positive (+) and FDG-PET negative (-) small intestinal neuroendocrine tumor (SI-NET) patients treated with Lutetium peptide receptor radionuclide therapy (177Lu-PRRT). **Aim(s):** To identify a potential specific regulation of miR-196a in FDG-PET+ and FDG-PET– SI-NET patients at a late stage of disease. **Materials and Methods:** Total RNA of serum samples was isolated from 15 SI-NET samples (3 healthy donors Ctrl, 3 FDG-PET+ pre-177Lu-PRRT, 3 FDG-PET+ post-177Lu-PRRT, 3 FDG-PET– pre-177Lu-PRRT and 3 FDG PET– post-177Lu-PRRT) using the mirVana Paris Kit. Total RNA was converted to cDNA using TaqMan MicroRNA Reverse Transcription (RT) Kit. Pre-amplification was performed after the RT process to increase the sensitivity of target gene expression. **Results:** QRT-PCR analyses showed that serum of FDG-PET+ SI-NET patients expresses less miRNA196a than the one of FDG-PET– SI-NETs patients. Moreover, 177Lu-PRRT is able to enhance miRNA196a levels of FDG-PET+ SI-NETs patients, whereas is not altering miRNA196a expression of FDG-PET– SI-NET patients. **Conclusion:** We show that FDG-PET+ and FDG-PET– patients express different levels of miR196a that regulate several genes, also of the glycolytic metabolism. Thus, miRNA196a might be pivotal in controlling SI-NETs glycolytic metabolism. **Keywords:** Glycolytic metabolism, Peptide receptor radionuclide therapy (PRRT), Serum samples, miRNA, FDG-PET positive and -PET negative SI-NET patients.

R5

Comparing Real-Life Practice to Established Guidelines in the Management of Gasteroenteropancreatic Neuroendocrine Cancer Patients: A Tertiary Cancer Center Experience

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Introduction: Guidelines by ENETS in the management of Gastroenteropancreatic Neuroendocrine Tumors (GP-NETS) are intended as a clinical tool to practice evidence-based medicine. Its adaptability and translation in real-life setting has yet to be examined. **Aim(s):** Compare clinical practice versus ENETS guidelines in the management of GP-NET patients. **Materials and Methods:** Retrospective analysis of clinical records was performed in 27 patients diagnosed GP-NETS between 2008–2015. Initial clinical decision point was analysed. These included: initial laboratory and imaging investigations, classification on the pathological reports, medical and surgical management and time to referral to medical speciality. These points were compared to ENETS guidelines. **Results:** Total of 27 patients, Four (14.81%) patients had all of the recommended laboratory investigations. All 27 (100%) of patients were investigated by CT at diagnosis, of which four patients were further evaluated by additional imaging (2 by MRI, 2 by SSRS). Nine (33%) pathologic reports included mitotic count and Ki-67. A total of 10 (37%) patients underwent primary tumour resection without a biopsy. Referral to specialized centers was longer than 2 months in 7/27 (25%) patients. 9 (33.3%) patients with high-grade tumor were identified, of which all (100%) received chemotherapy. **Conclusion:** Guidelines as name suggests is to act as a guide. Nevertheless, complete adherence in the examined points to ENETS management guidelines was seen in only 4 patients. **Keywords:** Neuroendocrine, Tumour, Guideline.

R6

Versatile Goblet Cell Carcinoma of the Appendix – A Case Presentation

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Introduction: Goblet cell carcinoma of the appendix is a rare tumor that can be classified as a subtype of mixed adeno-neuroendocrine carcinomas. **Aim(s):** A 61 year old Caucasian male that presented with symptomatology of subocclusive syndrome was intraoperatively diagnosed with a stenotic ileal tumor with the involvement of the appendix. **Materials and Methods:** The resected specimens displayed an ileal and appendix tumoral proliferation with signet ring cell in a concentric pattern and perineural invasion. The immunohistochemical stain was positive for Chromogranin A, Synaptophysin and SSTR5, negative for SSTR2 and with 3–5% nuclear reactivity for Ki67%, suggestive for a goblet cell carcinoma of the appendix-G2 pT4bNxR1. A second tumor debulking was performed after 3 months, which revealed residual ileal and appendix tumors with hystopathological findings of mucinous adenocarcinoma invading the omentum. **Results:** The postoperative imagistic assessment of residual disease proved to be negative, with elevated serum Chromogranin A. Following the meeting of the multidisciplinary neuroendocrine team, the treatment choice was the combination of FOLFOX and Somatostatin analogs. **Conclusion:** We emphasize that somatostatin analogs could increase the sensibility to chemotherapy in this type of tumor. With this treatment regimen the 6 month evaluation revealed no progression of the disease. **Keywords:** Goblet cell carcinoma, Neuroendocrine tumor, Somatostatin analogue.

R7

Neuroendocrine Tumours: A Retrospective Analysis in a Single Irish Institution

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Introduction: Neuroendocrine tumours (NETs) are heterogenous group of tumours. **Aim(s):** We conducted a retrospective analysis in a tertiary centre to evaluate these patients' clinicalhistopathological characteristics, treatments and outcomes. **Materials and Methods:** All non-metastatic and metastatic NETs (all grades and sites) diagnosed from April 2011 to May 2015 were included. Small-cell lung neuroendocrine carcinomas were excluded. **Results:** 67 patients, 40 females and 27 males. Mean age was 49 years (9 to 83 years). 57 (85%) were low grade tumours, 6 (9%) intermediate grade and 4 (6%) high grade. Primary tumour sites were appendiceal (29%), jejunoileal (19%), gastric (13%), pancreatic (10%), lung (9%), colorectal (8%), caecal (3%), goblet cell carcinoma (3%) and unknown (6%). 39% (26/67) had metastatic diseases, including four high grade NETs (Ki67 ≥20%) treated with platinum-based chemotherapy, three MANEC (mixed adenoneuroendocrine carcinomas) treated with surgery plus FOLFOX and four low grade pancreatic NETs (pNET) treated with somatostatin analogues (SSA). Despite metastatic stage, primary surgeries were performed on two high grade lung NETs (lobectomy), three MANEC (right hemicholectomy) and one pNET (distal pancreatectomy). One metastatic pNET had liver metastasectomy. OS for high grade NETs was 3-12 months and metastatic MANEC was 24-27 months. One confirmed MEN-1. **Conclusion:** Although limited by number and heterogeneity, this study results were consistent with published data. As a rare disease, NETs patients deserve personalised approach at specialised centres. **Keywords:** Neuroendocrine.

R8

Pharmacokinetic (PK) Differences between Subcutaneous and Intramuscular Administration of Lanreotide: Results from a Phase I Study

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Introduction: Data have shown that 38% of intended gluteal intramuscular (IM) injections with long-acting release octreotide were mistakenly given subcutaneously (SC); in carcinoid syndrome patients, this significantly increased the rate of flushing (P = 0.005; Boyd 2013, Pancreas). Lanreotide depot (LD) recently became FDA-approved for the treatment of gastroenteropancreatic neuroendocrine tumors (120 mg Q4W) as a deep SC injection. **Aim(s):** To evaluate PK of LD SQ vs. IM. **Materials and Methods:** In a phase I study, healthy adult volunteers received 1 mg LD (IV bolus) followed by 60 mg 0.246 mg/mg deep SC or IM. Serial blood samples were analyzed. **Results:** Of 42 volunteers (mean [SD] age 25 ± 6 years, weight 66 ± 10 kg), 11 received the same LD dose (60 mg 0.246 mg/mg) as SC (n = 5) or IM (n = 6), 30 received other doses/concentrations, and 1 was excluded. Between 14 and 112 d, comparable mean concentration-time profiles were observed for both routes. The mean Cmax (5.8 ± 4 vs. 6.8 ± 3 µg/L) and mean T1/2 (33 ± 14 vs. 23 ± 9 d) were deemed comparable, as were median Tmax (8 vs. 16 hours) and median residence time (last) in serum (28 vs. 20 d). Slightly lower AUClast (1651 ± 54 vs. 2007 ± 172 h·µg/L) and AUCinf (1843 ± 134 vs. 2100 ± 193 h·µg/L) were observed with SC vs. IM injections. **Conclusion:** Lanreotide depot 60 mg 0.246 mg/mg SC and IM injection had similar PK profiles in this small cohort, leading to further development of SC, due to more LD availability in the late-release phase after SC injection. Study sponsored by Ipsen. **Keywords:** Lanreotide, Somatuline, Pharmacokinetic, PK.

R9

Budget Impact of Somatostatin Analogs (SSAs) as Treatment for Metastatic Gastroenteropancreatic Neuroendocrine Tumors (mGEP-NETs) in US Hospitals

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Introduction: Lanreotide depot (LAN) was recently approved by the FDA to treat mGEP-NETs to improve progression-free survival. **Aim(s):** To determine real-world costs of two therapies for mGEP-NETs. **Materials and Methods:** A hypothetical cohort of 500 GEP-NET patients is considered the treated population in the model, with the proportion treated with an SSA estimated using published epidemiologic data. Drug acquisition, preparation, dosing and administration costs are included based on a national pricing database and published literature. Published estimates of real-world dosing of octreotide (OCT) are utilized as a model assumption. As LAN was approved recently, real-world dosing was unavailable and the model assumed labeled dosing. **Results:** The model-predicted average per-patient cost for LAN is $71,442 compared to $75,508 for OCT. This leads to a decrease in total costs to the hospital with increase in LAN utilization. In the base case, 313 of the initial 500 GEP-NET patients are treated with an SSA. With a hypothetical increase in LAN utilization from 5% to 30% of this population, the model projects that the annual costs to the hospital will decrease by approximately $318,000. When varying inputs in one-way sensitivity analyses, results were most sensitive to changes in dosing assumptions. **Conclusion:** Results from this real-world model suggest that factors beyond drug acquisition cost can influence the overall hospital budget impact with SSA treatment for GEP-NETs. Study sponsored by Ipsen. **Keywords:** GEP-NETs, Budget impact, Somatostatin, Lanreotide.

R10

Establishment and Characterization of a Continuous Cell Line from a Human Familial Medullary Thyroid Carcinoma

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Introduction: A new continuous cell line 'SCHWE' was established from the primary tumor of a 50 year-old male with familial medullary thyroid carcinoma (FMTC). **Aim(s):** We report the establishment of a new continuous cell line 'SCHWE' from tissue that was obtained from the primary tumor of a 50 year-old male with familial medullary thyroid carcinoma (FMTC). We used isolated DNA from the tumor as well as from peripheral blood to screen for specific sequence variants in the RET proto-oncogene. We found a previously known causative mutation in exon 13, codon 781 (CAG>CGG) and also a well-known disease-irrelevant heterozygous single nucleotide polymorphism in codon 769 (CTT>CTG). CytoScan HD SNP-array (Affymetrix®) analysis revealed a widespread homozygosity as well as complex copy number abnormalities with an extraordinary multiplication of chromosome 20. Owing to an apparent ploidy increase together with variable mosaic levels made a clear-cut delineation and exact enumeration of distinct abnormalities extremely difficult. However, the combined deletion/and copy neutral homozygosity pattern of the 10q region, which contains the RET gene, suggested that one allele

was lost before the other one got duplicated. Molecular genetic analysis revealed a pure wild-type pattern and therefore the loss of the two apparently linked sequence variants originally present in the tumor. **Materials and Methods:** We used isolated DNA from the tumor, from cultured cells as well as from peripheral blood to screen for specific sequence variants in the *RET* proto-oncogene. **Results:** We found a previously known causative mutation in exon 13, codon 781 (CAG>CGG) and also a well-known disease-irrelevant heterozygous single nucleotide polymorphism in codon 769 (CTT>CTG). CytoScan HD SNP-array (Affymetrix®) analysis revealed a widespread homozygosity (all chromosomal regions except for chromosomes 2p25.3-q37.3, 3, 4p16.3-q13.1, 7p, 8q, 10p, 15, 16q, and 20) as well as complex copy number abnormalities with an extraordinary multiplication of chromosome 20. Owing to an apparent ploidy increase that was also noted in cytogenetic examinations together with variable mosaic levels made a clear-cut delineation and exact enumeration of distinct abnormalities extremely difficult. However, the combined deletion/and copy neutral homozygosity pattern of the 10q region, which contains the *RET* gene, suggested that one allele was lost before the other one got duplicated. Molecular genetic analysis of the respective region revealed a pure wild-type pattern and therefore the loss of the two apparently linked sequence variants that were originally present in the tumor. The elimination and replacement of the allele carrying the predisposing mutation is an unexpected and rather surprising finding which requires further exploration. **Conclusion:** These findings suggest a primary haploidization and subsequent duplication/polyploidization events that concurred with a certain karyotype instability and the development of closely related sub-clones. We foresee that our newly established cell line can become very useful for *in vitro* studies of novel treatments for FMTC. **Keywords:** Familial mtc, Continuous cell line, Characterisation, Authentication, Xenografts.

R11

Design of a Phase 3, International, Prospective, Randomized, Double-Blind, Placebo (PBO) Controlled Study Assessing Efficacy and Safety of Lanreotide Autogel/ Depot (LAN) 120 mg in Patients with Well-Differentiated, Advanced Typical and Atypical Lung NETs

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Introduction: The international phase 3 CLARINET study showed that treatment with the somatostatin analog (SSA) lanreotide was associated with significantly prolonged PFS vs. PBO in GEP-NETs, leading to a new indication approved in more than 35 countries. Like GEP-NETs, lung NETs express somatostatin receptors. **Aim(s):** To evaluate antiproliferative effect of lanreotide in NETs of the lung. **Materials and Methods:** This multi-center study will enroll an anticipated 216 patients with typical/atypical metastatic and/or un-resectable lung NETs that have positive somatostatin imaging and who are treatment naïve or have had no more than 1 course of systemic chemotherapy (cytotoxic, molecular targeted therapy or interferon). Patients will be randomized 2:1 to receive monthly LAN 120 mg via deep subcutaneous injection plus best standard of care or PBO. An estimated 175 PFS events (disease progression or death) on both arms will provide a 90% power to detect a statistically significant treatment effect using a two-sided log rank test at a significance level of $\alpha = 0.05$. **Results:** Anticipated results include the primary endpoint of PFS in both arms, as well as secondary endpoints which include objective radiologic response rate, overall survival, effects on plasma chromogranin A, and safety/tolerability. **Conclusion:** Therapeutic agents for the treatment of lung NETs are currently limited. This study will provide data on the efficacy of LAN for patients with these understudied malignancies. Study sponsored by Ipsen. **Keywords:** Lung NETs, Lanreotide.

R12

Quality of Life (QoL) and Psycho-Social Distress in Patients with Neuroendocrine Neoplasias (NEN) – Correlation with Tumor Stage, Clinical Status and Treatment

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Introduction: Pat. with NEN require long-term therapy potentially associated with an impairment of QoL. **Aim(s):** To determine the QoL and psycho-oncological stress of patients with NEN in correlation to tumor stage, clinical status and treatment. **Materials and Methods:** Prospective evaluation of 148 NEN patients. Qol was assessed by EORTC QLQ-C30/QLQ-GI. NET 21 questionnaires, psychosocial distress by the NCCN distress thermometer and the HADS-D scale. **Results:** The global QoL (QLQ-C30) was 62 (of 100) and thus significantly higher than in pat. with pancreatic cancer (43) but well below the score of a healthy control population (76). The scores for physical-, emotional-, cognitive- and social-function were significantly lower compared to healthy controls with the emotional function being most impaired. Physical function scales showed sign. impairment for fatigue, diarrhoea, insomnia, appetite loss. Mean scores for anxiety and depression were 6.4 and 4.9 with increased risk-scores for an anxiety disorder or depression in 28% and 19% respectively. In patients receiving SSA a significantly better social function was found as compared to other treatments or watch and wait. The mean NCCN distress level (1-10) in all patients was 4.25, in metastatic disease 4.82 and in progressive disease 5.48. 46% of pat. expressed the desire for psychooncological support. **Conclusion:** NEN patients show significant impairment of QoL and increased psychosocial distress. Early identification of pat. at risk are important goals for an optimized treatment. **Keywords:** Psychooncology, Quality of life.

R13

To Evaluate Patient's Understand of the Neuroendocrine (NET) Multidisciplinary Team (MDT) Meeting Process at a ENETs Centre of Excellence

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Introduction: Multidisciplinary teams serve to streamline the patient journey by developing individual treatment plans that are based on 'best practice'. National and local guidelines govern the MDT process. There is little focus on the patient's understanding and expectations of how and when the MDT recommendations are communicated. **Aim(s):** The objective of this study was to gain insight into patients' understanding of the MDT process and to identify service improvements. **Materials and Methods:** In this single-centre (The Christie) prospective study, 49 consecutive patients with a diagnosis of a NET (any stage or primary), whose cases had been recently discussed at the NET MDT, completed a questionnaire (August 2015). **Results:** A total of 49 patients were included; 62% understood what a referral to a NET MDT involved; 59% were aware that their case had been discussed and 81% had been informed of the MDT recommendation. In response to their preferences: 45% of patients believed that they should be informed of the MDT outcome within 7 days; 67% would prefer to be informed in clinic by a Consultant. Overall, 41% of patients would like additional information on the MDT process. **Conclusion:** There are a number of patients who appear not to understand what the MDT process involves or that their cases were discussed. Of those informed, most preferred to be notified in clinic. A greater provision of information on the role of the MDT and process for notification of the outcome should be encouraged at the first relevant consultation. **Keywords:** Patient MDT.

R14

To Evaluate How the Outcome of Neuroendocrine Tumour (NET) Multidisciplinary Team (MDT) Meeting Decisions Are Conveyed to Patients at a ENETS Centre of Excellence (The Christie) and How This Service Can Be Further Improved

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Introduction: It is recommended that people with cancer should be managed by an MDT and the outcomes should be communicated in a 'timely manner'. However, it does not specify when this should be done, or by whom. **Aim(s):** To review how MDT recommendations were communicated at a ENETs Centre of Excellence. **Materials and Methods:** In this single-centred retrospective study, case-notes of 55 patients who had been discussed at the NET MDT (April-June 2015) were reviewed. **Results:** All MDT recommendations were documented in case-notes within 7 days of the MDT; 62% of patients were informed of the outcome: of these, 88% were informed in clinic. Patients were informed by a Consultant (33%), Senior doctors (46%) or the Nurse Clinician (21%). Of the 62%, 94% had been informed of the MDT outcome within 14 days (median time: 6 days [range 0–21]). Thirty-four percent of General Practitioners (GPs) were informed; of these, 78% received communication within 8 days (range 0–28). Ninety-four percent of the recommended actions from the MDT were conducted within 14 days (median time: 5 days [range 0–60]). **Conclusion:** Compliance of case-note documentation and ensuring MDT recommendations were actioned within 2 weeks was above 90%. In most cases, patients were informed of the MDT outcome during a clinic consultation by a member of the NET team. There was evidence that only 62% of patients and 33% of GPs were informed of the MDT outcome, therefore greater attention to communication and documentation of this communication is required. **Keywords:** Patient communication MDT.

R15

Clinical Nurse Specialist in NET Patients at Institut Català d' Oncologia – ICO

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Introduction: A Functional Unit model brings together multidisciplinary professionals participating in a committee. Its aim is to optimize diagnostic and therapeutic intervals, get consensus on the best-individual treatment option & best evidence. Our unit-NET, was establish 10 years ago & last 4 got a clinical nurse specialist-CNS. **Aim(s):** To describe competences & activities of clinical nurse specialist in NET's patient care at a cancer center. **Materials and Methods:** Annual descriptive. Type of patient, tumor location NET. Distribution health care activity & management. **Results:** Total 336 patients/year.

– First visits 60. Welcoming – Information telephone & support circuits – Social & emotional assessment – Referral other professionals. Participate in Tumors Committee – Additional tests.

– Education specific x treatment: 24 visits. Deliver oral & written information by scheme.

– Visit Control QT toxicity: 72visits/year. Adverse effects & toxicity adjust.

– Telephone symptoms control 92.

– Nurse administration inyections 36: Somatostatin analogues.

– Radionuclide's treatment Uppsala 36: Program, review, coordinate patient & family documentation to submit.

– Review results 24: Complementary & analytical tests.

– TACE Coordination 12: Planning, coordination&patient admission, procedure & monitoring. **Conclusion:** CNS has an essential role in coordinating the process, be reference to patient/family & team working.

Management includes; coordination & treatments, provided compliance intervals. Nurse met care needs; health education & follow-up. **Keywords:** Clinical nurse.

R16

Identifying and Prioritising Gaps in Neuroendocrine Tumour Research – Results of the Delphi Consensus Project of the Commonwealth Neuroendocrine Tumour Research Collaboration (CommNETS)

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Introduction: The newly formed CommNETS group used the robust Delphi methodology with broad stakeholder engagement to form a strategic research agenda. **Aim(s):** To identify gaps in NET research and develop research priorities. **Materials and Methods:** A 3 round Delphi (2 online surveys plus final round at the Inaugural CommNETS meeting) was performed with wide participation from stakeholders including subject experts (medical, nursing, scientific) and consumers (patients, families, advocates). Round 1 identified gaps in NET research and CommNETs' strengths compared to USA & Europe; Round 2 identified research priorities; Round 3 ranked priorities after extensive workshops and established project groups. **Results:** Round 1 had 203 participants (64% experts; 36% consumers; 52% Canadians, 32% Australians, 17% New Zealanders); of which 132 undertook Round 2. Rankings from experts and consumers were similar except for early diagnosis (mean rank of 17 priorities for experts 9.6, SD = 5.8; consumers = 4.0, SD = 5.2). Final priorities (from 147 votes) were: biomarkers (33%); PRRT (16%); new drugs/trials in advanced NET (12%); functional imaging (10%); sequencing therapies for metastatic NET including validated surrogate endpoints (10%); pathological classification (9%); early diagnosis (7%); interventional therapeutics (3%). 6 working groups were founded. **Conclusion:** A robust set of CommNETS research priorities was developed by consensus through the Delphi process. Collaborations have commenced to address the research questions. **Keywords:** Research, Gaps, Priorities, Delphi.

R17

CommNETS: Formation of an International Commonwealth Countries NET Partnership

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Introduction: Neuroendocrine tumours (NETs) care is challenging in Canada, Australia and New Zealand due to small populations in large geographical space, limited drug funding, and lack of NET awareness. There is a need for collaboration to focus research and improve care and outcomes for NET patients in these nations with similar health systems. **Aim(s):** To create multi-nation NET collaboration. **Materials and Methods:** A multidisciplinary group of clinicians, researchers and patients from all three nations attended an inaugural meeting to create the Commonwealth Neuroendocrine Tumour Society (CommNETS) in Nov 2015. A modified Delphi process was undertaken to set priorities for the new group using a web-based questionnaire. **Results:** Forty-eight participants including surgeons, medical oncologists, endocrinologists, scientists, nuclear medicine physicians/physicists, pathologists, and patients attended. Day One consisted of examination of recent NET developments and the final round of the Delphi process (two rounds were held prior to the meeting). Day two consisted of establishing research collaborations and development of working groups to further the CommNETS agenda. **Conclusion:** Canada, Australia and New Zealand share a common health system and similar challenges in NET care. CommNETS provides a new, ongoing structure to further collaboration for NETs research, based on a robust process to define priorities and strengths of the group. As ongoing funding has been obtained, CommNETs is a promising forum to improve NETs care. **Keywords:** Research, Society.

R18

Exploring Gastrointestinal Symptoms and Their Impact on Quality of Life in Patients with Neuroendocrine Tumours

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Introduction: Treatments in NETs have been studied for effects on tumour progression and carcinoid syndrome with minimal evidence on gastrointestinal (GI) symptom burden and impact on quality of life (QoL). **Aim(s):** To determine whether patients with NETs receiving treatment experience GI symptoms, and to explore their impact on QoL. **Materials and Methods:** A prospective cohort of 46 patients with histologically confirmed NET visiting endocrine and oncology clinics completed GSRS (gastrointestinal symptom rating scale) and EORTC QLQ-GINET21 QoL questionnaires prior

to establishment of a gastroenterology NET service. **Results:** The majority of patients had midgut (70%) or pancreatic (15%) primary with 96% having metastatic disease. Duration of diagnosis was 42 months (range 2–249), 91% having stable disease. The majority of patients reported GI symptoms including:abdominal cramps (80%), bloating (74%), excess wind (87%) and faecal urgency (87%). 50% had stool frequency of >5 times a day and 71% scored type 5 or higher on the Bristol Stool Chart. 54% of patients reported greasy/oily stool. 60% scored their QoL to be <7 out of 10. When asked how much bowel symptoms were affecting QoL, 58% of patients scored more than 5 out of 10. 97% reported their illness to be distressing for those close to them. **Conclusion:** This study represents the first systematic analysis of specifically defined GI symptoms experienced by NET patients. Despite having stable disease, many patients frequently experience GI symptoms which have a negative impact on QoL. **Keywords:** Quality of life, Symptoms.

R19

How Long Is the Piece of String? – How Patients Negotiate the Uncertainties of a NET Diagnosis

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Introduction: NET Patient Interviews. **Aim(s):** The aim was to explore challenges patients with NETs face due to their incurable but slow-growing nature. **Materials and Methods:** Semi-structured interviews with 30 patients (12 female, 18 male) treated for NETs at a hospital in Queensland, Australia. The data was analysed using NVivo10. **Results:** 4 major themes emerged. (1) Despite the poor long term prognosis a proportion of participants sought to adopt a positive outlook or denied the severity of their condition; (2) On reflection, symptom management was accompanied by uncertainty about available treatment options, disease progression, quality of life and life expectancy; (3) Participants perceived contradictions in how their NET prognosis was framed by different health professionals involved in their care; (4) Some participants expressed feelings of fear, guilt and social isolation due to the uncertainties of the NET diagnosis. **Conclusion:** We highlight challenges for NET patients to resolve the tension between a terminal prognosis and a slow but unpredictable disease progression. They often struggle to explain their condition to significant others or fully understand the nature of their illness themselves. This is exacerbated by – and in turn exacerbates – the limited public awareness of NETs inviting some to lead 'double lives' in which NETs are dealt with secretly. Improved expertise among health professionals and communication with patients and their families to enhance the recognition of NETs could potentially alleviate these issues. **Keywords:** Interviews.

R20

Caregivers' Burden of Patients with Neuroendocrine Tumor and Related Factors

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Introduction: Rare and increasing rapidly, patients with NETs have got more and more attention. With so many unknown and the long course of the disease, the caregaviers should bear a long and huge burden. However, the relative reviews are rare. **Aim(s):** To investigate burden on caregivers of patients with NETs and to explore possibly related factors. **Materials and Methods:** Use the ZBI scale to investigate the burdens on major caregivers since Jan2015 to Oct2015, and the multi-linear regression method to explore related factors. **Results:** 185 major caregivers were recruited. The ZBI score was 0-62, (35.41 ± 11.67) in average, which was similar to that of caregivers for patients with other cancer and stroke ($P > 0.05$), but higher than that of caregivers of patients with COPD, DM, hypertension/heart disease ($P < 0.05$). There were only 13.5% caregivers had no burden. Most (52.4%) were under moderate burden. The related factors included: age, gender, education background, duration of care giving, the lasting time of the patients' disease, and the family's income ($P < 0.05$). **Conclusion:** Nearly 90% caregivers of patients with NETs were under burdens in different degree, mostly on a moderate level. And the burdens were even higher when the caregivers were advanced in age, female and highly educated, and when the duration of care giving was long, the lasting period of the patients' disease was long, and the patients' family income was low, to which special attention should be paid, and more education and support should be provided. **Keywords:** NETs, Caregiver burden.

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