Abstracts of the 11th Annual ENETS Conference for the Diagnosis and Treatment of Neuroendocrine Tumor Disease

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Guest Editors

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Abstracts

Basic Science – mTOR and Other Pathways, Signalling, Receptors

A1

The Effect of Autophagy Inhibitors Alone or in Combination with mTOR Inhibitors in a Neuroendocrine Tumor Cell Model

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Introduction: Most patients with neuroendocrine tumors (NETs) require systemic treatment, often with a limited therapeutic effect. RAD001 and Torin1 are mTOR inhibitors (mTORi) known to suppress cell proliferation in NETs. However, cancer cells may use mTORi-induced autophagy to escape the anti-proliferative effect and to prolong cell survival. Chloroquine (CQ) and hydroxychloroquine (HCQ) inhibit autophagy.

Aim(s): To explore the effect of autophagy inhibitors in combination with mTORi on NET cell proliferation.

Materials and Methods: NET cell line BON1 was treated with RAD001, Torin1, CQ and HCQ alone or in combinations. Cell viability was examined by XTT method. Flow cytometry and Western blot were used to assess drug effect on cell cycle, apoptosis, PI3K/Akt/mTOR and autophagy pathways.

Results: Torin1 significantly decreased BON1 viability, whereas CQ and HCQ only mildly suppressed it. The combination of RAD001 with CQ or HCQ did not increase the inhibitory effect. The combination of Torin1 with CQ or HCQ significantly reduced cell viability. Torin1 significantly arrested cells in G0/G1, inducing a higher degree of apoptosis mainly in combination with CQ and HCQ. The combination of mTORi and autophagy inhibitors significantly increased the accumulation of LC3-II, a marker for autophagy inhibition, indicating a possible relationship of the inhibition to increased apoptosis. Conclusion: The combination of the mTORi Torin1 with autophagy inhibitors seems promising for the inhibition of NET cell proliferation.

Keywords: NETs, autophagy, mTOR inhibitors.

A2

Cyclin D1 Levels are Involved in the Resistance to m-TOR Inhibitors in Human Bronchial Carcinoids

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Introduction: Bronchial carcinoids (BC) are still orphans of medical therapy. We previously demonstrated that the typical BC human cell line NCI-H727 is sensitive to Everolimus, in terms of cell viability reduction, while the atypical human BC cell line NCI-H720 is not. However, the mechanisms underlying this phenomenon have not been fully clarified.

Aim(s): To investigate the mechanisms of resistance to mTOR inhibitors in BC cells.

Materials and Methods: Cell cycle protein profiling was performed throughout G0/G1/S phases evaluating important complexes regulated during these transition phases at different cell-cycle times, such as CDK2/Cyclin E, CDK4/CyclinD1 and p27Kip1.

Results: The two BC cell lines showed different levels of cell cycle-regulating proteins during cycle progression. We found that under starvation, the resistant cell line (NCI-720) still expressed most of the cell cycle regulating protein, while in the sensitive cell line (NCI-727), proteins such as p27, cyclin D1 and E were highly downregulated. In addition, we observed that, during cell cycle progression, CyclinE/CDK2 complex seems to be more expressed in resistant NCI-H720 cells as compared to NCI-727 cells. In contrast, CyclinD1/CDK4 is more expressed in the sensitive NCI-H727 cell line, while p27 does not show a different expression pattern during cell cycle progression in the two cell lines.

Conclusion: The pattern of proteins involved in cell cycle regulation is clearly different suggesting a possible involvement in mTOR inhibitors resistance. Keywords: BC, mTOR.
Forkheadbox Proteins as Novel Drug Targets in Gastroenteropancreatic Neuroendocrine Tumor Disease: Inhibition of FoxM1 Exerts Antiproliferative Effects in GEP-NEN Cell Lines

A4

Expression and Prognostic Role of CXCR4/CXCL12/CXCR7 and mTOR Pathways in Neuroendocrine Tumors (NETs)

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Introduction: The chemokine receptor CXCR4 interacts with the ligand CXCL12 to exert proliferative and chemotactic effects. CXCR4 activates mTOR through phosphorylation of its two effectors downstream: 4EBP1 and S6K. Aim(s): To evaluate expression and prognostic role of CXCR4-CXCL12-CXCR7, as well as mTOR pathways in a consecutive series of patients with endocrine tumors (NETs). Materials and Methods: 53 human NETs were included: 16 P-NET, 19 GI-NET, and 18 MTC were analyzed for expression of CXCR4, CXCL12 and CXCR7 by qRT-PCR. Moreover, CXCR4, CXCL12 and CXCR7 and mTOR pathway was evaluated by immunohistochemistry (IHC) in the patient cohort. Results: CXCR4, CXCR7 and CXCL12 mRNA was significantly overexpressed in tumors as compared to normal tissue (p < 0.001, p < 0.009 and p < 0.0013, respectively). The IHC score of CXCR4 (p < 0.001), p-mTOR (p < 0.05), p-4EBP1 (p < 0.05), p-S6K1 (p < 0.001) was significantly higher in G1/G2 tumors, while CXCR7 and CXCL2 score was higher but not significantly in G3 tumors. Preliminary prognostic evaluation suggest that CXCR7, CXCL12 and pS6K1 correlate with unfavorable prognosis (p < 0.01). We are evaluating the expression of CXCR4-CXCL12-CXCR7 and the effect of CXCR4 and mTOR targeting drugs on human NET cell lines (NH727, BON, TT). Conclusion: CXCR4-CXCL12-CXCR7 and mTOR pathways are variably expressed in NETs according to tumor grading and might represent a prognostic factor in these tumors. Concomitant inhibition of CXCR4 and mTOR pathway may improve effectiveness and overcome resistance. Keywords: chemokine, mtor, nets, clinical outcome.

A5

The Cytotoxic Effect of Sunitinib on Human Bronchial Carcinoid Cell Lines and Primary Cultures is Counteracted by EGF and IGF-1, but not by VEGF

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Introduction: Bronchial carcinoids (BC) are rare tumors originating from endocrine cells dispersed in the respiratory epithelium. The main BC treatment is surgery, but which is not feasible for large, infiltrating and metastatic disease. In these settings, medical therapy is often tried. Therefore it is important to identify new therapeutic targets and new molecules capable of providing adequate medical treatment for patients with BC. Sunitinib is an oral, small-molecule, multi-targeted receptor tyrosine kinase inhibitor. Aim(s): To verify if Sunitinib is active in inhibiting human cell viability and what are its targets in these cells. Materials and Methods: Human BC cell lines (NCH-727, NCI-H727 cells) and human BC primary cultures were treated with Sunitinib 5 μM and/or EGF 30 nM, IGF1 50 nM, or VEGF 10 nM. Cell viability and caspase 3/7 activation were measured after 48 h of treatment. Results: Sunitinib is capable of inhibiting cell viability of BC cell lines and primary cultures (by 20–50% vs. control); moreover Sunitinib activates caspase 3/7 (by 20–100% vs. CT). Both events are counteracted by EGF and IGF-1 at concentration similar to those found in plasma, but not by VEGF although its receptors are usually considered the main target of Sunitinib. Conclusion: These data indicate that Sunitinib is a potential therapeutic agent for treatment of BC, and that its mechanism of action
could be mediated, at least in part, by EGFR and IGF1R. Further experiments are needed to better understand this issue. **Keywords:** bc, rtk, sunitinib.

### A6

**Normal Gastrointestinal Neuroendocrine Cells Lack E-Cadherin**

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**Introduction:** E-cadherin plays a crucial role in the adhesion between epithelial cells and thus epithelial integrity. Moreover, germ line mutations in the E-cadherin gene (CDH1) causing loss of E-cadherin function (adhesion) leads to hereditary gastric cancer of the diffuse type, according to Laurén. Even sporadic gastric carcinomas of the diffuse type often lose E-cadherin expression due to mutations. Lack of E-cadherin has been recorded at an early phase in such carcinomas. **Aim(s):** The present study was done to examine whether normal neuroendocrine cells in the gastrointestinal tract express E-cadherin or not. **Materials and Methods:** During upper gastrointestinal endoscopy, biopsies were taken from normal oxyntic mucosa, gastric carcinoids, gastric carcinomas and from the duodenum. Tissues were examined by immunohistochemistry using antibodies towards chromogranin A, synaptophysin and E-cadherin. Isolated mucosal cells were prepared from biopsies from normal mucosa and examined by antibodies against the same markers by immunofluorescence. **Results:** Normal gastrointestinal NE cells did not express E-cadherin as assessed by immunohistochemistry or immunocytochemistry. No expression of E-cadherin was found on tumor cells from gastric carcinoids or cancer of diffuse type examined by immunohistochemistry. **Conclusion:** Our finding may explain why there is a discrepancy between lack of atypia and malignant biological behavior of such tumors. **Keywords:** e-cadherin, neuroendocrine cell, gastric cancer, adhesion molecules, neuroendocrine tumors, carcinoid.

### A7

**The pan-TRK Inhibitor GNF5837 Inhibits Cell Viability and Akt and MAPK Signaling in Human Neuroendocrine GOT1 Tumor Cells**

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**Introduction:** The tropomyosin receptor kinase family (TRKA, TRKB, TRKC) effects tumor cell growth in various models. Recent preclinical studies in neuroendocrine carcinoma of the lung cell lines have shown that Trk receptors might be a therapeutic target for neuroendocrine neoplasias. **Aim(s):** Therefore, we investigated the antitumoral activity of the pan-Trk inhibitor GNF5837 (Tocris Bioscience) in different human neuroendocrine tumor (NET) cell lines. **Materials and Methods:** Human neuroendocrine pancreatic BON1 cells, bronchopulmonary H727 cells and midgut GOT1 cells were treated with different concentrations of GNF5837 (0.1 nM – 500 nM) and the effects on cell viability (Cell Titer 96 Proliferation Assay, Promega) and signaling pathways (Western Blot analysis) were examined. **Results:** GNF5837 exhibited no effects on cell viability of Bon1 and H727 cells, but dose- and time-dependently inhibited GOT1 cell viability. After treatment with GNF5837 5 nM and 50 nM for 48 hrs, cell viability of GOT1 cells decreased to 77±6% (p < 0.05) and 73±5% (p < 0.05). Western blot analysis with a pan-Trk and a specific TrkA antibody both showed a specific band in GOT1 cell lysates, but not in BON1 and H727 cells. Incubation with GNF5837 (1 nM–10 nM) for 2 to 48 hrs inhibits phosphorylation of Akt-S473 and ERK1/2-T204/Y202 in GOT1 cells. **Conclusion:** The pan-TRK inhibitor GNF5837 shows antiproliferative effects in human neuroendocrine GOT1 tumor cells. TRKs might be a potential therapeutic target for the treatment of NETs. **Keywords:** neuroendocrine tumor, trk receptor.
as FoxM1/survivin, are interesting new targets in neuroendocrine lung tumors and should be further evaluated. **Keywords:** bronchial, nets, pi3k, foxm1, survivin, cell lines, sclc.

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**A9**

**Evaluation of VEGF and Endocan/ESM-1 Expression in pNETs and Correlation with Ki-67 and Prognosis**

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**Introduction:** Endocan has been reported as specific of endothelial tumor cells and was shown to be expressed by tip cells during the angiogenesis process. **Aim(s):** The assessment of immunohistochemical VEGF and Endocan expression in functioning and non-functioning pNETs and the comparison of these markers with clinical features, Ki-67 and TNM staging. **Materials and Methods:** We collected a total number of 79 pNET surgical specimens for immunohistochemistry (IHC). The population chosen was classified according to type of diagnosis, sex, age, grading and staging. **Results:** We report the preliminary results of IHC for VEGF and Endocan performed on 46 patients. The expression of Endocan is limited to endothelial cells within neoplastic tissue. VEGF is expressed in the cytoplasm of tumoral cells. VEGF and Endocan expression is strictly connected, considering that Endocan expression upon endothelial cells is stimulated by VEGF production by neoplastic cells (P < 0.001). The grading is directly correlated to the stage and in our series, this finding is confirmed (P 0.001). We correlated Endocan and VEGF expression to Ki-67 and TNM classification. We found a significant correlation between Endocan and VEGF expression and metastatic disease (P 0.005 and <0.001, respectively). **Conclusion:** These preliminary data seem to show that Endocan and VEGF immunohistochemical expression in pNETs may be predictive markers of aggressiveness. **Keywords:** gep-net, endocan, vegf.

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**A10**

**Expression of the Truncated Somatostatin Receptor Variant Sstr5TMD4 in Medullary Thyroid Carcinoma**

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**Introduction:** Medullary thyroid carcinoma (MTC) is a rare tumor originating from thyroid parafollicular C cell. The only available treatment is surgical resection, which is not always feasible. Somatostatin and its receptors are expressed both in normal human thyroid C cells and in MTC, but their role has not been fully elucidated. The discovery of a truncated isoform of Sstr5, Sstr5TMD4, associated with increased invasiveness and aggressiveness in breast cancer, has opened new insight in the role of Sstr in cancers. **Aim(s):** To evaluate Sstr5TMD4 expression in a series of human MTC at different stages, and to explore the role of Sstr5TMD4 in TT human MTC cell line. **Materials and Methods:** Sstr5TMD4 expression correlates with disease stage and that it is higher in MTC metastases v. primary site and in sporadic v. hereditary cases. **Results:** Sstr5TMD4 overexpression in TT cells increases growth rate, alters the epithelial phenotype and confers a greater invasion capacity. TT cells overexpressing Sstr5TMD4 displayed a reduced expression of E-cadherin and p-β-catenin, and an increased vimentin expression, confirming that Sstr5TMD4 induces epithelial-mesenchymal transition. We found that Sstr5TMD4 overexpression associates with a reduction in basal pERK1/2 and pAkt levels and with an increase in basal pGSKβ3 and pSMAD2/3 levels. **Conclusion:** This is the first evidence that Sstr5TMD4 is expressed in human tissues of MTC, where it correlates with invasion. Sstr5TMD4 may therefore represent an useful prognostic marker in MTC. **Keywords:** mtc, sstr5tmd4.

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**A11**

**Combined Therapy with RAD001 e BEZ235 Overcomes Resistance of PET Cells to mTOR Inhibition**

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**Introduction:** Since the PI3K/Akt/mTOR proliferation axis is often deregulated in PETs, the mTORC1 complex inhibitor Everolimus (RAD001) represents an effective treatment for PETs. However, RAD001 leads to a re-activation of PI3K activity and phosphorylation of Akt, which may promote resistance to the treatment. Thus, direct inhibition of PI3K may represent a novel potential target for PETs. **Aim(s):** To test PI3K inhibitors in models of responsiveness or resistance (primary and secondary) to RAD001. **Materials**
and Methods: Three novel PI3K inhibitors (BEZ235, BKM120 and BYL719) were evaluated on BON-1 (50–60% of inhibition of cell proliferation caused by RAD001) and QGP-1 (primarily unresponsive to RAD001) cells and on BON-1 cells acquiring a secondary resistance. 

Results: BEZ235 was the most efficient in inhibiting cell proliferation in PET cell lines (60–70% inhibition). Furthermore, combination of BEZ235 with RAD001 showed an additive effect (80–90% inhibition). Combined therapy is effective also in BON-1 that acquired resistance to RAD001 after chronic exposure to this inhibitor (BON-1 RR). BON-1 RR cells showed increased eIF4E/4EBP1 ratio, which may account for acquired RAD001 resistance. Importantly, combined therapy was more efficient than single agents in inhibiting the PI3K/Akt/mTOR axis and cell growth, even at 10-fold lower concentration of the drugs. Conclusion: These results indicate that co-treatment with BEZ235 may represent suitable therapy to counteract primary and acquired resistance to RAD001 in PETS. Keywords: mtor, pi3k, resistance.

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A12

Interference of Nutrient/Oxygen Availability with mTOR Activation and Inhibition in Lung Carcinoids: A Tissue and Cellular Study


Materials and Methods: TMA blocks including 75 typical and 19 atypical carcinoids were tested using immunohistochemistry for mTOR pathway molecules (p-mTOR, p-S6K, p-AMPK, p-RAPTOR, RICTOR) and nutrient transporters (GLUT-1, SLC6A14, LAT-1). Rapamycin sensitivity of neuroendocrine tumor cell lines (lung H720, pancreatic BON-1 and C-cell TT) was tested under glucose deficiency or increased availability and hypoxia.

Introduction: mTOR is capable of coupling cellular nutrient sensing to metabolic homeostasis. However, little is known of the interactions between cancer-specific metabolic pathways and profiles of responsiveness to mTOR inhibition in neuroendocrine tumors. Aim(s): To analyze the interference of nutrient availability with mTOR pathway activation and inhibition in lung carcinoids. Materials and Methods: TMA blocks including 75 typical and 19 atypical carcinoids were tested using immunohistochemistry for mTOR pathway molecules (p-mTOR, p-S6K, p-AMPK, p-RAPTOR, RICTOR) and nutrient transporters (GLUT-1, SLC6A14, LAT-1). Rapamycin sensitivity of neuroendocrine tumor cell lines (lung H720, pancreatic BON-1 and C-cell TT) was tested under glucose deficiency or increased availability and hypoxia. Results: A significant inverse correlation was observed between GLUT-1 and p-mTOR expression, whereas SLC6A14 and LAT-1 were positively correlated with pAMPK and RICTOR, respectively. Low expression of LAT-1 was significantly associated with positive nodal status (p = 0.004) and aggressive clinical behavior (p = 0.001). In all cell lines, both low and high glucose concentrations were associated with decreased rapamycin efficacy to inhibit cell viability and mTOR phosphorylation. Hypoxia also exerted the same effects in BON-1 cells. Conclusion: These data show that mTOR pathway activation is associated with the expression of nutrient transporters and that glucose/oxygen impairment affects responsiveness to mTOR inhibitors. Keywords: lung, carcinoid, mtor, metabolic pathway.

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A13

Effect of Combined Treatment with mTOR Inhibitors (mTORi) and Dopamine Agonists on Cell Proliferation in a Human Typical Lung Carcinoid Cell Line

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Introduction: The mTOR pathway and dopamine receptors are potential targets for treatment of neuroendocrine tumors (NET). Aim(s): To evaluate the in vitro effect of combined treatment with the mTORi rapamycin (RAP) or everolimus (EVE) and the dopamine agonist cabergoline (CAB) on cell proliferation in a human typical lung carcinoid cell line (H727). Materials and Methods: The expression of some components of mTOR pathway and D2 receptor was assessed by RT-qPCR and immunostaining. The effect of mTORi and CAB on cell viability and cell cycle was evaluated by MTT assay and flow-cytometry, respectively. Results: H727 cells express D2 receptor, mTOR, p70S6K and 4EBP1 at transcript and protein levels. Both mTORi induced a significant time- and dose-dependent inhibition of cell viability; maximal inhibition was 18%, 30% and 30% with RAP and 15%, 35% and 43% with EVE at three, six and nine days, respectively, with a similar IC50 (10–8 M). CAB alone did not significantly inhibit cell viability but co-treatment with equnimolar concentration (10–8 M) of mTORi induced a significantly higher inhibition of cell viability (62% and 65% with RAP plus CAB and EVE plus CAB, respectively), compared with mTORi alone (30%) after nine days of treatment. EVE determined a G1 phase cell cycle arrest. CAB alone did not have an effect on cell cycle but had a synergistic effect with EVE. Conclusion: CAB potentiates the effects of mTORi on cell proliferation, suggesting that a combined therapy might be a potential treatment option for lung carcinoids. Keywords: mtor, dopamine.

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A14

Inducing, Understanding and Overcoming Resistance to Everolimus in Pancreatic Neuroendocrine Tumors


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Introduction: Treatment with the mTOR-inhibitor everolimus improves progression-free survival in advanced pancreatic neuroendocrine tumors (PNETs). However, adaptive resistance to mTOR inhibition is described. Aim(s): Materials and Methods: QGP-1
and BON-1, two human PNET cell lines, were cultured with increasing concentrations of everolimus during 20 to 22 weeks to reach a final dose of 1000-fold and 250-fold the initial IC50, respectively. BON cell lines with induced resistance were compared with the initial cell line using whole exome sequencing. The cell lines with induced everolimus resistance were treated with BEZ-235, a combined PI3K-mTOR inhibitor. Results: Everolimus dose-response measurement in both everolimus-treated cell lines showed a strong reduction in everolimus sensitivity in comparison to vehicle-treated cells. Initial results of whole exome sequencing of BON-1 untreated, vehicle- and everolimus-treated cells revealed predicted protein-damaging nucleotide changes in 19 genes. Interesting mutated genes include the pro-apoptotic BNIP2, the DNA polymerase-associated POLDIP2 and the chemotherapy-resistance-associated FPGS genes. Initial results using BEZ-235 had effect on cell proliferation in both everolimus-sensitive and resistant BON-1 and QGP-1 cell lines. Conclusion: Everolimus resistance was induced in two PNET cell lines. Exome sequencing revealed 19 possible resistance related genes in BON-1. Analysis is ongoing for QGP-1. Dual blocking the PI3K-Akt-mTOR pathway might overcome everolimus resistance. Keywords: everolimus.

Basic Science – Genetics, Epigenetics, miRNAs

B1 Gene Expression Characterization of Gastroenteropancreatic Neuroendocrine Tumors [GEPNETS: Gastrointestinal and Pancreatic NETs (GINETs and pNETs)] and Their Correlation with Clinical Factors and Tumor Behavior


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Introduction: GEP-NETs are a heterogenous group of tumors with different molecular backgrounds and clinical outcome. Aim(s): To further characterize GEP-NET gene expression with correlation with clinical characteristics and tumor behavior.

Materials and Methods: Forty fresh-frozen tumor samples (20 G1-2 GINETs and 20 G1-2 pNETs) were collected from 12 Spanish centres. Tumor mRNA expression (copy number) of sst4, PDGF, RET, VEGFR, angiopoietin (Ang1), Ang2, Tie2, β-catenin, E-cadherin, HIF1A, HIF1B, THBS1, adrenomedullin (AM), CD34, PTEN, Notch and mTOR was analyzed by quantitative PCR.

Results: Median age was 57 yrs, 53% males, 65% G2 NETs, 53% stage IV at diagnosis and 20% functioning tumors. Median expression of sst4 and RET transcripts was significantly higher in GINET than in pNET samples (591 v. 95, p < 0.04 and 3180 v. 735 p < 0.04). Median expression of both Ang1 and Tie2 transcripts was significantly higher in G1 than G2 tumors (513 v. 158, p < 0.03 and 320 v. 145, p < 0.02). Functioning tumors expressed more CD34 (2635 v. 910, p < 0.03) and less AM (528 v. 1623, p < 0.04) than non-functioning tumors. Significant associations were observed between CgA levels and HIF1A expression (r = 0.54, p < 0.03) and between sst4 and RET (r = 0.38, p < 0.01) or Notch expression (r = 0.66, p < 0.001). Conclusion: GEP-NET transcriptional profile substantially differs according to primary tumor site, tumor grade and functionality. Molecular profiling may help improve stratification, diagnosis and management of this heterogeneous family of tumors. Keywords: sst4, ret, angioinvasion, gep-net.

B2 Identification of Hypoxia Induced Epigenetic Changes in the Development of Pancreatic Neuroendocrine Tumors

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Introduction: In VHL syndrome, pancreatic NETs develop through bi-allelic inactivation of VHL with subsequent HIF pathway activation. This also occurs in sporadic pancreatic NETs. Aim(s): We sought to determine the epigenetic modifications occurring in VHL-related tumorigenesis in PNETs. Materials and Methods: VHL knockdown in the human pancreatic NET cell line BON1 was carried out by lentiviral transduction. Cells were cultured in normoxic and hypoxic [1% O2] conditions for 1, 4, 8, 16, 48, 72 and 168 hrs. Genome-wide methylation analysis was performed using Infinium HumanMethylation450 Arrays and gene expression analysis was performed using Illumina HT12 arrays. Results: Methylation analysis identified marked differential methylation following 48 hrs of hypoxic culture compared with normoxic controls. Hypoxia-pathway genes such as HIF1A (av.beta 0 hrs v. 48 hrs = 0.47664 v. 0.32044), HIF3A (0.96676 v 0.07799), VEGFA (0.85109 v. 0.56265), VEGFC (0.94871 v 0.09468), CA-9 (0.95749 v. 0.19811), and the chemokine receptors and ligand CXCR4 (0.90320 v. 0.10798), CXCL12 (0.98152 v. 0.08550). An associated correlation in gene expression was also observed. Further analysis of biological replicates is ongoing. Conclusion: Following VHL knockdown the HIF pathway is further activated in this PNET in vitro model through epigenetic modification within 48 hours of hypoxia treatment. These findings sug-
gest that hypoxia may contribute to long-term epigenetic changes in VHL related tumorigenesis. **Keywords:** neuroendocrine, von hippel-lindau (vhl), hypoxia, epigenetics.

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**B3**

**ACTG2 Inhibits Growth and Is Epigenetically Repressed in Small Intestinal Neuroendocrine Tumors**

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**Introduction:** Small intestinal neuroendocrine tumors (SI-NETs) originate from the enterochromaffin cells in the ileum. Actin gamma smooth muscle 2 (ACTG2) is downregulated in lymph node metastases from SI-NETs. ACTG2 and microRNA-145 (miR-145) are aberrantly expressed in other cancers and ACTG2 can be induced by miR-145. **Aim(s):** To investigate the cause for down-regulation and function of ACTG2 in SI-NETs. **Materials and Methods:** ACTG2 protein expression was analyzed in SI-NETs (n = 24) by immunohistochemistry. The SI-NET cell line CNDT2.5 was treated with 3-deazaneplanocin (DZNep), a selective EZH2 inhibitor (EPZ-6438) and a DNA hypomethylating agent (5-aza-dC). Cells were transfected with ACTG2 plasmid and miR-145. Western blotting analysis, qRT-PCR, colony-forming and viability assays were performed, and miR-145 expression levels measured in tumor samples (n = 24). **Results:** Most tumor cells did not express ACTG2 protein. Treatment with DZNep, or transfection with miR-145, induced ACTG2 expression (more than 10-fold), but no differences were detected after treatment with EPZ-6438 or 5-aza-dC. ACTG2 inhibited cell growth and viability by approx. 25%. **Conclusion:** Protein expression of ACTG2 is repressed. The gene is epigenetically regulated by histone methylation and microRNA-145. ACTG2 inhibit cell growth and is a potential new tumor suppressor gene in SI-NETs. **Keywords:** si-net, actg2, mir-145, epigenetics.

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**B5**

**Metabonomic Profiling: A Novel Approach in Neuroendocrine Neoplasias**

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**Introduction:** There is a substantial unmet need for novel biomarkers for neuroendocrine neoplasms (NEN). **Aim(s):** An analytical platform was developed to define a diagnostic metabolic phenotype for NEN. **Materials and Methods:** Forty-nine patients with NEN were prospectively recruited: 15 small bowel NEN (SBNN); 21 pancreatic NEN (PNEN), 13 other NEN. There were 21 healthy controls. Urine samples were subjected to 1H nuclear magnetic resonance spectroscopy on a Bruker Avance III 600 MHz spectrometer. Acquired spectral data were imported into SIMCA-P for supervised and unsupervised multivariate analysis. Selected samples were used for two-dimensional nuclear magnetic resonance spectroscopy (2D-NMR) for metabolite identification in an 800 MHz Bruker Avance II spectrometer. **Results:** Partial least squares-discriminant analysis differentiated between NEN and healthy controls with accuracy (R²Y = 0.65, Q²Y = 0.22). Orthogonal partial least squares-discriminant analysis distinguished between SBNN and PNEN (R²Y = 0.82, Q²Y = 0.10). Subclass analysis showed class separation between functioning and non-functioning NEN. Hippurate metabolic variations might be playing a role in discriminating metastatic v. non metastatic NEN. SBNN expressed higher levels of both serotonin and 5-HIAA compared to PNEN. Compared to healthy controls, both SBNN and PNEN showed higher levels of 5-HIAA. **Conclusion:** Metabonomic analysis suggests that subgroups of NEN may possess a stratified metabolic phenotype that can be used as a novel biomarker for NEN. **Keywords:** metabolomics, nen.
Promoter Hypermethylation at RASSF1 is a Feature of Small Intestinal Neuroendocrine Tumors


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Introduction: Promoter hypermethylation of RASSF1 has been reported in many tumor types. Aim(s): Unbiased molecular analysis of small intestinal neuroendocrine tumors (SI NETs) has been performed which identified significant differential methylation of RASSF1 between SI NETs and normal tissue. Materials and Methods: Methylation analysis (Infinium HumanMethylation450 Array) was performed on 94 samples from 56 cases; gene expression analysis (HumanWholeGenome DASL Array) was performed on 64 samples from 55 cases; plasma circulating free DNA (cfDNA) hypomethylated RASSF1 detection (methylation sensitive restriction enzyme digestion and RT-PCR) was performed on 12 samples. Results: RASSF1 was hypermethylated in tumor (av.beta = 0.42) v. normal (0.32) tissue (p = 2.64e-12), and a trend towards hypermethylation in liver metastases v. SI primaries (0.51 vs 0.40) and of higher grade v. low grade tumors (0.51 vs 0.39) was identified. Gene expression analysis indicates a trend towards reduced expression of RASSF1 in tumors v. normal tissue (av.signal 827 vs 1198, p = 0.06). Initial cfDNA analysis demonstrated hypomethylated RASSF1 in 4/12 patients (v. 0/2 controls). Conclusion: RASSF1 hypermethylation and loss of expression is common in SI NETs and may be associated with metastatic progression or high grade disease. Determination of the utility of cfDNA RASSF1 methylation as a prognostic non-invasive biomarker, and integrated analysis of epigenetic, genomic and transcriptomic data from a wider tumor cohort is ongoing. Keywords: epigenetics, methylation, rassf1.

Distinct Expression of Splicing Variants of the Human MEN1 (Multiple Endocrine Neoplasia Type 1) Gene in Various Pituitary Adenomas


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Introduction: MEN1 is an autosomal-dominant tumor syndrome characterized by the occurrence of tumors in multiple endocrine tissues, including parathyroid, enteropancreatic neuroendocrine and anterior pituitary. The MEN1 gene consists of 10 exons transcribed into a 610 a.a. protein. It was reported that heterogeneity of human MEN1 gene transcripts related to variation in their 5’ UTR. Six distinct exons (e1A-e1F) were isolated using RNA from thymus, pancreas and kidney. Aim(s): To investigate the transcription start sites in several human pituitary adenomas. Materials and Methods: 1) To obtain the 5’ end of the MEN1 cDNA, 5’RACE was performed using Marathon-Ready cDNA libraries for pituitary, hypothalamus and adrenal gland. Amplification products were subcloned into the pGEMT-Easy plasmid and sequenced. 2) The 5’ end and splice variants was determined using cDNA and PCR from 5 GH-secreting adenomas, five prolactinomas, five Cushing disease and five non-functioning adenomas. Results: 1) 5’RACE revealed the ratio of utilizing exon1 as follows. Pituitary: e1A, 7%; e1C, 7%; e1D, 85.7%, Hypothalamus: e1B, 25%; e1C, 25%; e1D, 50%, Adrenal gland: e1B, 29.4%; e1D, 70.6%. 2) Although no e1B variant was expressed in normal pituitary, significant expression of e1B was observed in GH-secreting adenomas and prolactinomas. e1D were expressed in all types of pituitary tumors. Conclusion: Distinct usage of exon1 was observed among pituitary, hypothalamus and adrenal gland. The usage of exon1 variants might be a biomarker for type of pituitary tumors. Keywords: men1, pituitary.

MicroRNA Expression in Serum of Small Intestine Neuroendocrine Tumor Patients and miR-196a Biological Function in Neuroendocrine Tumor Cells

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Introduction: We have previously identified five upregulated and four downregulated miRNAs in small intestinal neuroendocrine tumor (SI-NET) tissue. We extended our analysis to serum samples of SI-NET patients to depict miRNAs functions. Aim(s): 1) To analyze the expression of nine miRNAs in serum from SI-NET patients. 2) To explore the biological functions of their potential miRNA target genes. Materials and Methods: Total RNA of serum samples from 21 SI-NET patients at different stage of disease, and seven healthy donors was used to study miRNAs expression by using QRT-PCR analysis. Functions of miRNAs were investigated by using QRT-PCR and NET cells as in vitro models. Results: MiRNA-96, -182, -183, -196a and -200a were upregulated; whereas miR-129-5p, -133a and -215 were downregulated in serum of SI-NET patients v. healthy donors. To silence miR-196a altered GAN, HOXA9, HOXB7, LRP4, RSPO2 and TYP1 genes expression in NET cells. Conclusion: Eight miRNAs are expressed and regulated in serum of SI-NET patients at different stage of disease. Silencing MiR-196a affects six genes in NET cells. Further functional studies of the eight miRNAs might be critical either to elucidate tumor progression mechanisms or develop novel therapeutic targets. Keywords: neuroendocrine tumors, serum mirna expression, mirna, target functions.
**B9**

**Specific MicroRNA Profiles are Associated with Pathological Features in Lung Carcinoids**

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**Introduction:** Data on miRNA expression in lung carcinoids are scarce. **Aim(s):** To analyze miRNA expression profiling in lung carcinoids as compared to clinical and pathological features. **Materials and Methods:** Seven-hundred and twenty miRNAs were analyzed using PCR-based array method in a pilot series of 12 lung carcinoids. The significance of these miRNAs was confirmed by hierarchical clustering and the five miRNAs more significantly down-regulated in metastatic carcinoids (miR 409-5p, miR 409-3p, miR 185, miR 129-5p and miR 431-5p) were validated in 37 cases (22 TCs, four with lymph node metastasis and 15 ACs, seven with lymph node metastasis), and in 10 high grade neuroendocrine carcinomas. **Results:** Twenty-four miRNAs were differentially regulated in ACs v. TCs and 29 in metastatic v. non-metastatic cases. MiR 129-5p, miR 409-3p and miR 409-5p were up-regulated in carcinoids overall as compared to high-grade carcinomas (p = 0.001, p = 0.005 and p = 0.003, respectively) and in TCs v. ACs (p = 0.02, p = 0.006 and p = 0.005, respectively). MiR 409-3p, miR 409-5p and miR 431-5p confirmed to be down-regulated in carcinoids with lymph node metastases (p = 0.01, p = 0.05 and p = 0.004, respectively). Moreover, down-regulation of all miRNAs except miR 185 was associated with vascular invasion. Predictive analysis in silico of specific target genes showed that the five miRNAs are potentially implicated in several cellular functions. **Conclusion:** Lung carcinoids express specific miRNA profiles which might have potential implications as diagnostic tools or clinical biomarkers. **Keywords:** lung, carcinoid, mirna.

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**B10**

**Upregulation of Somatostatin Receptor Type 2 Expression in Neuroendocrine Tumors by Epigenetic Modulation**


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**Introduction:** The somatostatin receptor type 2 (sst2) is a target for treatment of neuroendocrine tumors (NETs). However, epigenetic mechanisms might account for the high variability in sst2 expression and treatment response between patients. **Aim(s):** Determine expression of sst2 in NET cell line BON and NET tissues, as well as the effect of the demethylating agent 5-aza-2'-deoxycytidine (5-aza-dC) and histone deacetylase inhibitor Valproic Acid (VPA) on sst2 expression and epigenetic modifications in BON. **Materials and Methods:** BON cells were exposed four days to IC50 of 5-aza-dC or VPA. Sst2 mRNA values were determined by Q-RT-PCR, CpG methylation by pyrosequencing and H3K9 acetylation by chromatin immunoprecipitation (ChIP). Sst2 mRNA expression and promoter methylation was also determined in 18 NETs. **Results:** Sst2 mRNA expression in BON increased with 5-aza-dC and VPA treatment. No CpG methylation was detected while activating histone mark H3K9Ac was enriched in treated cells. In NET tissues, although high variability in sst2 mRNA expression was found, methylation was low in all cases. **Conclusion:** In BON, 5-aza-dC and VPA increased sst2 expression. Although CpG methylation was not detected in the sst2 promoter region, ChIP analysis showed epigene drug induced enrichment of H3K9Ac. In NET tissues high variability in sst2 mRNA expression was found, which was not reflected in the CpG methylation. BON data suggest that histone modifications play a role in regulating sst2 gene expression, which is currently investigated in NET tissues. **Keywords:** gep-net, sst2, epigenetics.
Electron Microscopy of Pancreatic Beta Cell Neuroendocrine Tumors (NETs) in Multiple Endocrine Neoplasia Type 1 (MEN1) Knockout Mice Reveal an Adenomatous Phenotype with Depletion of Insulin Granules and Increased Mitochondrial Content

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Introduction: Insulinomas are β cell neuroendocrine tumors (NETs) that secrete insulin, and ~4% of insulinoma patients have multiple endocrine neoplasia type 1 (MEN1). One in ten MEN1 patients present with an insulinoma. Previous reports describe insulinomas as possibly having typical granules (46.4%) or atypical smaller granules (34.3%), both associated with adenomas, or agranular cells (14.3%) associated with carcinomas. MEN1 knockout (Men1+/–) mice develop pancreatic NETs that are mostly insulinomas, and their ultrastructural phenotype is unknown. We hypothesized that these may resemble the adenoma phenotype with atypical granules.

Aim(s): To investigate the ultrastructure of NETs from Men1+/– mice, compared to normal beta cells from wild type (Men1+/+) mice, by electron microscopy. Materials and Methods: Pancreatic NETs and normal islets (n = 4 per group) were examined by transmission electron microscopy at x 8000 magnification and organelle density quantified per unit cytoplasmic area. Results: Granule density of beta cells from Men1+/+ mice was 99.41±2.58. NETs of Men1+/– mice contained significantly less granules (43.14±6.20; P < 0.0001) with <5% atypical forms. Furthermore, Men1+/– NETs contained significantly more mitochondria (16.82±1.60) than beta cells from Men1+/+ mice (6.62±0.46; P < 0.0001). NETs of Men1+/– mice had a 5-fold higher granule: mitochondria ratio compared to normal beta cells from Men1+/+ mice. Conclusion: Thus, pancreatic NETs of Men1+/– mice had an adenomas phenotype with low granule density and atypical forms. Keywords: gep-net.
C3

Cancer-Associated-Fibroblasts in Neuroendocrine Neoplasms: A Role in Cancer Progression

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Introduction: Cancer-associated-fibroblasts (CAFs) secrete soluble factors that enhance tumor growth and invasion. Neuroendocrine tumor (NET) cells recruit fibroblasts within the lesional sites. Aim(s): CAFs affect NET cells transcriptional profile thus postulating their hyperactive cross-talk with stroma. Materials and Methods: We established cultures of CAFs from enterochromaffin cell (ECL) hyperplasia, G1, G2, G3 NETs. Fibroblasts from perilesional tissue of NETs and WI-38 were used for control. Adherent cells were immunostained for CD34, CD45, CD56, CD73, CD90 and CD105. H720, H727, H835, BON1, CM and QGP1 NET cells were cultured with CAF conditioned medium (CM); their viability was assessed by MTS test while their proliferation by CFSE in the presence or not of inserts and by flow-cytometry. Results: CAFs were identified for their expression of mesenchymal markers and absence of hematopoietic and neuroendocrine markers. MTS test showed a decrease of viability of NET cells in the presence of CM from WI-38 and normal perilesional fibroblasts. A significant increase of NET cell viability was found in H727, H720 and H835 cells cultured in the presence of CM from NET and ECL hyperplasia, confirmed by CFSE. Conclusion: CAFs stimulate the proliferation of NET cells by soluble factors rather than by physical interactions, despite normal fibroblasts, thus implying that modifications of their transcription profile take place during NET tumorigenesis. Keywords: caf, microenvironment, neuroendocrine tumors.

C4

Cerebellar and Hypothalamic Regulation of Vestibular Compensation After Unilateral Labyrinthectomy in Rat

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Introduction: The mechanisms of inhibitory regulation of neuronal activity of the vestibular system in health and in the vestibular compensation (VC) occurred with participation of the cerebellum, while non-cerebellar pathways are essential in restoring the stability of visual orientation during movement. Aim(s): We investigated manifestations of the post stimulus excitatory and inhibitory activity of the Deiters’ neurons in response to high-frequency stimulation of I-V lobules of the cerebellar cortex. Post stimulus activity appeared in the form of tetanic potentiation and depression, followed by post tetanic potentiation and depression. Materials and Methods: In Deiters’ neurons to HFS of the cerebellar anterior cortex were predominantly revealed TD in intact rats, more pronounced at 100 Hz. On the third day after the unilateral labyrinthectomy, even to stimu-
**C6**

The Effects of cAMP in Different Neuroendocrine Tumorous Cells: The Role of Epac and PKA in Cell Proliferation and Cell Adhesion


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**Introduction:** cAMP is implicated in the inhibition or stimulation of proliferation depending on cell type. Although the effects exerted by cAMP were initially attributed to the PKA activation, two cAMP-activated guanine nucleotide exchange (Epac1/2) have been later identified as cAMP targets. **Aim(s):** To investigate the cAMP effects in neuroendocrine tumorous cells on cell proliferation and adhesion to determine the role of Epac and PKA in mediating these effects. **Materials and Methods:** We tested the effects of different cAMP analogs (Epac-selective, PKA-selective, or non selective) on cell proliferation, evaluating also the cyclin D1 and p27 expression, and on cell adhesion, in neuroendocrine primary culture (gastroenteropancreatic-NET and bronchial carcinoid) and in appropriate cell lines (QGP1 and H727). **Results:** cAMP activation by forskolin caused a 35% and 50% stimulation of cell proliferation in GEP-NET and QGP1 cells, respectively; whereas it exerted an inhibitory effect on H727 cells (~35%), data were confirmed by CD1 and p27 expression. These opposite effects were mimicked by the Epac and PKA selective analogs. Moreover, Epac and PKA activators caused a significant increase of cell adhesion both in QGP1 and H727 cell lines. **Conclusion:** Our study indicates that cAMP induces positive or negative effects on neuroendocrine cell proliferation, depending on the cell type, and that both Epac and PKA participate by activating different and partially unidentified signaling pathways. **Keywords:** cAMP, pka, epac, gep-net.

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

**D1**

Incidence and Prevalence of Neuroendocrine Tumors (NETs) of the Ileum and Colon (Excluding Appendiceal NETs) in Northern Ireland (NI) Over a 25-Year-Period (1988–2012)

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**Introduction:** Incidence of NETs is quoted to be 2/100,000 with approximately 25% being tumors of the midgut, (0.5/100.000). Incidence is increasing. However, this may be in part due to improved diagnosis but it is also thought to be a true increase. **Aim(s):** To establish incidence and prevalence of MGC in NI and to identify trends over 25 years. **Materials and Methods:** We have interrogated the Northern Ireland Cancer Registry, NET specialist clinic registry, pathology laboratory reports and clinical chemistry laboratory reports, and clinical records to identify patients diagnosed with MGC diagnosed or current between 1/1/1988 and 31/12/2012. Diagnosis using pathology reports or using biomarkers with syndrome and/or positive somatostatin scintigraphy was accepted. Population in NI 1988–2012 has been obtained from population census data. **Results:** The population in NI has increased 1.59–1.81 million between 1988 and 2012. Three-hundred and thirteen individuals with MGC were diagnosed or current between 1/1/1988 and 31/12/2012. Diagnosis was secured by pathology in 94%. M/F ratio was 52/48. Incidence of MGC rose from 0.47 to 1.14/100,000 and prevalence from 2.60 to 6.38/100,000. **Conclusion:** A small increase in incidence of MGC is identified over the 20 years 1988–2007 with an almost doubling of incidence in the last five years 2008–2012. Prevalence rose steadily over the 25 years. **Keywords:** mge.

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**D2**

Neuroendocrine Tumors of the Appendix: A Study of Presentation, Investigation and Management

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**Introduction:** Causes of appendicitis include infection, inflammatory bowel disease, faecoliths and neoplasm. Rarer causes of obstruction, such as neoplasm, may present in an identical manner to...
common causes, such as infection, and remain undiagnosed without histological analysis of appendicaecal tissue. Neuroendocrine tumors of the appendix are most commonly detected incidentally by histological analysis of appendicaecal tissue following appendicectomy.

**Aim(s):** To study the presentation, investigation and management of NETs detected following appendicectomy in East Kent University Hospital Trust. To compare investigation and management to ENETS Guidelines.

**Materials and Methods:** Cases over a 5-year period (September 2008-August 2013) across three hospital sites were identified from trust history databases. Presenting features, laboratory investigations, histological findings and follow-up imaging/surgery were identified from patient notes and computer databases.

**Results:** Twenty-eight cases were identified in the time period. The most common presenting feature was abdominal pain (89% patients) with nausea (77%) and pyrexia (4%) being associated. EKLH is compliant with guidelines for histological analysis but fell short in follow-up and management.

**Conclusion:** Clinical presentation and laboratory results for NETs were similar to all-cause appendicitis, thus it is difficult to identify NETs prior to surgery. Appropriate histology and imaging is vital for staging, determining prognosis and investigating rare NETs.

**Keywords:** appendix, histology, guidelines, nets.

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**D3**

**NETs in a Hospital Registry at a Russian Cancer Centre**

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**Introduction:** We aimed at a retrospective evaluation of patients diagnosed with NETs between 1980 and 2013. **Aim(s):** To describe the frequency of patients with NETs, clinical symptoms, diagnosis, follow-up of NET patients.

**Materials and Methods:** Data regarding 435 NET pts were evaluated: 238 pts with GEP-NET, 142 with BNETs, and 65 with rare NETs (head and neck, kidney, breast, skin).

The maximum increase in incidence occurred for pancreas and bronchial NETs, the minimum – for appendices and small intestine. There was female predominance (63%). Median age of pts: 49 years for females, 51 for males. In our study, 39.8% of pts had pain in abdomen, lumbago zone, subcostal area, 32.7% of pts had cough, shortness, bleeding in lungs, pneumonia, 15.7% – weakness, 6.1% – high temperature. Overall survival (OS) of GEP NETs pts was 61.1%. Out of 238 GEP NET pts, only 194 pts were operated. OS of 80 radically operated GEPNET pts was 74.8% and for 24 non-radically operated – 51.3%. OS of GEPNET pts was 100% at grade 1, 88% at grade 2 and 64% at grade 3. OS for 115 BNET pts was 84.9%. OS for 94 radically operated – 95.1%, for 21 non-radically operated – 39.0% (p = 0.001).

**Results:** Incidence rate of NETs has significantly increased in the past 30 years. In the period 1980–1994, there were 31 pts; 1995–1999 – 66 pts, 2000–2012 – 338 pts.

**Conclusion:** We detected fewer NETs located in the small intestine and appendix. Although 50.3% GEPNET pts had distant metastases at diagnosis, the median survival was 68.6 months.

**Keywords:** neuroendocrine carcinoma, ki-67, immunohistochemistry, treatment.

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**D4**

**Treatment Practices in European Centers with Interest in Neuroendocrine Carcinomas and High Grade (G3) Neuroendocrine Tumors**

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**Introduction:** Aggressive neuroendocrine neoplasms (NEN) encompass both poorly differentiated carcinomas (NEC) and high grade neuroendocrine tumors (G3-NET) with a Ki-67 index >20%; WHO 2010. **Aim(s):** We wished to examine as to whether NEC and G3-NET are considered differently.

**Materials and Methods:** An electronic survey of 39 questions on NEC and G3-NET was constructed on physician practices about characteristics, diagnosis and therapy. Sent to KN members from 23 centres with an interest in NET (20 centers responded).

**Results:** The majority of respondents (83%) distinguished between NEC and G3-NET (proportion of G3-NET <20%). Synaptophysin and Ki-67 are always in the pathology-report, mitotic index in 53% of the cases. Most frequent Ki-67 index range for NEC was considered 51–80% (53%) and <30% for G3-NET (81%). FDG-PET was deemed useful in 85%, somatostatin receptor imaging in 30%. Treatment of G3-NET: surgery (67%) and PRRT (67%) were considered. Surgery was considered in 5% of the cases in NEC. Ki-67 index influenced therapeutic decisions in 60% of G3-NET but not in NEC. First line chemotherapy using platinum/etoposide is used in 88% of NEC patients, only in 20% of G3-NET (STZ+5-FU/Doxorubicin: 27%; TMZ-based: 27%; FOLFOX: 13%; etoposide is used in 88% of NEC patients, only in 20% of G3-NET) (STZ+5-FU/Doxorubicin: 27%; TMZ-based: 27%; FOLFOX: 13%; etoposide is used in 88% of NEC patients, only in 20% of G3-NET). Somatostatin receptor imaging in 30%. Treatment of G3-NET: surgery (67%) and PRRT (67%) were considered. Surgery was considered in 5% of the cases in NEC. Ki-67 index influenced therapeutic decisions in 60% of G3-NET but not in NEC. First line chemotherapy using platinum/etoposide is used in 88% of NEC patients, only in 20% of G3-NET (STZ+5-FU/Doxorubicin: 27%; TMZ-based: 27%; FOLFOX: 13%; etoposide is used in 88% of NEC patients, only in 20% of G3-NET). Somatostatin receptor imaging in 30%. Treatment of G3-NET: surgery (67%) and PRRT (67%) were considered. Surgery was considered in 5% of the cases in NEC. Ki-67 index influenced therapeutic decisions in 60% of G3-NET but not in NEC. First line chemotherapy using platinum/etoposide is used in 88% of NEC patients, only in 20% of G3-NET (STZ+5-FU/Doxorubicin: 27%; TMZ-based: 27%; FOLFOX: 13%; etoposide is used in 88% of NEC patients, only in 20% of G3-NET).

**Conclusion:** Greater than 80% of the responding physicians distinguish between NEC and G3-NET. Management strategies clearly differ between these two entities which displays a definite trend towards subclassification of high grade NEN (Ki-67>20%).

**Keywords:** neuroendocrine carcinoma, ki-67, immunohistochemistry, treatment.

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**D5**

**Pancreatic Neuroendocrine Tumors: Experience in a Spanish Reference Center**

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**Introduction:** Pancreatic neuroendocrine tumors (pNET) derived from the hormone-producing cells in the pancreas whose actual prevalence, natural history and optimal treatment raises con-
Epidemiology/Natural History/Prognosis – Prognosis

E1 Lymph Node Involvement to Predict Survival in Pulmonary Neuroendocrine Tumors – A Single Center Experience

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Introduction: Typical (TC) and Atypical carcinoid (AC) tumors are well-differentiated neuroendocrine tumors of the lung. Aim(s): This study aimed to examine lymph node (LN) status and Ki-67 scores in 51/94 patients. KM survival curves demonstrated superior survival in patients with a Ki-67 score <5, however, this was not statistically significant, p = 0.139. Conclusion: This study highlights the aggressive nature of ACs in comparison to TCs. It also suggests LN status is of paramount importance within the AC group and is a useful prognostic marker. We suggest that the more aggressive nature of AC tumors and the significance of positive LN status support the use of adjuvant chemotherapy for these patients. Keywords: lung, neuroendocrine, cancer, lung cancer.

E2 Gastroenteropancreatic Neuroendocrine Neoplasms: The Experience of an Oncology Center


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Introduction: Gastroenteropancreatic neuroendocrine neoplasms (GEP-NEN) are a heterogeneous group of tumors and an exponential increase in its incidence has been noticed over the past decades. Aim(s): Retrospective study of patients with GEP-NEN admitted in our institution between 2008 and 2011. Materials and Methods: Demographic, primary location, WHO classification, staging, hormonal hypersecretion (HH) and survival (Kaplan-Meier method) were analyzed. Results: One-hundred and five patients (pts), 56 M and 48 F, aged between 19 and 90 years (59.6±13.4 years). Regarding location, 65% were gastrointestinal (GI) (32% gastric, 31% jejunum-ileum, 13% rectum, 7% duodenum, 6% colon, 4% appendix, 4% other locations), 27% pancreatic (P) and 8% with unknown primary (UP). They were classified (WHO2010) as NETG1, NETG2 and NEC, respectively, 54%, 34% and 12% of patients. Regarding staging (ENETS, AJCC/UICC): 30% were classified as stage (S)I, 6% as SII, 12% as SIII and 52% as SIV. In most cases, there was no evidence of HH (69%). Among functioning tumors (31%), 75% had GI and 25% P origin. Overall 5-year survival (OS) was 71%, depending mainly on WHO classification (p < 0.0001), tumor location (p = 0.007) and presence of distant metastasis (p < 0.0001). Conclusion: Compared previous data (1986–2008), there was an increase in the number of pts and an increase in OS. This being an oncology hospital, a large number of severe cases are referred. The decrease in UP cases is probably related to new diagnostic modalities (68Ga-DOTANOC PET/CT). Keywords: neuroendocrine, neoplasia, survival.
E4

Experience of a Single Italian Center with NET Patients

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Introduction: The management of neuroendocrine tumors involves a multidisciplinary approach, so in 2004 the Endocrinology and Metabolic Unit developed a local/regional network to manage NET patients and to increase physician awareness of the disease. Aim(s): A retrospective study of patients diagnosed with NET from 1990 to 2012 was gathered, including data regarding NET epidemiology in order to examine some characteristics of the health care/assistance process. Materials and Methods: Data collection from the hospital’s computerized clinical charts, old hand-written records, and the ‘NET Management Study’ database. Besides the demographic-epidemiological data, information was acquired regarding the dates of the initial symptoms, of the first clinical visit, of confirmed diagnosis and first endocrinological visit. Results: Of 319 patients with confirmed diagnosis, sufficient data were collected in 285 patients (89.3%), 146 males (51.2%) and 139 (48.7%) females. The average age at diagnosis was 54.6 years (range, 19-98 yrs), with no significant difference between GEP-NET and T-NET, and with a slight predominance of women in GEP (51.3%) and men in T-NET (53.8%). Between 2002–2012, the incidence rate was 18.8 cases per 100,000 NET. The analysis examined the time elapsed between the patient’s first visit concerning his/her health problem and his/her first endocrinological visit, and the time between the date of diagnosis and his/her first endocrinological visit. Conclusion: In this region, too, NET incidence has been increasing. The implementation of a network helped increase the local physicians’ knowledge and assure a quicker diagnosis/referral to the endocrinologist. Keywords: epidemiological net.

E5

Characteristics and Treatments of Patients with G3 Gastroenteropancreatic Neuroendocrine Tumors (G3-NET) and Neuroendocrine Carcinoma (NEC): An European Multicenter Retrospective Study

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Introduction: Data on G3-NET and NEC are limited. No standard therapy following platinum-etoposide failure is established and first-line therapy in G3-NET is not codified. Aim(s): To evaluate clinical and pathological characteristics of diagnosis, therapies and outcome in NEC G3. Materials and Methods: Retrospective study of patients (pts) with G3-NET and NEC from five European centers diagnosed between 01/01/00 and 01/09/13. Results: As of 28/11/13, 177 pts were analyzed (median age 60 years, 61% male). Primary locations were pancreas (31%), colon (16%) and unknown (16%). At diagnosis, 73% were metastatic, mainly to the liver (66%). Eighty-eight percent had poorly differentiated NEC (small/large cell 41%/59%) and 12% well-differentiated G3-NET. Median Ki-67 index was 70%. 18F-FDG PET and SRS imaging were positive in 55 (82%)
and 75 (52%) pts. Systemic chemotherapy was given in 83%, mainly platinum-etoposide. Second- and third-line therapy was feasible in 76 (44%) and 41 (24%) pts, respectively. G3-NET pts received first-line a non-platinum-etoposide regimen in 74%. Median overall survival for all pts was 25 months (19 months for NEC) with median follow-up of 16 months. **Conclusion:** In this large series of G3-NET/NEC pts seen in tertiary centers, overall survival seems longer than in published data, although nearly 90% was poorly differentiated with median Ki-67 of 70%. In G3-NET choice of treatment and outcome needs to be confirmed by larger sample size and long-term follow-up. **Keywords:** gastrointestinal cancer, neuroendocrine carcinoma, grade 3 net, ki-67, chemotherapy.

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**E6**

**Prognostic Value of Somatostatin Receptor Scintigraphy on High-Grade Neuroendocrine Neoplasms and Impact on the Treatment Decision of Intermediate-Grade Neuroendocrine Neoplasms**


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**Introduction:** Somatostatin receptor scintigraphy (SRS) could detect not only somatostatin receptors but also tumor images in patients with neuroendocrine neoplasms (NENs). **Aim(s):** To evaluate the clinical utility of SRS in the prognosis and management of patients with NENs. **Materials and Methods:** We retrospectively analyzed 49 pts with non-resectable and pathologically confirmed NENs who underwent SRS. **Results:** Among 49 pts with NENs recruited from 1/2010–11/2013, four were low-grade (G1), 27 were intermediate-grade (G2) and 17 were high-grade (G3). Thirty-seven pts were SRS positive (three of G1, 21 of G2 and 13 of G3) in which 12 were p-NENs and seven were GI-NENs. Twelve pts were SRS negative (one of G1, six of G2 and five of G3) in which four were p-NENs and seven were GI-NENs. Among 17 G3 pts, the overall survival of SRS positive and SRS negative pts were 18.8 mos and 21.2 mos, respectively, with no significant difference (p = 0.77). Of 18 SRS positive G2 pts who received first-line therapy, response was detected in 0/9 pts treated with somatostatin analog (SSA) and in 4/9 pts treated with targeted therapy or chemotherapy. However, there was no significant difference in progression-free survival between SSA and other treatment (8.5 mos and 9.6 mos, respectively). **Conclusion:** Somatostatin receptor status didn’t affect the prognosis of G3 pts. For SRS positive G2 pts, the efficacy of SSA is non-inferior to targeted therapy or chemotherapy. However, this conclusion needs to be confirmed by larger sample size and long-term follow-up. **Keywords:** neuroendocrine, srs, prognosis.

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**E7**

**Analysis of Somatostatin Receptors Expression in Neuroendocrine Tumors**

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**Introduction:** Clinical studies have suggested anti-tumor efficacy of somatostatin analog (SSA) in the treatment of neuroendocrine tumors (NETs). **Aim(s):** We investigated the prognostic significance of expression of somatostatin receptors (SSTRs) in patients with NETs generally, and in a subset of patients treated with SSA. **Materials and Methods:** We evaluated immunohistochemical expression of SSTR1, 2, 3 and 5 in a cohort of archival NETs. We correlated expression levels with clinical outcomes after adjusting for other clinical prognostic variables. **Results:** Within 172 primary tumors, high expression of SSTR2 was associated with improved overall survival (OS) (multivariate HR 0.44, p = 0.019). In patients with metastatic small intestinal NETs (SINETs) (n = 75), high expression of SSTR2 was also associated with improved OS (multivariate HR 0.36, p = 0.0083). We additionally investigated associations between SSTR expression and PFS in patients with SINETs treated with SSA (n = 53). In SSA-treated patients, high expression of SSTR2 was associated with improved PFS (multivariate HR 0.38, p = 0.0084; median PFS: 2.8 years for SSTR2-high v 1.3 years for SSTR2-low). There was no significant association between other SSTRs and clinical outcomes. **Conclusion:** High expression of SSTR2 appears to be a general favorable prognostic factor in patients with NETs. In addition, SSTR2 expression is associated with longer PFS in SINET patients treated with SSA. Studies examining whether SSTR2 expression is predictive of SSA response are warranted. **Keywords:** sstr2, ssa, net, os, pfs.

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**E8**

**Prognostic Role of Smoking in Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET)**


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**Introduction:** Large retrospective series identified several prognostic factors for GEP-NET such as sex, race, age, primary localization, stage or tumor grade. Several studies suggested a prognostic role of smoking in many cancer types. However, no data has been reported in GEP-NET. **Aim(s):** To assess prognostic role of smoking in GEP-NET. **Materials and Methods:** We reviewed the records of 94 patients (pts) with GEP-NET from our institution diagnosed between 1998 and 2013. Patients and disease characteristics (demographic data, histologic grade, location, stage) and survival outcome were compared between never smokers (NS) (n = 53) and current or former smokers (S) (n = 39). **Results:** For both groups, median age...
was 63 years (range 23–88). Male rate was 41.5% in NS and 69.2% in S (p = 0.008). No differences between NS and S were seen in primary tumor localization and stage at diagnosis. Although not statistically significant, there was a trend towards less frequent ENETS/WHO 2010 grade 3 (G3) in NS than S (11.3% v. 25.6%, p = 0.093). With a median follow-up of 30.2 months, 2-years Overall Survival (OS) was 86% and 62% for NS and S, respectively (p = 0.025). Univariate analyses also showed that male gender, age >50 y, hindgut localizations, stage IV and G3 were also predictors of poor OS. In the multivariate analyses, only G3 was independently associated with poor OS. Conclusion: In this retrospective study, smoking was associated with G3 tumors and male gender, and with a poor prognosis. Keywords: smoking, prognostic, gastroenteropancreatic, neuroendocrine tumor.

E9
Association between Tumor Expression of VEGFA, VEGFR1 (FLT1), VEGFR2 (KDR), and Clinical Outcomes in Neuroendocrine Tumors
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Introduction: Clinical studies have suggested efficacy of VEGF pathway inhibitors in the treatment of advanced neuroendocrine tumors (NETs). Aim(s): We investigated the prognostic significance of expression of VEGF pathway components in NET patients generally, and in a subgroup of patients treated with bevacizumab. Materials and Methods: We evaluated immunohistochemical expression of VEGF, VEGFR1, and VEGFR2 in a cohort of archival NETs and evaluated associations with overall survival (OS) and progression-free survival (PFS) after adjusting for other clinical prognostic variables. Results: Among 173 primary NET of various origins, high expression of VEGFA was associated with shorter OS (multivariate HR, 2.14; P = 0.03) whereas high expression of VEGFR1 was associated with improved OS (multivariate HR, 0.46; P = 0.03). In the subgroup of patients with metastatic small intestinal NET (SINET) (n = 76), high expression of VEGFA was also associated with shorter OS (multivariate HR, 3.13; P = 0.013). However, in bevacizumab-treated SINET patients (n = 19), high expression of VEGFA was associated with improved PFS (multivariate HR, 0.01) and high expression of VEGFR1 was associated with shorter PFS (multivariate HR, 30.5). Conclusion: Expression of VEGFA appears to be an adverse prognostic factor, and expression of VEGFR1 may be a favorable prognostic factor in patients with NET. VEGFA and VEGFR1 may be specifically associated with the treatment effect of bevacizumab in patients with advanced SINET. Confirmatory studies are warranted. Keywords: vegf, bevacizumab, net survival.

E10
Brain Metastases in Neuroendocrine Tumor Patients: Frequency and Outcome
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Introduction: Brain metastases are rarely reported in patients with neuroendocrine carcinoma (NEC) of non-lung origin and neuroendocrine tumors (NETs) of the gastroenteropancreatic or bronchopulmonary system. Symptomatic brain metastases are associated with dismal prognosis, so early detection and treatment could be advisable. Aim(s): To analyze frequency, origin, treatment and outcome of brain metastases in a single centre cohort of NET and non-lung NEC patients. Materials and Methods: In 1998, we established a database for patients with NETs and NECs of gastroenteropancreatic or unknown origin. We searched this clinical database for all patients with documented brain metastases. Results: We identified 16 out of 975 patients (1.6%) with brain metastases (11 women, five men). Thirteen of 16 patients (81.3%) had non-functioning tumors, hormone syndromes included two gastrinoma and one ectopic ACTH-syndrome. Nine of 16 patients (56.3%) had NEC (1% of all NET patients), six patients (37.5%) had NEC (6/65 = 10.1% of NEC patients). Most patients had bronchial (n = 6; 37.5%; 6/65 patients with bronchial NET = 10.7%) and pancreatic (n = 5; 31.3%; 5/279 pancreatic NET = 1.8%) primaries. In 14 of the 16 patients (87.4%), distant metastases were present at diagnosis. Median survival after diagnosis of brain metastases was only seven months (0.5–159), two patients survived more than five years. Conclusion: Screening for brain metastases could be advisable in NEC patients and patients with NET of bronchial origin. Keywords: brain metastases, net, nec, prognosis.

E11
Diagnostic and Outcome Differences Between Sporadic and Familial Cases of Medullary Thyroid Cancer: A Retrospective Cohort Study
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Introduction: Hereditary Medullary Thyroid Cancer (MTC) accounts for 20–30% of cases and has some clinically relevant peculiarities. Aim(s): To analyze differences in diagnosis and outcome between sporadic and familial cases of MTC. Materials and Methods: All genotyped patients with MTC (n = 35) diagnosed at Hospital Clínic San Carlos between 1984–2012 were included; 40% were germline mutation carriers (38.5% ATA-A, 53.9% ATA-B/C, 7.6% ATA-D). Median follow-up was 55 months (IQR 16–94).
A comparative analysis was performed using Mann-Whitney U test, chi-squared test and Breslow test. **Results:** Median age at diagnosis was 33.9 years in familial cases, and 63.6 years in sporadic cases (p = 0.001); local or distant metastases were present in 38.5% of familial cases and 57.1% of sporadic cases (p = 0.29). Most of the familial cases (64.3%) were asymptomatic and diagnosed after genetic screening. Six months after total thyroidectomy, 28.6% of sporadic cases and no familial cases developed distant metastases (p = 0.06, median time 19 months [IQR 6–43]). Progression-free survival and distant metastasis-free survival (DMFS) were longer in familial cases (p = 0.08 and p = 0.03, respectively). **Conclusion:** Age at diagnosis was significantly lower in familial cases of MTC. Genetic testing allowed for early diagnosis in asymptomatic mutation carriers; therefore familial cases had a better outcome and significantly longer DMFS. **Keywords:** medullary thyroid cancer, multiple endocrine neoplasia.

**E12**

**Diagnostic and Outcome Differences between Sporadic and Familial Cases of Pheochromocytoma and Paraganglioma: A Retrospective Cohort Study**


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**Introduction:** Hereditary Pheochromocytomas (PCC) and Paragangliomas (PGL) account for 30–35% of cases and have some clinically relevant peculiarities. **Aim(s):** To analyze differences in diagnosis and outcome between sporadic and familial cases of PCC/PGL. **Materials and Methods:** All genotyped patients (n = 31, 24 with PCC and seven with PGL) diagnosed at Hospital Clínico San Carlos between 1988–2012 were included; 35.5% were germline mutation carriers (27.3% pseudohypoxic phenotype [PH], 72.7% MAP-kinase phenotype [MAPK]). Median follow-up was 55 months (IQR 23–91) for 28 patients. A comparative analysis was performed using Mann-Whitney U test, chi-squared test and Breslow test. **Results:** Median age at diagnosis was 35.1 years in familial cases, and 56.5 years in sporadic cases (p = 0.007). Most of the sporadic cases were diagnosed incidentally (75% vs. 18.2%, p = 0.007). Multifocality was more frequent in familial cases (45.5% vs. 10%, p = 0.07). Recurrent disease after surgery was present in 37.5% of familial cases and in no sporadic cases (p = 0.012, median time 64 months [IQR 19–64]); it was more frequent in the PH group (66.7%) than in the MAPK group (16.7%, p = 0.14). Progression-free survival (PFS) was longer in sporadic cases (p = 0.007). **Conclusion:** Age at diagnosis was significantly lower in familial cases of PCC/PGL. Malignant behavior and multifocality were associated with familial cases. Genetic testing allowed the earlier diagnosis in asymptomatic mutation carriers; although sporadic cases had significantly longer PFS. **Keywords:** pheochromocytoma, paraganglioma.

**E13**

**Hepatic Metastases of Gastroenteropancreatic Neuroendocrine Tumors: A 17-Year Single Center Prospective Study**

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**Introduction:** Gastroenteropancreatic neuroendocrine tumors (GEP NET) with hepatic metastases (HM) have a poorer prognosis in comparison with localized GEP NET. **Aim(s):** Primary endpoints of the study are overall survival from the diagnosis of liver metastases (OS), progression-free survival (PFS) and treatment effectiveness. **Materials and Methods:** Among 186 consecutive patients with diagnosed GEP NET from 1995 to 2012, 74 had HM. Prognostic factors and survival times of GEP NET with HM with different treatments were calculated using Kaplan-Meier method and regression analysis. **Results:** Median OS (range) was 96 (3–201) months. Prognostic factors for OS were grading, presence of extrapancreatic disease (EHD) and treatment (p < 0.0001). Ten patients (14%) achieved complete remission, 18 (24%) partial remission, 18 (24%) stable disease, and 28 (38%) progression of disease. Among responsive patients median PFS was 84 (4–180) months. Prognostic factors for PFS were grading and presence of EHD (p < 0.001). Five- and 10-year survival rate were 86% and 71% for radical surgery (RS), 82% and 58% for palliative surgery (PS) with radioreceptor therapy (RT), 58% and 37% for PS and medical treatment (MT), and 23% and 8% for MT alone. **Conclusion:** Overall survival of GEP NET with HM resulted high, as described from other authors. Interestingly, we found that OS and PFS of patients treated with RS are similar to those of patients treated with PS and RT. Main prognostic factors for GEP NETs with HM are grading and EHD. **Keywords:** neuroendocrine tumors, hepatic metastases.
E14

Challenging in Predicting Response in Treatment of Neuroendocrine Pancreatic Tumors: Nutritional Factors


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Introduction: Neuroendocrine pancreatic tumors (NEPT) include a heterogeneous neoplasms group in pathophysiology, clinical manifestations, treatment and prognosis. Aim(s): To evaluate the nutritional factors which better predict the response to surgical treatment, disease-free survival and total survival. Materials and Methods: Twenty-six NEPTS intervened surgically in our center between 2009 and 2013 were reviewed. Data about lost weight, albumin, total protein and lymphocytes pre-intervention were collected. Complications after surgery, overall survival and disease-free survival to date were also reviewed. Results: Four patients of the cohort lost weight before surgery (~6.4 kg±1.2 kg). Medium level of albumin reported was 3.84±0.73 g/dL, medium level of lymphocytes was 2,529±3,864 cells/mm³ and level of total proteins was 6.59±1.06 g/dL. 30.8% of patients had albumin levels below 3.5 g/dL, 57.7% patients had less than 2000 lymphocytes and 26.9% had total proteins underneath 6.3 g/dL. There was a significant negative correlation between total proteins and postsurgical morbidity (p = 0.05) and a significant positive correlation between albumin and disease-free survival. A statistically significant difference was observed among well-nourished and poorly nourished patients in total survival and disease-free survival. Conclusion: Nutritional status significantly influences PNET prognosis. Low levels of total proteins, albumin and lymphocytes are predictors of poor response. Keywords: nutritional status, neuroendocrine tumors, pancreas.

F1

Evidence of Improved Survival When Patients Are Referred on to a Specialist NET Clinic with Multidisciplinary Team Management

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Introduction: ENETs and UKNETs Guidelines emphasize that patients with NETs should be referred to NET specialist clinics (NSC) and these clinics should use a multidisciplinary team (MDT) for decision making. In Belfast there has been an NSC for several decades and an MDT since 2000. Aim(s): To assess survival in patient referred or not to an NSC. Materials and Methods: All patients with midgut NETs in Northern Ireland, current between 2000 and 2012 were identified. Those referred to the NSC and those managed in other hospitals were noted. The NI Cancer Registry, the NSC and the NET specialist Lab were used to identify patients. Patients were followed to 31/9/2013 or to death. Patients confirmed by pathology or biomarkers, syndrome and/or somatostatin scintigraphy +ve were included. Patients were also age matched at diagnosis to closest age match, (limits +/-6 M) to remove age bias in the clinic group. Results: Two-hundred and fifty-four patients were identified. Any who died within three months of diagnosis were excluded (19). 110 patients were age matched at diagnosis for further analysis. Of patients attending the NSC median age at diagnosis was 63.3 Y. Survival at 1, 2, & 5 Y was 90.1, 89.1 & 61%. In those not attending median age was 72.5 Y and survivals were 69.5, 56.3 and 33.3. In the age matched group, survival in clinic patients remained significantly better at 1, 2 & 5 Y. Conclusion: Improved survival is noted in patients referred to a NSC. Keywords: net clinics.

F2

Incidence of Secondary Neoplasia in Patients with Neuroendocrine Tumor: An Analysis of the SwissNET Database

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Introduction: NET are believed to be associated with an increased risk for secondary neoplasia. Previous studies suggest incidence rates between 7% and 46%. Aim(s): To determine the inci-
Thyroid Disturbances in Neuroendocrine Tumors: A Romanian Retrospective Study

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Introduction: For the last decades, neuroendocrine tumors (NETs) was a large area of investigation. Aim(s): We present thyroid pathology in NETs: nodules, function, autoimmunity. Materials and Methods: Study design: retrospective observational study (between 2008–2013) in NET patients. Exclusion criteria: medullary thyroid cancer. Endocrine assessment: TSH, Free T4, serum calcitonin, thyroid ultrasound, antithyreoperoxidase antibodies. Selected cases: thyroid fine needle aspiration, pathological and IHC exam. Results: Demography: 44 females and men; mean age: 56.0±5.4 yrs. Grading: G1 45%, G2 26%, G3 29%. Tumor primary sites: 26% unknown origin, 23% midgut, 16% lung, etc. Mean TSH: 3.41 (Normal <4) μUI/mL. Primary hypothyroidism: 19% of cases (one case had iatrogenic thyrotoxicosis under levothyroxin therapy). High thyroid antibodies: 9.6% of cases (Hashimoto thyroiditis). Thyroid nodules at ultrasound: 31.81% of cases. Total thyroidectomy was performed in 12.9% of cases (only two malignant thyroid cases were among them: a female with thyroid metastases and a man with associated papillary thyroid cancer). Mean serum calcitonin: 3.4 (normal <4.8) ng/mL. Two women with pancreas, respective pulmonary NET had persistent hypercalcitoninemia within two years from diagnosis. Conclusion: Non-thyroid sources of hyper-calcitoninemia should be considered. Thyroid function may be influenced by NET therapy. This study indicates various thyroid disturbances in NETs, thus we encourage a thyroid check-up in every NET. Keywords: neuroendocrine, thyroid, calcitonin.

Secondary Hormonal Syndromes in Patients with Sporadic Neuroendocrine Tumors

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Introduction: Neuroendocrine tumors (NETs) are characterized by secretion of peptide hormones that may cause distinct syndromes. Although most patients with hormonal secretion are diagnosed upon primary diagnosis, a significant proportion of pancreatic NET patients develop secondary hormonal production later on in the disease. Aim(s): To determine the frequency of symptomatic secondary hormonal production in NETs. Materials and Methods: This was a retrospective analysis of patients (n = 972) with NET treated at our institution; Uppsala Academic Hospital, Uppsala, Sweden. We selected sporadic patients with symptoms of secondary hormonal excess (conversion) that were confirmed by biochemistry testing. Results: Thirteen NET patients had secondary hormone production causing clinical symptoms, 12 (12/177) originating from pancreatic/duodenum and one (1/517) from the small intestine. Hormonal conversion occurred exclusively in patients with tumors corresponding to ENETS grade 2 or 3. The median time to conversion was 46 months from the primary diagnosis. Patients with secondary insulin production had a median survival following conversion of 10 months, lower than that of other converters (p = 0.03). Conclusion: Secondary hormonal production was observed in 6.7% of sporadic pancreatic NETs and may be regarded as extremely rare in NETs of other origin. Patients with secondary insulin production had a short survival following conversion with severe hormone related morbidity. Keywords: neuroendocrine tumor, prognostic factors.
**F5**

**Scoping Study on Quality of Life (QL) in Patients (pts) with Neuroendocrine Tumors (NET) of the Digestive Tract in Argentina: Preliminary Results**

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**Introduction:** Patients with NET compound a specific cancer population: their survival used to be longer than other cancer patient populations and they received drugs (eg. somatostatin analogues) rarely used on others. The systematic measure of QL in these patients could lead to better understanding of the impact of the disease and treatments, not only in terms of symptom prevalence but also in relation to daily concerns. **Aim(s):** Description and measurement of QL in patients with NET in relation to symptom burden, psychosocial concerns and impact of disease and therapies on daily activities. **Materials and Methods:** A unique researcher interviewed 43 consecutive pts with metastatic well-differentiated NET of digestive tract (F/M = 14/29) using a Mac Gill QL questionnaire. Primary tumor: gut (22), pancreas (11), unkown (10). **Results:** Global QL was low scored by four pts (9%), but considering questionnaire items scored >5/10, we find that 26 pts (60%) complain of physical symptoms, mainly: meteorism (30%), pain (19%), fatigue (14%), diaphoresis and insomnia (12%), diarrhoea (7%); 11 pts (26%) report depression and 22 pts (51%) report being worried about potential disease progression; 22 pts (51%) report family concerns and 14 pts (33%) complain of sexual disorders, both in relation to the disease. **Conclusion:** This scoping study demonstrates that patients with digestive tract NET suffer from a wide number of symptoms and psychosocial concerns, and they would benefit from a systematic supportive care approach. **Keywords:** net, quality of life, symptom burden, supportive care.

**F6**

**Clinicopathological Characteristics of Colorectal Neuroendocrine Tumor in Chinese Patients**


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**Introduction:** Colorectal neuroendocrine tumors (cNET) are increasing, but rarely do studies report the clinicopathology in Chinese patients. **Aim(s):** To summarize the clinicopathological characteristics of cNET in China. **Materials and Methods:** A retrospective analysis was conducted from a single cancer center between 1998 and 2013. Data included patient characteristics, presentation, treatment, recurrence and tumor biology. **Results:** Eighty-one patients with cNET validated from surgical examples were analyzed. The mean age of patients was 56.6±3.0 y, and subjects were predominantly male (69.1%). Thirty-eight patients were asymptomatic, and the most common presentation was melena (27.1%). Abdominal pain was also frequently found (17.2%). All of the patients had undergone colonoscopy, and ascending colon tumors were the most prevalent (71.6%). The mean tumor diameter was 1.9±0.3 cm. Randomly, patients were conducted with hemicolecotomy or endoscopic resection. All the patients underwent radical resection. During a median follow-up of 34 months, two patients were recurrent in the endoscopic resection group; while in hemicolecotomy group there were no recurrences. Seventy-two patients were grade 1 or 2 tumors, most of which showed a diffusely positive staining for synaptophysin and chromogranin A. The staining in grade 3 tumor samples was mainly focal. **Conclusion:** Our study showed different clinicopathological characteristics from Caucasian, which may help physicians diagnose and manage these rare tumors in Chinese patients. **Keywords:** colorectal, net, clinicopathology, chinese.

**F7**

**Treatment with Somatostatin Analogs of Recurrent Type I Gastric Carcinoid in Patients with Autoimmune Chronic Atrophic Gastritis**

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**Introduction:** The treatment of type 1 gastric carcinoids (GC1) is still debated, in view of their usual benign behavior. **Aim(s):** To evaluate the outcome of patients with recurrent GC1 treated with somatostatin analogs (SSA). **Materials and Methods:** From January 2000 to September 2013, among 111 patients with chronic autoimmune atrophic gastritis, 23 patients were diagnosed with GC1. After they had the GC1 endoscopically removed, they underwent regular clinical and endoscopic follow-up. Plasma chromogranin A (CgA) and gastrin levels were measured in all patients. Patients showing recurrent GC1 were treated with SSA until gastrin fell below 400 pg/mL and there was no endoscopic/histological evidence of GC1. **Results:** Twelve patients (52%) showed GC1 recurrence and were treated with SSA for a median time of 13 months. At baseline, median gastrin and CgA levels were 719 pg/mL and 33 U/L, respectively, and they decreased to 389 pg/mL (p = 0.001) and 14 U/L (p = 0.005), respectively, after a six-month treatment period. In all but one patient, GC1 disappeared after a median treatment of 12 months. In one case it was necessary to extend the therapy for 32 months to achieve GC1 disappearance. After SSA discontinuation, four patients (36%) showed GC1 recurrence after a median of 19.5 months and they were successfully retreated with a schedule of 12 months on treatment alternated to six months off treatment. **Conclusion:** This cohort study confirms that GC1 tend to recur. SSA, administered in cycles of 12 months, represent an effective treatment. **Keywords:** gastric carcinoid, nen.
Abstracts

F8

Rectal Neuroendocrine Tumors: A Review of Clinical Outcomes

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Introduction: Rectal neuroendocrine tumors (rNETs) are increasing in incidence, with more found incidentally on routine colonoscopy. Aim(s): To retrospectively analyse a cohort of rNETs to characterize diagnostic features and clinical behavior. Materials and Methods: Patients (pts) with confirmed diagnosis of rNET were identified from a database. Results: Sixty pts evaluated. 29/60 pts had tumor <1 cm, 7/60 pts 1–2 cm, 22/60 >2 cm, 2/60 unknown. 24/60 pts had metastases at presentation, 5/60 developed metastases during follow-up (of these 29 pts 86% liver, 40% bone, 10% lung). Chromogranin A was available in 23/29 pts: was normal in 83%. Of 29 metastatic pts, 19/29 had chemotherapy, 10/29 somatostatin analogues (SST), 15/29 surgery and 10/29 peptide-receptor-radionuclide therapy (PRRT). Chemotherapy: 1/19 pts partial response, 2/19 stable disease (SD), 12/19 progressive disease (PD) (median time to progression four months (m)); 4/19 no data. PRRT: 4/10 had SD, 4/10 PD (median time to progression 4 m, range 2–9); 2/10 no data. SST: two sustained SD (range 12–27 m), 7/10 PD, (median time to progression 3 m, range 2–5); 1/10 no data. During median follow-up of 20 m (range 3–170), 100% of pts with primary tumor <1 cm, 86% with size >2 cm have poorer outcome than the other two groups (p < 0.001). Conclusion: Tumors >2 cm are associated with poor prognosis. Chromogranin A is mostly normal even in advanced disease. Prospective studies are needed to determine progression-free survival data. Keywords: rectal nets.

F9

Clinical Characteristics of 144 Patients (pts) Included in a Multidisciplinary Group, with Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs) G2 (WHO 2010). Grupo Argentum

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Introduction: Neuroendocrine tumors (NETs) G2 of the digestive tract are a heterogeneous group of tumors. Several treatment options including chemotherapy and target therapy are used, but there is a lack of prospective trials assessing the role of predictive factors in this population. Aim(s): To analyze prognostic factors and clinical characteristics in a population of patients with GEP-NETs G2. To determine the role of Ki-67 in the stratification of the G2 population. Materials and Methods: Study population was obtained from our database (Argentum Group). Survival was estimated using the Kaplan-Meier method and compared between Ki-67 quartiles using the log-rank test. Value of Ki-67 to discriminate mortality was assessed with an ROC curve analysis. Results: Of 144 pts, mean age 54.9 (± 14.7), 46.7% male. One-hundred and two (70.8%) pts with metastatic disease, mainly hepatic in 97 pts (67.4%), 67.9% underwent surgery. Thirty-four per cent received chemotherapy, and 10.9% target therapy. Median Ki-67 was 6 (IQR 4–10), ROC curve = 0.62 (95% CI 0.53 a 0.72 p = 0.021. cut-off: 6.5 (sensitivity 62.2%, specificity 57.7%). Median survival was 97, 67, 51 and 27 months, according to stratification by quartile (p<0.001). Forty-five pts have died (31%). Conclusion: Our results suggest that among GEP-NET G2 tumors, there is a heterogeneous group of neoplasms with significant differences in survival. Despite current recommendations, chemotherapy was used with increasing frequency through Ki-67 quartiles. Our study was underpowered to detect differences between Ki-67 quartiles. Keywords: neuroendocrine tumor, g2, survival.

F10

Usefulness of the WHO Classification and of the ENETS TNM Staging System to Predict Prognosis in Patients with Rectal NENs

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Introduction: WHO classification and TNM staging system have been proposed for rectal neuroendocrine neoplasia (NENs). However, their prognostic accuracy is not validated yet. Aim(s): Assess the ability of WHO classification/ENETS TNM staging system to predict survival of patients with rectal NENs. Materials and Methods: Retrospective analysis of patients with rectal NENs referred to the Beaujon Hospital (Clichy, France) and the S. Andrea Hospital (Rome, Italy) from 1990 to 2013. Results: One-hundred and nine (62 male) consecutive patients (pts) were evaluated (median age 56 yr, IQR 45–64). Median tumor size was 6 mm (IQR 4–12). Forty-four per cent of pts were treated endoscopically, whereas 25% of pts underwent surgical treatment. Ki-67 value was available in 71 pts (65%). According to the WHO classification, 62% of pts had NET G1, whereas 20% had NET G2, and the remaining 18% had G3 NEC. Stage was available in 98 pts (90%): 74% of pts had local disease (stage I-IIa), whereas 26% had advanced disease (stage III-IV). Follow-up data were available in 57% of pts. During a median period
of 17 months (IQR 7–35.5), 12.9% of pts died (all these pts had stage IV G2/G3 tumors). Overall, 5-yr survival rate was 77.4% (100% in NET G1, 43.9% in NET G2/NEC G3). Ki-67 >2% and advanced stage at diagnosis were associated with worse survival probability (p = 0.004 and p = 0.0002, respectively). **Conclusion:** These results show that, even in the setting of rectal NENs, WHO classification and ENETS TNM staging system are able to predict patients’ survival.  
**Keywords:** rectal nens, survival, prognosis.

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**F11**  
The Second Non-Metastatic Tumor in Romanian Patients with NETs  
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**Introduction:** NETs involve aggressive evolution as progression of primary tumor. Some cases associate a second apparently non-related tumor. **Aim(s):** We evaluate the tumor profile in NET patients.  
**Materials and Methods:** Retrospective study in NET patients (Parhon National Institute of Endocrinology, Bucharest, Romania). Inclusion criteria: confirmed diagnosis of NETs, adult age at diagnosis. Exclusion criteria: medullar thyroid cancer. The database and statistics used Excel. **Results:** Thirty patients; studied group with a non-NET tumor+NETs (n = 8, M/F ratio = 1); control group with NETs only (n = 22, M/F ratio = 0.5). Age at diagnosis: 57.5 ± 56.86 yrs (p = NS), G1/2/3 percents: 50%/25%/25% vs. 36.36%/31.81%/31.81%. The origin of the NETs varied in group 1 and it was mostly in the pancreas, lung and unknown in control group. Somatostatin analogs were not used in 25% v. 40.9% of patients. The serum serotonin at diagnosis was: 250.86 v. 366.14 ng/ml (p = 0.3), and chromogranin A: 531.61 v. 517.85 ng/ml (p = 0.5). Genetic syndromes were identified only in two cases of non-NET group: VHL and NF-1. The non-NET tumors had various locations, such as pituitary: a growth hormone producing and a non-functional adenoma; adrenal: phaeochromocytoma. **Conclusion:** The phenotype in NETs might be complicated with a second endocrine (malign or not) tumor: this may be caused by a common genetic background, or this may be incidental in patients who already have consistent serial imagery scan follow-up.  
**Keywords:** neuroendocrine, tumor, chromogranin A.

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**F12**  
From E.L.I.O.S. (Educational Learning Investigational Observational Study) an Initial Update on Neuroendocrine Tumors (NETs) in the Southern Italy  
Tafuto S.\(^a\), Faggiano A.\(^b\), Riccardi N.\(^c\), Palmieri G.\(^b\), Tatangelo F.\(^a\), Tozzi L.\(^d\), Nappi O.\(^e\), De Divitiis C.\(^f\), Mocerino C.\(^g\), Leo S.\(^h\), Battista C.\(^i\), Colao A.M.\(^j\)  
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**Introduction:** Elio is an Educational Learning Investigational Observational Study. **Aim(s):** To develop epidemiological studies and clinical trials on NET, involving five centers of Southern Italy: Federico II University of Naples, NCI of Naples, AORN Cardarelli, Naples; Casa Sollievo Hospital, S G Rotondo; Lecce City Hospital.  
**Materials and Methods:** This is an observational Italian multicenter study: data have been collected through an e-CRF and stored and processed in a centralized computer database. Both retrospective data from 2005 and prospective data from March 2012 to November 2012 were included. **Results:** At now, 548 patients with gastrointestinal/pulmonary/thoracic or soft tissue NETs have been recruited and at least 429 were evaluable. Median age was 59.9 yrs (range, 18–86 yrs), gender ratio was balanced. At diagnosis, 9% of cases had functional NETs mainly with diarrhea (40%), flushing (26%), hypertension (21%) and abdominal pain (40%). NET were located in GEP trait (49%), lung (24%), skin and soft tissues (5%), thyroid (4%) and genitourinary system (4%). Forty-one pts have an unknown primary tumor. Tumor grading was as follows: G1 81 (23%) G2 122 (35%) and G3 145 (41%) pts. The initial therapeutic approach was surgery and somatostatin analogues; loco-regional therapies and chemotherapy in metastatic and progressive diseases. **Conclusion:** ELIOS study is becoming a promising reference in the assessment of data related to epidemiological and clinical aspects of NET in Southern Italy. **Keywords:** neuroendocrine tumor, epidemiology, ssa.

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**F13**  
E.L.I.O.S. (Educational Learning Investigational Observational Study): An Initial Update on Neuroendocrine Tumors (NETs) in the Southern Italy  
Tafuto S.\(^a\), Faggiano A.\(^b\), Riccardi N.\(^c\), Palmieri G.\(^b\), Tatangelo F.\(^a\), Tozzi L.\(^d\), Nappi O.\(^e\), De Divitiis C.\(^f\), Mocerino C.\(^g\), Leo S.\(^h\), Battista C.\(^i\), Colao A.M.\(^j\)  
\(^a\)National Cancer Institute, Naples, Italy; \(^b\)Federico II University, Naples, Italy; \(^c\)Aorn Cardarelli, Naples, Italy; \(^d\)Casa Sollievo Hospital, S G Rotondo, Italy; \(^e\)Second University, Naples, Italy; \(^f\)City Hospital, Lecce, Italy

**Introduction:** Elio is an Educational Learning Investigational Observational Study. **Aim(s):** To develop epidemiological studies and clinical trials on NET, involving five centers of Southern Italy: Federico II University of Naples, NCI of Naples, AORN Cardarelli, Naples; Casa Sollievo Hospital, S G Rotondo; Lecce City Hospital.  
**Materials and Methods:** This is an observational Italian multicenter study: data have been collected through an e-CRF and stored and processed in a centralized computer database. Both retrospective data from 2005 and prospective data from March 2012 to November 2012 were included. **Results:** At now, 548 patients with gastrointestinal/pulmonary/thoracic or soft tissue NETs have been recruited and at least 429 were evaluable. Median age was 59.9 yrs (range, 18–86 yrs), gender ratio was balanced. At diagnosis, 9% of cases had functional NETs mainly with diarrhea (40%), flushing (26%), hypertension (21%) and abdominal pain (40%). NET were located in GEP trait (49%), lung (24%), skin and soft tissues (5%), thyroid (4%) and genitourinary system (4%). Forty-one pts have an unknown primary tumor. Tumor grading was as follows: G1 81 (23%) G2 122 (35%) and G3 145 (41%) pts. The initial therapeutic approach was surgery and somatostatin analogues; loco-regional therapies and chemotherapy in metastatic and progressive diseases. **Conclusion:** ELIOS study is becoming a promising reference in the assessment of data related to epidemiological and clinical aspects of NET in Southern Italy. **Keywords:** neuroendocrine tumor, epidemiology, ssa.
Clinically Detected Gastroenteropancreatic Neuroendocrine Tumors are on the Rise: Epidemiological Changes in Germany

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Introduction: Aim(s): To study the epidemiological changes of GEP-NET in Germany, we analyzed two time periods: 1976–1988 and 1998–2006. Materials and Methods: We evaluated epidemiological data of GEP-NET from the former East German National Cancer Registry (1976–1988) and the Joint Cancer Registry (1998–2006). More than 10.8 million people were analyzed. Survival probabilities were calculated using life table analysis. In addition, GEP-NET patients were evaluated for one or more second primary malignancies. Results: A total of 2,821 GEP-NET were identified in the two registries. The overall incidence increased significantly between 1976 and 2006 from 0.31/100,000/year to 2.27 for men and from 0.57 to 2.38 for women. In the later period studied (2004–2006), the most common site. Neuroendocrine (NE) neoplasms of the small intestine showed the largest absolute increase in incidence, while rectal NE neoplasms exhibited the greatest relative increase. Only the incidence of appendiceal NET in women showed little change between 1976 and 2006. Overall survival of patients varied for sex, tumor site and the two periods studied but improved significantly over time. Interestingly, about 20% of the GEP-NET patients developed one or more second malignancies. Conclusion: GEP-NET increased about five-fold in Germany between 1976 and 2006. Their anatomical distribution changed, and the survival of GEP-NET patients improved significantly. Second malignancies are common and influence the overall survival of GEP-NET patients. Keywords: gep-net, germany.

Pathology, Grading, Staging

G1

Prognostic Value of Histopathological Features of Pancreatic Neuroendocrine Tumors


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Introduction: Pancreatic neuroendocrine tumors (NETs) are rare neoplasms. NETs are clinically diverse and can be divided into functioning and non-functioning tumors. Aim(s): To assess the clinical relevance about histopathological characteristics related to disease-free survival and total survival. Materials and Methods: Data from 26 consecutive NET patients who received surgical intervention in our center between 2009 and 2013 were collected and analyzed. Dates about overall histopathological and survival were analyzed. Results: The study cohort comprised 26 patients with NETs (six functioning tumors and 21 non-functioning tumors). Medium age was 59 years. In the multivariate analysis the absence of necrosis, perineural, vascular and lymphatic invasion, as well as the high degree of differentiation, was related to increased disease-free survival (p < 0.001). About prognostic factors, vascular and lymphatic invasion are linked to increased total survival. The presence of metastasis was related to tumor size and tumor grade. A statistically significant difference was observed between Ki-67 in total survival but not disease-free survival. Conclusion: Histopathological characteristics on NET should be considered for prognostic stratification. Keywords: pancreatic neuroendocrine tumor, survival, prognostic factors.
Pancreatic Neuroendocrine Tumors (PNETs): Role of Endoscopic Ultrasound-Fine Needle Aspiration (EUS-FNA) and Accuracy of Ki-67 Measurement on Cytological Specimens
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Introduction: The role of EUS-FNA in preoperative diagnosis and grading of pNETs is well-established, but it is unclear how Ki-67 expression on cytological specimens obtained by EUS-FNA reflects the value found on surgical specimens. Aim(s): To report our experience, to describe the feasibility of measurement of Ki-67 on cytological samples, to evaluate its accuracy if compared with the Ki-67 measurement on surgical specimens. Materials and Methods: Retrospective analysis of all cases of pNETs diagnosed by means of EUS-FNA from August 2003. Cytological Ki-67 expression was compared with definitive surgical Ki-67 results. Results: Seventy-four pts (range 22–84 years). Ki-67 immunostaining performed on all high cellularity EUS-FNA samples (66/74, 89%). Surgery in four pts (range 22–84 years). Ki-67 immunostaining performed on 11th Annual ENETS Conference surgical specimens. Conclusion: EUS-FNA is a valuable and safe method in the detection and diagnosis of pNETs. Ki-67 measurement is easy to be assessed on high-cellularity specimens. Overall agreement rate was ‘moderate’ (Landis e Koch, 1977), while is ‘substantial’ when assuming high cut-off value (20%), which is the most important cut-off that can really affect clinical decisions in the management of pNETs. Reproducibility was in all cases ‘good’ (Fleiss, 1981). Keywords: pancreatic net, endosonography, grading.

Expression Patterns of Cellular Retinoic Acid Binding Protein-I in Neuroendocrine Tumors of the Lung: A Pilot Immunohistochemical Study
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Introduction: Cellular retinoic acid binding protein-I (CRABP-I), a member of the lipid-binding proteins family, plays an important role in retinoic acid-mediated cell proliferation and is essential for the development of various malignant neoplasms. The actual role of CRABP-I in tumor progression remains unknown. Aim(s): To investigate the expression patterns of CRABP-I in the different subtypes of the lung neuroendocrine tumors (NETs). Materials and Methods: CRABP-I expression was evaluated by immunohistochemistry in 57 histopathologically confirmed lung NETs, including 25 typical carcinoids, nine atypical carcinoids, 18 small cell lung carcinomas (SCLCs), five large cell neuroendocrine carcinomas (LCNECs). Results: All cases of lung NETs showed CRABP-I immunoreactivity, with both cytoplasmic and nuclear staining patterns identified. Cytoplasmic staining with heterogeneous intensity was more frequent in typical carcinoids. Twenty-one (72.4%) of 25 typical carcinoids showed no nuclear positivity. In contrast, nuclear CRABP-I staining was present in six (66.7%) of nine atypical carcinoids, with two cases having rare scattered positive tumor cells and four – more than 10% of cells. All 18 SCLCs demonstrated moderate to strong nuclear staining with 10 cases having more than 50% of positive tumor cells. However, CRABP-I nuclear accumulation was not found in LCNECs. Conclusion: The observed findings support the association of CRABP-I nuclear expression with the higher malignancy potential of lung NETs. Keywords: neuroendocrine tumor, lung, immunohistochemistry.

Grading of Metastases in Digestive Neuroendocrine Tumors (NET): Interest for Clinical Management?
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Introduction: Therapeutic strategy of NETs is highly dependent on tumor classification according to the WHO system. NETs are frequently classified based on the histological characteristics of the primary tumor associated with the ENETS grading, even for patients with metastases. Aim(s): To compare the tumor grade between primary NETs and their liver metastases which may exhibit differential proliferative characteristics. Materials and Methods: The cohort harvested seven patients with pancreatic NET and 18 patients with intestinal NET, without genetic syndrome and treated at our institution (13 males, median age 58 years, range 14–79 years). All presented synchronous (19 patients) or metachronous liver metastases. According to the WHO classification, tumor grading was evaluated for primary and metastatic NETs on the Ki-67 and mitotic count and classified as grade G1, G2 or G3. Results: Forty per cent and 60% of primary lesions were grade 1 and 2 respectively while 20%, 72% and 8% of the metastatic lesions were grade 1, 2 and 3. Out of 10 patients who had a Ki-67 >2 in the primary lesion, eight had a Ki-67 >2% (range 3–36%) with 4 Ki-67 ≥10% in the metastatic lesion (p = 0.11). From the 22 patients who had a MI <2 in the primary lesion, 10 had an MI ≥2 (range 3–36) in the metastasis. The mitotic index was higher in the metastatic lesions compared to the primary NET. Conclusion: This difference in tumor grading between the primary and the metastatic NETs could have a strong impact in the therapeutic management of patients. Keywords: net, grading.
G5
Outcome Predictors of Gastrinomas: The Role of ENETS Staging, Grading and Interdisciplinary Treatment

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Introduction: Gastrinomas are rare neuroendocrine neoplasias (NEN) presenting with Zollinger-Ellison-syndrome (ZES). Aim(s): The natural course, outcome of treatments and overall prognosis were analyzed. Materials and Methods: Data of 36 patients were studied by chi-square-, log-rank test and Kaplan Meyer analysis (statistical significance) with SPSS 19.0. Results: Thirty cases of histologically proven gastrinoma (20 males) and six cases of clinically and biochemically diagnosed ZES (five males) were found either in the pancreas (n = 15), duodenum (11), jejunum (two) or had a CuP-syndrome (eight). Mean age at initial diagnosis was 50.1 years (36.5 years in six MEN-1 cases); mean follow-up was 10.6 years (1–29 years). Median primary tumor size was 12 mm (1–150 mm). Median Ki-67-index was 5% (1–60%) and resulted in 13 G1, 10 G2 and two G3-NEN with a significantly better overall prognosis in G1 than G2 gastrinomas (p = 0.018). Early stage gastrinomas (stage I: 5, II: 3, III: 9) had a significantly better prognosis than advanced NEN (IV: 11; p = 0.046). Curative surgical resection resulted in 100% 5– and 10-year survival rates (YSR) as compared to no surgery 70 and 11; p = 0.046. Curative surgical resection was the strongest pronostic factors for outcome. PS (PS 0/1 vs PS 2/3) HR, 3.291; 95% CI, 0.92–11.72; P = 0.066. Previous surgery was also a significant factor (p = 0.020) but more cases are required in order to reach a significant HR. Conclusion: We have developed a stratification tool which requires further validation in a prospective cohort. Supported by Ipsen. The Knowledge Network is a continuous program of education focused on GEP-NETs. Keywords: classification system, pnets, neuroendocrine tumors.

G6
Determination of a Prognostic Classification System in Metastatic Grade 1 and 2 Pancreatic Neuroendocrine Tumors (PNETs)

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Introduction: There is no clinical prognostic risk stratification tool available for metastatic grade 1 and 2 PNETs, which are a heterogeneous group. Aim(s): This is of particular importance as there are a number of systemic therapies available for these patients. Materials and Methods: A retrospective case analysis was performed on 139 cases from seven NET centres based throughout Europe and South America. Eleven clinical and six laboratory data were collected and multivariate regression analysis was performed to identify a panel of prognostic markers. Inclusion criteria were grade 1 and 2 (based on Ki-67) pancreatic NETs, metastatic disease, and diagnosis at least five years ago. Familial syndromes were excluded. Results: Univariate analysis identified grade, performance status (PS), extent of metastases, CgA, bilirubin, LDH, haemoglobin and previous surgery as significant prognostic factors. These were analysed in a multivariate analysis. PS and extent of metastases were the strongest prognostic factors for outcome. PS (PS 0/1 vs PS 2/3) HR, 5.229; 95% CI 2.44–11.20; P = 0.023 and extent of metastases (unilobar v. bilobar liver mets) HR, 3.291; 95% CI, 0.92–11.72; P = 0.066. Previous surgery was also a significant factor (p = 0.020) but more cases are required in order to reach a significant HR. Conclusion: We have developed a stratification tool which requires further validation in a prospective cohort. Supported by Ipsen. The Knowledge Network is a continuous program of education focused on GEP-NETs. Keywords: classification system, pnets, neuroendocrine tumors.

G7
Grade Increases In Gastroenteropancreatic Neuroendocrine Tumor Metastases Compared to the Primary Tumor

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Introduction: The neuroendocrine tumor (NET) proliferation-based grading system (ENETS/WHO) has proved reliable for prognostic stratification of gastroenteropancreatic tumors (GEP). Although
anecdotes have been published, no single study has evaluated whether grade changes between primary site and metastases.

**Aim(s):** The aim was therefore to evaluate grade changes between primary tumor and metastases.

**Materials and Methods:** A total of 256 GEP-NETs (1993–2011) were identified from histopathology archives; 45 had tissue from the primary tumor and from local/distant metastases (28 synchronous; 8 metachronous). Grade was assigned on both primary and metastatic tumors and evaluated both as mitotic index and as proliferation index (by counting Ki-67 positive cells in 2000 neoplastic cells).

**Results:** Out of 28 patients with primary NET and synchronous; 8 metachronous). Grade was assigned on both primary and metastases (nodal, hepatic and mesenteric) while one changed from G2 to G3 in the nodal metastasis. Eight patients underwent surgical excision of metachronous metastases during follow-up (at least six months from initial surgery). Four (50% – two nodal; two hepatic) patients showed an increase in Ki-67 index in the metastatic site and a change in grade, from G1 to G2.

**Conclusion:** Primary NETs and their metastases may show differences in grade, in particular at metachronous sites, and this may prove to be important in patient management. **Keywords:** neuroendocrine, grade, ki-67.

**G8**

**Does Biopsy Reliably Identify Grade In Gastroenteropancreatic Neuroendocrine Tumors?**

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**Introduction:** A new proliferation-based grading system has proved important in establishing prognosis and guiding therapy in gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Biopsies are often performed for grading but little is known about their reliability in assigning grade.

**Aim(s):** To determine the accuracy of grade identification in virtual biopsies (VBs) of GEP-NETs.

**Materials and Methods:** Twenty cases of resected G1 (11) or G2 (9) GEP-NETs were selected and grade assigned on the whole section (WS) by mitotic index and Ki-67-index. VBs (total 411) were constructed by leaving different, randomly selected and progressively smaller (30–0.25 mm sqd) areas of the WS unmasked. Number of neoplastic cells, Ki-67 index and grade were quantified in each VB and compared with Ki-67 and grade assessed on the WS.

**Results:** In G1 cases nearly all 218 VBs of all sizes correctly identified grade; in one case an ultra-small VB over-graded the case as G2. Out of 193 G2-lesion VBs, 58% under-graded these lesions as G1. In each (except one) case, G2 case at least one of the VBs performed under-graded the lesion. G1 and G2 predictive values and overall concordance between VB and WS decrease with decreasing area and with WS Ki-67-heterogeneity.

**Conclusion:** Clinicians must be aware that grade identified on biopsy material can under-grade G2 cases (likely due to small biopsy size or intratumor heterogeneity). This may prove important in the clinical management of patients as choice of therapy depends ever more so on grade. **Keywords:** neuroendocrine, grade, biopsy.
ate the comparability of an automated and conventionally histopathologically examined SSTR expression. **Materials and Methods:** We examined 25 NET-patients and correlated their in vivo SSTR-PET/CT data (SUVmax, SUVmean) with the corresponding ex vivo-immunohistochemical (IHC) data of SSTR (1, 2A, 4, 5) expression. Exactly the same lesions were imaged by PET/CT, resected and analyzed by IHC in each patient. The IHC slides were then digitized and automatically evaluated for SSTR expression by Definiens Tissue Studio software. A virtual IHC score ‘BB1’ was created for comparing the manual and automated analysis of SSTR expression. **Results:** The virtual score BB1 showed a significant correlation with the corresponding, conventionally determined Her2/neu score of the SSTR-subtypes 2A (C: 0.57; p = 0.005), SSTR 4 (C: 0.44; p = 0.028) and 5 (C: 0.43; p = 0.044). BB1 of SSTR2A was also significantly correlated with the SUVmax (C: 0.41; p = 0.049) and the SUVmean (C: 0.62; p < 0.001). **Conclusion:** The evaluation of the SSTR status by automatic SSTR analysis using digitized slides corresponds well with the SSTR expression as determined by conventional histopathology. The BB1 score exhibited a significant association to the SSTR-PET/CT data in concordance to the high affinity profile of the SSTR analogues used for imaging. **Keywords:** sstr.

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**G11**

Ileal Neuroendocrine Well-Differentiated Tumors: Prognostic factors with Focus on Loss of Succinate Dehydrogenase (SDHB) Expression

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**Introduction:** Ileal Neuroendocrine Well-Differentiated Tumors (INWDT) are the most common neuroendocrine neoplasms in the gastrointestinal tract. Gene mutations of SDH complex drive pathogenesis of cancer cells through their role in angiogenesis and cell proliferation. **Aim(s):** To investigate the expression of SDHB levels in INWDT as a prognostic marker. **Materials and Methods:** One hundred patients with G1-G2 stage IV INWDT were selected. 76/100 patients had surgery on the primary tumor (T). We studied those patients through 138 samples. Mitotic index (M1), immunohistochemistry for SDHB and Ki-67 were carried out in 76 T and 62 liver metastases (M). SDHB was assessed according to the staining intensity, scored 1 (low) or 2 (high) on the basis of the internal control represented by normal cell. **Results:** High (2+) positivity for SDHB was found in 93.5% T, while loss of SDHB expression (1-) was detected in 97.3% M. These findings were inversely proportional, both to Ki-67 distribution and to M: Ki-67 was 1.7% in M and 0.6% in T, respectively, and M1 was between 0–1 mitosis in T and between 2–3 mitosis in M, respectively. The intensity of SDHB staining in tumor cells is related to the site of tumors and Ki-67 labeling index, as T bearing Ki-67 ≤1.3%, showed over 75% immunoreactive tumor cells. Likewise, significant associations were found among the site of tumors (p < 0.0001) or Ki-67 labeling index (p < 0.0001) and SDHB intensity. **Conclusion:** We showed the correlation between SDHB expression loss, Ki-67 increase and biological aggressiveness of INWDT. **Keywords:** ileum, neuroendocrine, sdhb, ki-67, mitosis.

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**G12**

Ewing Sarcoma a Dangerous Pitfall for Poorly Differentiated Neuroendocrine Carcinoma (PDEC) in Ileum

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**Introduction:** Ewing sarcoma (ES) primary to the ileum (IES) has rarely been documented, and shows close similarities in histology and clinical presentation with PDEC. EWSR1-FLI1 translocation is exceedingly rare in ES, as FEV expression is restricted to prostate, brain, and serotonin neuroendocrine cells (NE) and related tumors. **Aim(s):** Little is known about the pathogenesis and clinical implications of IES, which may be critical to identifying novel molecular markers. **Materials and Methods:** Among 445 ES cases, spanning a period of 20 years, seven (1.6%) were IES. Seven IES were investigated through immunohistochemistry, RT-PCR (EWSR1-FLI1,EWSR1-ERG and EWSR1-FEV transcripts), FISH analysis (EWSR1 break-apart and specific EWSR1-FEV translocation) and spectral karyotyping (SKY). Ten ileum neuroendocrine tumors (INET) made up the control group for EWSR1-FEV translocation. **Results:** Seven IES were immunoreactive for synaptophysin, CD99, FL1 and vimentin, FISH identified EWSR1 rearrangement in all cases, with EWSR1-FLI1 transcripts being detected in all but one tumor, which showed instead the uncommon EWSR1-FEV rearrangement upon SKY, RT-PCR and FISH confirmation. The mean survival of EWSR1-FLI1 patients was 14 months, whereas the EWSR1-FEV patient was alive after 15 years despite several recurrences successfully controlled by surgery alone. No INET showed EWSR1 translocation. **Conclusion:** Most IES share the common EWSR1-FLI1 translocation, but EWSR1-FEV rearrangement could be specific for tumors arising in the ileum and showing better prognosis. **Keywords:** ileum, neuroendocrine, ewing sarcoma, ewsr1.
G13

Heterogeneity in the Ki-67 Index of Neuroendocrine Tumors

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Introduction: Tumor heterogeneity due to tumor evolution is becoming more widely recognised. Neuroendocrine tumors (NET) are routinely graded using the Ki-67 index based on a single tumor location, however, this could lead to undergrading if the Ki-67 index is higher at the metastatic site. Aim(s): Assess the extent of Ki-67 index heterogeneity in NET. Materials and Methods: Ki-67 index was assessed in 31 NET patients, and determined in all lesions with available tissue. Immunohistochemical staining was done and the Ki-67 index determined according to standard criteria. In 23 patients, tissue was available from the primary and metastatic lesions and in two patients from multiple pancreatic lesions. Sections were taken at five points spaced evenly across metastasis from six explant livers from NET patients. Results: There was a change in Ki-67 between the different sites assessed in 19 (61.3%) of the 31 cases, median age was 57 (range: 35–81). Eleven cases had an increase in Ki-67, moving from G1 to G2 when the primary and metastasis were assessed and the two multiple pancreatic lesions cases shifted from G1 to G2, however, only one patient shifted from G2 to G3. Four out of six explant livers had a different grade, G1/G2 depending on the region of the metastasis assessed and 5/6 were G1 in the primary compared to G2 in the metastasis. Conclusion: Heterogeneity in Ki-67 index between primary and metastasis and within liver metastases is an important factor to consider in G1 NET since a single biopsy may not be representative of the true grade. Keywords: tumor heterogeneity, Ki-67.

G14

Prognostic Validity of the WHO 2010 TNM Staging and Grading Criteria for Pancreatic Neuroendocrine Tumors

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Introduction: The TNM staging and grading system developed by the WHO was designed to help prognosticate patients. Aim(s): To retrospectively stage and grade PNET patients and investigate whether the WHO system offers prognostic relevance. Materials and Methods: One-hundred and three patients with PNETs treated since 2004 were included in this study. Mean age at diagnosis was 57. Median duration of follow-up: 50.3 months. Results: Kaplan-Meier survival analysis demonstrated significant median survival differences between all grades: G1 (n/a), G2 (109 months), G3 (37 months). Analysis also demonstrated significant survival differences between stage IV and all other stages: 5-year survival stage I = 100%, II = 81%, III = 89%, IV = 54%. The proportion of incidental PNET diagnoses was highest for stage II disease (60%); however, early detection was not associated with improved survival. This insignificant difference in survival between stages II and III may be due to aggressive surgical treatment of stage IIIB patients. Overall median survival of PNET patients was 109 months with a 5-year survival of 78%, compared to historical reports of 27% (SEER). Primary resection was associated with improved 5-year survival compared to patients who declined resection (94% v. 41%). Conclusion: This patient series confirms that Ki-67 thresholds used in the current grading system offer prognostic relevance and may not need to be changed. Stage III survival is higher than reported elsewhere, which may be due to an aggressive surgical approach. Keywords: neuroendocrine, pancreas, Ki-67, grade.
G15

Mixed Adenoneuroendocrine Carcinoma (MANECs): A Rare and Challenging Subgroup of Neuroendocrine Neoplasia
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Introduction: Mixed Adenoneuroendocrine Carcinomas (MANECs) are rare entities in which at least 30% of neoplastic cells are neuroendocrine in nature (WHO 2010 classification). They result either from two independent lesions that merge together or are unique lesions with different cell populations intermingled. Aim(s): To elucidate the clinical and histopathological characteristics of MANECs and to compare them to classic Neuroendocrine Neoplasias (NEN).

Materials and Methods: Patients with NEN treated at two tertiary institutions were included in this analysis. A prospectively maintained database for NEN was searched for MANEC. The MANEC diagnosis was confirmed by conventional histopathology on surgical specimen. Ki-67 analysis was done on paraffin-embedded sections using immunohistochemistry. Grading was according to ENETS recommendations.

Results: We identified 17 MANECs (primary tumor: eight lung, three appendix, three stomach, two colon, and one pancreas), M:F (8:9), age 45–83 years (mean: 68). All bar one were resected according to oncological criteria for adenocarcinoma. Assessment of Ki-67% (40–95%, mean: 76%) identified the neuroendocrine components as high grade (G3), poorly differentiated Neuroendocrine Carcinoma. Conclusion: MANECs occur in the lung and in the enteropancreatic system with their clinical course being in line with the most aggressive component of the tumor. Patients should be treated according to recommendations for adenocarcinoma or NEC.

Keywords: mixed adenoneuroendocrine carcinoma, manec, neuroendocrine tumors.

G16

Comparison of Manual and Automatic Methods of Ki-67 Proliferation Index for Neuroendocrine Tumors: The Development and Validation of a Novel Digital Pathology Tool (Ki-67Counter)
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Introduction: Ki-67 proliferation index is an increasingly important biomarker used to grade neuroendocrine tumors. Manual counting methods are laborious and subject to inter- and intra-observer variability. Digital counting methods hold promise for fast and reproducible indices, however, they are fraught with technical difficulties. Aim(s): To develop an automated tool, Ki-67Counter, to improve the speed, reproducibility, and accuracy of automatic Ki-67 counting.

Materials and Methods: We have created digital Ki-67 slides of 46 biopsy and/or resections of pancreatic and gastrointestinal neuroendocrine tumors from the University of Kentucky. Results: The automated counting results are compared with both pathologists’ manual results and a commercially available image analysis platform. We found that both digital methods were able to count much faster than the manual methods (Aperio average 6.4 minutes, Ki-67Counter average 1.5 minutes, compared to manual average 21.6 minutes). Consistent with the literature, we also noted that the Aperio’s results were consistently higher than the manual counting results, due to inclusion of non-tumor cells (particularly lymphoid infiltrates) despite reasonable efforts to exclude these populations.

Conclusion: Ki-67Counter is superior to the Aperio in both analysis speed (1.5 minutes v. 6.4 minutes) and accuracy (three times more accurate than Aperio) due to Ki-67Counter’s excellent performance in differentiating tumor/non-tumor cells. Keywords: digital pathology, automated ki-67 counting, image analysis.

G17

Well-Differentiated Pancreatic Neuroendocrine Tumors: Prognostic Significance of Pathological Parameters
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Introduction: Well-differentiated (WD) pancreatic neuroendocrine tumors (pNET) are uncommon neoplasms and one challenge lies in predicting tumor behavior and managing these patients. Aim(s): To evaluate contemporary outcomes associated with the surgical management of WD pNET and to assess the prognostic and biological behavior differences between the 2 grades of WD pNET.

Materials and Methods: Patients with pancreatic neuroendocrine neoplasms in the last 15 years were retrospectively analysed. Histopathological findings and actual status of patients with grade 1(G1) and 2(G2) WD pNET were collected. Results: Forty-eight patients were classified as WD pNET: 16 as G1 and 32 as G2. G1 patients: mean tumor size 1.6cm. Two had vascular and/or neural invasion (12.5%), none was staged T3/T4, none had nodal metastasis and only one was M1. None showed local or distant recurrence and are actually disease-free. G2 patients: mean tumor size 4.1 cm. Seventeen had vascular and/or neural invasion (53%), 14 were staged T3/T4 (43%), 12 were N1 (37.5%), 10 M1 at diagnosis and two showed distant metastasis after two. Two showed local recurrence, two had metastasis recurrence and two died because of the pNET. Conclusion: Although G2 pNET are considered well-differentiated neoplasm and not labelled as carcinomas, they show aggressive behavior and a worse prognosis. G1 pNET are usually less than 2 cm and don’t show aggressive behavior. Preoperative samples are important and determine if a surgical approach is the best therapeutic option. Keywords: pancreas, well-differentiated g2.
**Introduction:** Lung neuroendocrine tumors are catalogued into four categories by the World Health Organization (WHO 2004) classification. Its reproducibility and prognostic efficacy was disputed. The WHO 2010 classification of digestive neuroendocrine neoplasms is based on a Ki-67 index and has proved prognostically effective. The WHO 2010 classification of digestive neuroendocrine neoplasms is based on a Ki-67 index and has proved prognostically effective. The WHO 2004 stratified patients into four categories by the World Health Organization (WHO 2004) classification. Its reproducibility and prognostic efficacy was disputed. The WHO 2010 classification of digestive neuroendocrine neoplasms is based on a Ki-67 index and has proved prognostically effective.

**Aim(s):** To compare the two classifications and to define a new prognostic grading system for lung. Materials and Methods: Three-hundred and ninety-nine patients who underwent surgery and with at least one year follow-up between 1989–2011. Twenty-one variables were collected and performance of grading systems and their components compared by Cox regression and multivariable analyses; all tests were two-sided. Results: WHO 2004 stratified patients into three major groups with statistically significant survival differences (typical v. atypical carcinoids, p = 0.021; atypical carcinoids v. large cell/small-cell lung neuroendocrine carcinomas, p < 0.001). Optimal discrimination in three groups was observed by Ki-67% (Ki-67% cut-offs G1 <4, G2 4–<25; G3 ≥25; G1 v. G2 p = 0.021 and G2 v. G3 p ≤0.001), mitotic count (G1 ≤2, G2 >2–47, G3 >47; G1 vs G2 p ≤0.001 and G2 vs G3 p ≤0.001) and presence of necrosis (G1 absent; G2 <10% of sample; G3 >10% of sample; G1 v. G2 p ≤0.001 and G2 v. G3 p ≤0.001) at uni and multivariable analysis. The combination of these three variables resulted in a simple and effective grading system. Conclusion: A three tier grading system with Ki-67, mitotic count and necrosis with specific cut-offs is prognostically accurate. Keywords: lung, neuroendocrine cancer, ki-67, grading.
reached. The survival analysis for PTEN showed better DFS for high PTEN expression pts (p = 0.001, median not reached) but not for OS (p = 0.089). Cox regression analysis showed LOXL2 as an independent prognostic factor for OS (p = 0.008) and PTEN for DFS (p = 0.013). No association between LOXL2 and PTEN expression was found. Conclusion: LOXL2 is a new biomarker candidate for GEP-NET. Keywords: loxl2, gep-net.

H2
Urinary 5-Hydroxyindoleacetic Acid In Serotonin-Producing Neuroendocrine Tumors: Correlation with Disease Features and Patients’ Survival
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Introduction: Urinary 5-hydroxyindoleacetic acid (U-5HIAA) is a useful marker for serotonin-producing neuroendocrine tumors (NETs). Its prognostic role, however, is yet to be fully elucidated. Aim(s): To evaluate U-5HIAA’s role as a prognostic marker and its relation to disease features. Materials and Methods: Two-hundred and seven patients were included. Rates of flushing and bowel movements, chromogranin-A (CgA) levels and radiological data, were recorded. Patients were grouped, based on 5HIAA levels (Group 1: ≤1x upper limit of normal (ULN), 2: 1-5x ULN, 3: 5-10x ULN, 4: >10xULN). Results: Increased U-5HIAA, at diagnosis, is associated with poorer survival in midgut NETs (mNETs). Five-year survival for Group 1 was 83%, 2 = 75%, 3 = 73%, 4= 50%. A significant difference in overall survival was also noted between groups (p = 0.014). There was an association between U-5HIAA and (i) rate of flushing (p = 0.001), (ii) bowel movements/day (p < 0.001), (iii) chromogranin A (p < 0.001) and (iv) percentage of liver involvement (p < 0.001). In a subgroup of patients with radiological progression, both median and mean levels of U-5HIAA were higher at the time of progression compared to previous levels (median 616 from 444, mean 963.3 from 452.4 umol/24 h). Conclusion: In mNETs : a) U-5HIAA, at diagnosis, seems to be a prognostic marker b) there is a strong correlation between U-5HIAA levels and patients’ symptoms, CgA levels, hepatic tumor burden and radiological progression. Keywords: u-5hiaa, symptoms, prognosis, survival.

H3
Plasma Chromogranin B as a Marker of Tumor Burden and Radiological Progression in Neuroendocrine Tumors
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Introduction: Chromogranin-B (CgB) is expressed in most neuroendocrine tumors (NETs), yet little is understood about its clinical utility as a biomarker. Aim(s): To investigate the role of CgB in follow-up of NET patients. Materials and Methods: Two-hundred and twelve patients [167 with midgut (mNETs), 45 pancreatic (pNETs)] with elevated plasma CgB levels were included. Correlations between CgB (normal <150 pmol/L), tumor burden and histological grade, as well as its predictive value for radiological progression (RP), were investigated. Results: One-hundred and sixty-nine patients had liver metastases. CgB levels (pmol/L) correlated with hepatic tumor burden in mNETs (H(2) = 11.23, p = 0.011), but not in pNETs (H(2) = 5.882, p = 0.112). There was no correlation between CgB and tumor grade (H(2) = 2.42, p = 0.29). In 74 progressive mNETs, 81 events of radiological progression were recorded. Median CgB was 125, 12 months before RP, and 164.5, six months before RP, suggesting that CgB might predict RP (Z = −3.00, p = 0.03). Median CgB at the event of RP (195.5) was also higher than CgB values 12 months before (125) and six months before RP (164.5) [Z = −3.00 p < 0.001 and Z = −3.63, p < 0.001, respectively]. For those patients, median CgA [at 12 (177) and six months (512.5) prior to RP] also showed a significant predictive value (Z = −2.90, p = 0.004). Conclusion: In patients with mNETs and CgB secreting tumors, both CgB and CgA can be used alongside imaging to monitor for disease progression. Keywords: chromogranin b, midgut nets, pancreatic net, progression.

H4
Correlation of Serum Chromogranin A Change with Radiographic Response in Patients with Non-Functioning Advanced Neuroendocrine Tumors
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Introduction: Numerous studies have suggested that CgA determination may be useful for the diagnosis and follow-up of neuroendocrine tumors (NETs). Aim(s): To determine the sensitivity of CgA in diagnosis of non-functioning NETs, and the correlation of CgA change with radiographic response in patients with advanced non-functioning NETs. Materials and Methods: Serial CgA determinations were performed in 29 patients (24 pNETs, five others, 80 visits) with locally advanced (n = 3) or metastatic (n = 26) non-functioning NETs on various treatments. Changes in CgA levels over
The plasma chromogranin A level is a reliable biomarker for identifying patients with advanced gastroenteropancreatic neuroendocrine tumors (GEP-NETs). **Aim(s):** To measure the baseline value and changes during antitumor therapy of the CgA level in patients with advanced GEP-NETs. **Materials and Methods:** Sixty patients with advanced GEP-NET treated at a single medical center between April 2010 and April 2013 were retrospectively enrolled. The plasma CgA level was measured and imaging performed concurrently at baseline and at regular intervals after antitumor therapy. The plasma CgA level was analyzed for correlation with the patient’s clinical outcome and the tumor response. **Results:** The median duration of follow-up was 11.2 months. The Eastern Cooperative Oncology Group performance score 0–1, WHO tumor grade 1–2, one organ affected by metastasis, and baseline CgA level (< twice the upper normal level) were independent favorable predictors of overall survival after multivariate analysis. The changes in consecutive CgA levels (∆CgA) of tumor response evaluation differed significantly between the partial response (PR) and stable disease (SD) (p = 0.015) and between the PR or SD and progressive disease (PD) (p < 0.001) tumor response groups. A ∆CgA of 3% per month distinguished PR or SD from PD with 97.1% sensitivity and 81.7% specificity. **Conclusion:** The baseline plasma CgA level and ∆CgA were valuable predictors of survival and tumor response. **Keywords:** neuroendocrine tumor, biomarker, chromogranin a.
**H7**

**O6-Methylguanine DNA Methyltransferase (MGMT) Expression and Ki-67 Index Predict Response to Temozolomide in Patients with Well-Differentiated Pancreatic Neuroendocrine Tumors (WDPNET)**

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**Introduction:** Temozolomide (TEM) showed encouraging results in WDPNET. Decreased MGMT expression and methylation of its promoter seems to correlate with better outcome in TEM-treated glioblastomas. **Aim(s):** To assess if MGMT expression and the methylation of its promoter can predict the efficacy of TEM in WDPNET.

**Materials and Methods:** Patients with WDPNET treated with TEM between 2006–2012 were included. Treatment efficacy was assessed by the best radiological response (RESEIC criteria). Expression of MGMT was assessed by an immunochemistry score based on intensity (0 to 3) x% of stained cells [0–300]. MGMT promoter methylation was assessed by pyrosequencing.

**Results:** Forty-three patients (21 men, 58 (27–84) years) with WDPNET, grade 1 (six pts) or 2 (37 pts) were included. Treatment efficacy was assessed by the best radiological response (RECIST criteria). Expression of MGMT was assessed by an immunochemistry score based on intensity (0 to 3) x% of stained cells [0–300]. MGMT promoter methylation was assessed by pyrosequencing.

- **Conclusion:** TEM is highly efficient in WDPNET. MGMT expression can predict OR and PFS in TEM-treated patients with a low Ki-67 index WDPNET. **Keywords:** mgmt, pancreatic net, temozolomide.

**H8**

**Chromogranin A is a Useful Marker in Japanese Patients with Pancreatic Neuroendocrine Tumors**

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**Introduction:** Although Chromogranin A (CgA) is known as a useful marker for pancreatic neuroendocrine tumors (pNET) in the West, the usefulness of CgA in Japanese patients with pNETs is unclear. **Aim(s):** To assess the potential usefulness of CgA for diagnosing pNET in Japan.

**Materials and Methods:** We evaluated the serum CgA level in 189 patients with various pancreatic diseases including with proven pNET (n = 69), pancreatic cancer (PC) (n = 50), chronic pancreatitis (CP) (n = 50), autoimmune pancreatitis (n = 20) and 112 healthy subjects (normals) by using an ELISA kit, Chromoaa (Cis Bioassays, France).

**Results:** The mean CgA level of patients with pNETs was significantly higher compared with that of any other group. Limiting patients without proton pump inhibitor (PPI) use, the CgA level of patients with PC or CP was not significantly different compared with that of normals. Discriminant analysis revealed the best cut-off value of CgA to distinguish patients with pNET from normals was 78.7 ng/ml, which has a sensitivity and specificity of 53.6% and 78.6%, respectively. Limiting patients with pNETs, significant factors associated elevated CgA level were tumor classification, tumor size, and presence of liver metastases in univariate analysis and PPI use and presence of liver metastases in multivariate analysis.

**Conclusion:** Serum CgA is a useful marker in Japanese patients to distinguish those with pNETs from other pancreatic diseases. As in the West, PPI usage is particularly important to consider in interpreting the CgA level. **Keywords:** chromogranin a, pnet, japanese.

**H9**

**Evaluation of the Clinical Utility of Plasma Biomarkers in Diagnosis of Neuroendocrine Tumors**

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**Introduction:** Neuroendocrine tumors (NETs) are rare cancers that usually develop in the gastroenterohepatic system. Diagnostic workup of these tumors includes measurement of plasma levels of marker peptides. Clinical experience suggests that these markers may be misleading if used before histological or imaging evidence of a NET is available. **Aim(s):** This study explored the clinical utility of chromogranin A (CgA), neurokinin A (NKA) and pancreatic polypeptide (PP) in the diagnosis of NETs.

**Materials and Methods:**
H10

Comparison of the Novel Cell Detector Method with Cell Search Technology in the Isolation of Circulating Tumor Cells in Neuroendocrine Tumors

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Introduction: Circulating Tumor Cells (CTCs) have been detected in patients with neuroendocrine tumors (NET) using the CellSearch platform. Their presence is associated with a worse clinical outcome but less than 50% patients have detectable cells. The GILUPI Cell Detector is an EpCAM coated wire that is inserted into a vein and has been developed to increase capture of CTCs. Aim(s): To compare the performance of Cell Search and the Cell Detector in patients with metastatic NETs. Materials and Methods: CTCs present in 7.5 ml blood were enumerated in NET patients by CellSearch as previously described. Concurrently, the Cell Detector wire was inserted into a vein in the anti-cubital fossa under sterile conditions for 30 mins. It was then withdrawn and analysed by immunofluorescence for cytokeratin, EpCam, DAPI and CD45. CTCs were enumerated by two operators blinded to clinical background and the inter/intra-assay reproducibility (<1.2). PCR exhibited sensitivity (85–98%) and specificity (93–97%), AUCs were <0.98 and significantly (Z-statistic 10.5–11.4, p < 0.0005) more accurate than CgA (correct call rate: 68%). PCR identified pancreatic and GI NETs with similar accuracy (>85%). Set 3 (prospective) NETs: PCR was positive in 145 (97%) compared to CgA (elevated in 77: 51%, Chi²=77.8, p < 10−19). PCR performance metrics were: sensitivity 97%, specificity 100%, PPV 100% and NPV 91% and the ROC-derived AUC was 0.998. These were significantly better than CgA (sensitivity 51%, specificity 74%, PPV 86% and NPV 34%, AUC = 0.64, z-statistic 7.21, p < 0.0001). When CgA was normal (32%), PCR was elevated (73%) with high specificity (99%). Conclusion: A key issue in NET management is the need for a specific and sensitive biomarker to detect disease and assess treatment. CgA is widely utilized but has limitations. Aim(s): Validate a 51 transcript blood NET signature for the detection of NETs.

H11

A Molecular Multi-Transcript Gene Blood Signature Significantly Outperforms Chromogranin A (CgA) in the Detection of Gut Neuroendocrine Tumors (NETs)

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Introduction: A key issue in NET management is the need for a specific and sensitive biomarker to detect disease and assess treatment. CgA is widely utilized but has limitations. Aim(s): Validate a 51 transcript blood NET signature for the detection of NETs.

Materials and Methods: PCR test in 2 independent NET sets (n = 115; n = 120) and in third prospective, blinded set of 150 NETs and 50 controls. Compare metrics to CgA (DAKO-ELISA). Results: Set 1 & 2: PCR analysis was robust (inter/intra-assay variation <2%; inter/intra-assay reproducibility <1.2). PCR exhibited specificity (93–97%), AUCs were <0.98 and significantly (Z-statistic 10.5–11.4, p < 0.0005) more accurate than CgA (correct call rate: 68%). PCR identified pancreatic and GI NETs with similar accuracy (>85%). Set 3 (prospective) NETs: PCR was positive in 145 (97%) compared to CgA (elevated in 77: 51%, Chi²=77.8, p < 10−19). PCR performance metrics were: sensitivity 97%, specificity 100%, PPV 100% and NPV 91% and the ROC-derived AUC was 0.998. These were significantly better than CgA (sensitivity 51%, specificity 74%, PPV 86% and NPV 34%, AUC = 0.64, z-statistic 7.21, p < 0.0001). When CgA was normal (32%), PCR was elevated in 94%. Conclusion: A multi (51)-gene NET panel is robust (~2% variation) and efficient (~97%) for GEP-NET detection. The test is significantly more sensitive than CgA (p < 10−19) and is elevated in ~95% of patients when CgA is normal. It provides an accurate and sensitive measure of GEP-NET disease irrespective of site. Keywords: biomarker, cga, net, pcr.
pancreatic NETs (n = 91, including 42 pancreatic and 40 small intestinal NETs), carcinoids of unknown primary (n = 18) and other sites (n = 16). Group 2 included prospectively collected non-NET patients receiving PPIs (>1 months) (dyspepsia: n = 19, GERD: n = 6, pancreatic: n = 4) and 50 controls. All samples were analyzed by PCR (NET marker genes) and ELISA (DAKO-CgA). Results: Group 1: 123 NETs were PCR-positive compared to 50 by CgA (Chi² = 97.3, p < 10–26). Significant differences (p < 0.001) were noted: pancreas: PCR 95% v. CgA 29% (p < 10–9), small intestine: 100% v. 58% (p < 10–4). The multigene test was elevated in 97% of NETs when CgA was normal. Group 2: PPI use increased CgA in 83% of patients. CgA was elevated in 13 (26%) of controls. False positives for PCR were zero. PCR metrics were: sensitivity 98.4%, specificity 100%, PPV 100%, NPV 97.8% and the ROC-derived AUC was 0.997. These were significantly better than CgA (all metrics <60%, AUC: 0.54, z-statistic 10.44, p < 0.0001). Conclusion: A 51 panel blood transcript analysis is significantly more sensitive than plasma CgA for detection of NETs and is unaffected by acid suppression therapy. Keywords: biomarker, cga, net, pcr.

H13
The Predictive Value of Gastrin Levels for the Diagnosis of Gastric Enterochromaffin-like Cells Hyperplasia, in Patients with Hashimoto’s Thyroiditis
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Introduction: Gastrin and chromogranin A (CgA) levels have been tested for the diagnosis of enterochromaffin-like cell hyperplasia (ECLH), in patients with type 1 diabetes and autoimmune atrophic gastritis but there are no data for patients with Hashimoto’s thyroiditis (HT). Aim(s): To develop receiver operating characteristic (ROC) curves for gastrin and CgA levels and other clinical and biochemical parameters as a means for pretest probability of gastric ECLH in patients with HT. Materials and Methods: One-hundred and fifteen patients with HT were prospectively studied for a median period of four years (2–7 years). Gastrin, CgA, vitamin B12, anti-parietal cell antibodies, free-thyroxine, thyrotropin, and neuron-specific enolase level measurements. Results: Thirteen patients (11.3%) had ECLH. The areas under the curve for gastrin and CgA level were 0.898 (p < 0.001) and 0.853 (p < 0.001), respectively. The product: sensitivity X specificity was 0.803 and 0.653 for gastrin and CgA levels >89.5 ng/ml and >89.1 ng/ml, respectively. Normal gastrin and CgA levels had two and four patients with ECLH, respectively. The most specific combined parameters for ECLH were gastrin >89.5 ng/ml with concomitant low B12 levels (96.1% specificity). Conclusion: Gastrin levels have high diagnostic accuracy for ECLH identification in patients with HT, and are highly specific when combined with low B12 levels. However, they should be interpreted with caution, as few patients may harbor gastric ECLH even if gastrin levels are normal. Keywords: enterochromaffin-like cell hyperplasia, gastrin, thyroiditis.

H14
Predictive Biomarkers of Response in Patients with Extraluminal Neuroendocrine Tumors (EPNET) Treated with Platin-Based Chemotherapy
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Introduction: EPNET, particularly advanced and Grade 3 (G3) tumors are often treated with chemotherapy. While many patients experience tumor response, those rarely live for more than two years. Predictive markers could potentially help us to tailor the best treatment for these patients (pts). Aim(s): To evaluate the influence of biomarker expression on the response rate (RR) and overall survival (OS) in patients with inoperable grade 2 (G2) and G3 EPNET who received chemotherapy. Materials and Methods: Retrospective analysis of pts with G2/G3 EPNET treated with platinum-based chemotherapy. Clinical and laboratorial data were collected from an electronic database. Pts had their paraffin-embedded tumor tissues tested for ERCC1, BCL2, timidylate synthase (TS) and Lin28 by immunohistochemistry (IHC). Expression score was based on the intensity of staining (graded as 0–3). Results: From July 2006 to August 2013, 60 pts were identified. Thirty-five (58.4%) were male, median age was 56 years and 28% had pancreatic tumors. Ninety percent had G3 tumors. At baseline, 73.4% had an ECOG-PS of 0/1. With a median of five cycles, RR by RECIST criteria was 41.5%. Median OS was 19.2 months and median PFS was nine months. Through IHC, Bcl-2, ERCC1, Lin28 and TS were positive in 51.7%, 95%, 93.3% and 78.3%, respectively. None of them were predictive of response. Conclusion: We observed a high expression of ERCC1, Lin28 and TS in the analysed pts. However, we could not identify a predictive marker for tumor response among these biomarkers. Keywords: biomarker, neuroendocrine tumors.

H15
The Chemokine Receptor CXCR4 – Differential Expression in Bronchopulmonary Neuroendocrine Neoplasms
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Introduction: The CXCR4 is a plasma membrane chemokine receptor, which is involved in organogenesis, hematopoiesis and inflammation. Additionally, an over-expression is described for many
neoplastic tissues. Here, an involvement in tumor progression, metastasis, adaptation to hypoxia and in stem cell survival is postulated. **Aim(s):** In the present study, the expression of the CXCR4 was evaluated in a panel of neuroendocrine tumors of the lung, comprising typical carcinoids (TC), atypical carcinoids (AC) and small cell lung cancer (SCLC). **Materials and Methods:** CXCR4 expression was assessed by means of immunohistochemistry (IHC) using the novel rabbit anti-CXCR4 antibody UMB-2 and by qRT-PCR. The staining was quantified with three different scoring systems. Both IHC and qRT-PCR results were correlated with patient data. Additionally, endogenous CXCR4 expression was assessed in different cancer cell lines by means of immunocytochemistry. **Results:** The CXCR4 was predominantly localized at the plasma membrane of the tumor cells. It was found to be expressed very strongly in almost all of the 30 SCLC samples investigated. In TC and AC, in contrast, it was present only in a small number of cases and the staining was, in general, less intense. Statistical analysis revealed a significant correlation between IHC and qRT-PCR data and between CXCR4 expression and tumor grading. **Conclusion:** Due to the high expression rate, the CXCR4 may serve as an additional diagnostic parameter and as a new therapeutic target in SCLC. **Keywords:** neuroendocrine, tumor, sclc, cxcr4, ihc.

**H16**

**Soluble VCAM-1 and Its Relation to Clinical Staging and Histological Grading in Neuroendocrine Neoplasms (NENs)**

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**Introduction:** Cellular adhesion molecules play an important role in tumor progression and metastasis. **Aim(s):** The assessment of the endothelial cell adhesion molecule (sVCAM-1) serum levels and NEN markers (chromogranin A (CgA), serotonin (5-HT), 5-hydroxyindoleacetic acid (5-HIAA)) concentrations and its relevance in predicting metastasis and progression of NENs. **Materials and Methods:** Eighty-two patients with NENs, aged 25 to 81 years and 26 healthy controls. NEN markers concentration, such as CgA, 5-HT and 5-HIAA, and sVCAM-1 serum levels were assessed, and statistical analysis of the obtained results was made. **Results:** The concentrations of NEN markers (CgA, 5-HT, 5-HIAA) and sVCAM-1 were significantly higher in the patients with NEN compared with the control group. In 82 patients with NEN: CgA, 5-HT, 5-HIAA and sVCAM-1 did not differ significantly between the two groups of women and men. Both the clinical stage of the disease (metastases in the lymph nodes and distant metastases) and histological grade (G2 and G3 compared to G1) was associated with significantly higher levels of 5-HT and sVCAM-1. **Conclusion:** sVCAM-1 serum concentrations may be of value as markers of the disease stage evaluation in patients with NENs, possibly related to histological grade and clinical stage. **Keywords:** neuroendocrine neoplasms, svcam-1, histological grade, clinical stage.

**H17**

**Variation between Chromogranin A Assays in the Diagnosis of Gastric Carcinoid Type 1**

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**Introduction:** Chromogranin A (CgA) is not very accurate for the diagnosis of gastric carcinoid type 1 (GC1). Clinical interpretation of CgA results may be affected by the heterogeneity between CgA assays. The commercial CgA assay, DAKO (DAKO, Denmark A/S, Glostrup, Denmark) is an ELISA which recognizes a 23 kD C terminal fragment of CgA; the Imperial Supra-regional Assay Service radioimmunoassay (SAS Hammersmith Hospital, Imperial College, London) is a competitive radioimmunoassay raised against the whole pancreatic astatin molecule. **Aim(s):** To compare CgA-DAKO and CgA-SAS to determine their accuracy in the diagnosis of GC1. **Materials and Methods:** Patients diagnosed with GC1 and available plasma CgA measurements according to two different assays (SAS, DAKO) were retrospectively reviewed. CgA values were ranked in four groups: 1. normal values, 2. increase <2 upper normal limit (ULN) 3. increase between 2–5 ULN 4. increase >5 ULN. **Results:** Twenty-five patients (16 female, nine male, median age 58 years) were identified. Median CgA-DAKO were significantly higher than median CgA-SAS (81 IU/l, normal range <27 IU/l v. 35 pmol/l, normal range <60 pmol/l, T = 38.5, p = 0.001). The results confirmed median ranked CgA-DAKO significantly higher than median ranked CgA-SAS (3 v. 1, T = 0, p < 0.001). Sensitivity was 76% and 8% for CgA-DAKO and CgA-SAS, respectively. **Conclusion:** CgA-DAKO shows a better sensitivity than CgA-SAS for the diagnosis of GC1. Further prospective studies are needed highlighting the importance of variation between CgA assays. **Keywords:** gastric carcinoid type 1, chromogranin a.
recognised yet. **Aim(s):** To investigate the role of CgA as a predictor of radiological progression. **Materials and Methods:** Patients with metastatic NETs and evidence of radiological progression (RP) were identified. Plasma CgA levels were measured at six and 12 months (m) before RP and at RP. **Results:** One-hundred and fifty-two patients (91 midgut NETs (mNETs), 61 pancreatic NETs (pNETs)) were included. Fifty-six patients had G1 NETs, 65 G2, 10 G3, and 21 unknown. Median CgA for all patients was 213 pmol/L at 6 m, and 166 pmol/L at 12 m, before RP (p = 0.07). Significant differences were found in pNETs [median CgA 6 months before RP was 100 pmol/L, at 12 m was 52 pmol/L, (p = 0.048)], but not in mNETs [median CgA 6 m before RP was 385.9 pmol/L, at 12 m was 319 pmol/L, (p = 0.39)]. Both mNETs and pNETs had significantly higher CgA values at RP than 12 m before [267 v. 166, (p = 0.03)]. Overall, G1 tumors had a significantly higher median CgA at 6 m than CgA at 12 m prior to RP [181 v. 149.5, (p = 0.048)]. **Conclusion:** CgA appears to be of predictive value 6 m prior to RP for pNETs and G1 tumors. This observation is of value to identify those patients who will benefit from a more intense follow-up or an earlier intervention, in cases of increasing CgA levels. Prospective studies are needed. **Keywords:** chromogranin a, neuroendocrine tumors, radiological progression.

**H19**

**Role of Epithelial-to-Mesenchymal Transition Markers in Predicting Bone and Visceral Metastases from NETs**

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**Introduction:** Epithelial-to-mesenchymal transition (EMT) of tumor cells has been recently postulated as a pivotal mechanism driving metastatic spread. **Aim(s):** A tumor-specific gene signature may be useful to predict the susceptibility of neuroendocrine tumors (NETs) to metastasize toward the skeleton. **Materials and Methods:** Twenty-one NETs were grouped in two arms based on the presence or absence of metastases. Tumor sections were immunostained to molecules involved in metastatic homing (CXCR4, RANK, and EMT (TGFβ1, SNAIL, CTGF, PTHrP, IL11)) and the data interpreted by Allred score. H727, H720, H835, CM, QGP1 and BONI cells were screened with RT-PCR for genes enrolled in osteoclastogenesis (RANK, TNFα, PTHrP, TRACP, vATPase, MMP9, MMP13) and in osteoblastogenesis (Osteocalcin, Osterix, RUNX2, COL1A1, ALP). **Results:** Eleven patients were metastatic, 10 showed limited disease. The expression of CXCR4, RANK, PTHrP and CTGF was higher in metastatic tumors, in particular in the three bone metastasizing primaries, rather than in the nonmetastatic ones. TGFβ1 expression was high in the two groups while both SNAIL and IL11 was alternatively high and low in all examined slides. Moreover, while BON1 and H727 showed a transcriptional profile enriched in osteoblastogenic cues, the other NET cells expressed mainly osteoclastogenic cues. **Conclusion:** Increased expression of CXCR4, RANK, PTHrP, CTGF and TGFβ1 in the tissue may predict the risk of metastases. Genes involved in osteoblast or osteoclast function may predict the nature of bone metastases. **Keywords:** emt, biomarker.

**H20**

**Vimentin and E-cadherin Expression in Primary Neuroendocrine Tumors by Grade**

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**Introduction:** The prognostic evaluation of radically removed neuroendocrine tumors (NETs) represents an important issue. The cardinal tumor features can be studied as biomarkers. **Aim(s):** To study cell adhesion and mesenchymal differentiation in primary NETs by grade. **Materials and Methods:** Consecutive surgically treated NETs were identified by retrospective archive search revealing 48 G1 and 22 G3 NETs of gastroenteropancreatic (44) and pulmonary (26) origin. Neuroendocrine markers (chromogranin A, synaptophysin, CD56), proliferation activity (Ki-67) and presence of e-cadherin (E-CAD) and vimentin (VIM) was detected by immunohistochemistry. Expression of E-CAD and VIM was scored semiquantitatively (0, negative; 1, weak; 2 moderate; 3 intense) and evaluated by the pattern as well. Descriptive statistics including 95% confidence interval (CI) calculation was performed. **Results:** G1 NETs revealed membranous E-CAD expression (100%; 95% CI:90.4–100) with variable (1–3) and heterogeneous (40.9%; 95% CI:27.7–55.6) intensity. G3 NETs showed loss (18.2%; 95% CI:6.7–39.1) or cytoplasmic E-CAD expression (36.4%; 95% CI:19.6–57.1), contrasting to the absence of such patterns in G1 NETs (0%; 95% CI:0–9.6). VIM was found in 17.4% (95% CI:8.8–31.0) of G1 and 50.0% (95% CI:30.7–69.3) G3 NETs. **Conclusion:** G3 NETs show aberrations in cell adhesion and trend to epithelial-mesenchymal transition. Frequent VIM expression and heterogeneous E-CAD in low grade NETs necessitates further investigation as possible prognostic biomarkers. **Keywords:** nets, vimentin, e-cadherin.
formed with ELISA Kit (CisBio) from fasted pts. The decreased/elevated CgA was defined as <50%/>50% level from baseline. We computed LM tumor burden from CT/MRI scan with less than 5 mm thin slices including most of detectable metastases by a semi-quantitative three-dimensional reconstruction approach. Change in LM tumor burden was defined as response or progression using RECIST criteria. **Results:** Among 109 samples (36.7% G1 and 63.3% G2), the CgA was significantly elevated in NF-PNETs with LM (n = 51) compared to those without LM (n = 58) (median: 95 v. 60 ng/ml, P < 0.001). The CgA level correlated with LM tumor burden (R = 0.55, P < 0.001). When categorizing LM tumor burden as <50 cm³ (n = 34), 50–200 cm³ (n = 12) or >200 cm³ (n = 5), the CgA level was also related to the extent of LM spreading (median: 77, 189, 501 ng/ml, P < 0.001). As for therapeutic response, pts defined as response (n = 11) had decreased CgA, meanwhile, pts defined as progression (n = 7) had elevated CgA, whereas in one pt with response only the CgA increased (P < 0.001). **Conclusion:** Serum CgA level corresponds well with the extent of LM spreading and could be used to evaluate the therapeutic response. **Keywords:** cga nf-pnets lm.

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**Imaging (Radiology, Nuclear Medicine, Endoscopy)**

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**I1 Intra and Interobserver Reproducibility of CT and MRI for Measurement of Liver Metastasis as a Basis of RECIST Evaluation in Patients with Neuroendocrine Tumors**

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**Introduction:** The reliability of RECIST evaluation in patients with NET has not yet been analyzed. **Aim(s):** To determine intra and interobserver reproducibility of CT and MRI for the measurement of NET liver metastases. **Materials and Methods:** Retrospective study on 54 patients with well-differentiated NET liver metastasis (22 patients underwent CT and 32 MRI). Patients were treatment-naïve or under somatostatine analogs. We analyzed triphasic abdominal CT or liver MRI (T2, T1 and T1 after injection of gadolinium on HAP and PVP). A maximum of five liver target lesions per patient was defined and three radiologists independently measured those target lesions on each sequence, in two sessions. A total of 1,656 measurements for CT and 3,384 for MRI were analyzed. **Results:** Among 109 samples (36.7% G1 and 63.3% G2), the CgA was significantly elevated in NF-PNETs with LM (n = 51) compared to those without LM (n = 58) (median: 95 v. 60 ng/ml, P < 0.001). The CgA level correlated with LM tumor burden (R = 0.55, P < 0.001). When categorizing LM tumor burden as <50 cm³ (n = 34), 50–200 cm³ (n = 12) or >200 cm³ (n = 5), the CgA level was also related to the extent of LM spreading (median: 77, 189, 501 ng/ml, P < 0.001). As for therapeutic response, pts defined as response (n = 11) had decreased CgA, meanwhile, pts defined as progression (n = 7) had elevated CgA, whereas in one pt with response only the CgA increased (P < 0.001). **Conclusion:** Serum CgA level corresponds well with the extent of LM spreading and could be used to evaluate the therapeutic response. **Keywords:** cga nf-pnets lm.

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**I2 Serial 89Zr-bevacizumab PET in Patients with Neuroendocrine Tumors before and on Everolimus Treatment**


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**Introduction:** Everolimus increases PFS in patients with advanced NETs. Currently, no biomarkers are available for early selection of patients who will benefit from everolimus. Everolimus can reduce VEGF-A production by tumor cells. **Aim(s):** Therefore, we aimed to investigate the effect of everolimus on tumor uptake of radioactive labelled VEGF-A antibody bevacizumab with PET in NET patients. **Materials and Methods:** Fourteen patients with advanced progressive well-differentiated NET underwent 89Zr-bevacizumab PET scans before, and at two and 12 weeks on everolimus treatment. 89Zr-bevacizumab uptake was quantified by SUVmax. Tumor response and % change in sum of target lesion diameters was determined according to RECIST1.1 on CT 3-monthly. **Results:** In four of 14 patients, no tumor lesions were visualized with 89Zr-bevacizumab PET. In the remaining patients, 19% of tumor lesions ≥1 cm known by CT were visualized. Tumor SUVmax decreased during everolimus treatment with median –7% at 2 w (P = 0.09) and median –35% at 12 w (P < 0.001). A SUVMax at 2 and 12 w correlated with % change on CT at 6 mo (r² = 0.51, P < 0.05, r² = 0.61, P < 0.01, respectively). **Conclusion:** This study demonstrates variable 89Zr-bevacizumab PET tumor uptake in NET patients. 89Zr-bevacizumab tumor uptake diminished during everolimus treatment. Serial 89Zr-bevacizumab PET might be useful as an early predictive biomarker of anti-VEGF directed treatment in NET patients. Supported by a research grant of Novartis, NL. **Keywords:** neuroendocrine tumors, 89zr-bevacizumab pet, vegf-a, everolimus, biomarker.
Detection Limitation of Occult NET Using Gallium-68 Dotatoc Scan Plus FDG PET

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Introduction: The modalities detection of gastroenteropancreatic neuroendocrine tumors (GEP-NET) includes sonogram, abdominal CT and MRI, but the detection rate is limited. Iodium-111 Octreotide scan is another choice. Ga-68 Dotatoc scan is very rapid and more sensitive than Octreoscan. The Ga-68 Dotatoc scan plus FDG-PET is useful for detecting active NETs. Aim(s): The detection rate and affect factors of Ga-68 Dotatoc scan plus FDG-PET were studied. Materials and Methods: Twelve cases with elevated chromogranin A and failure to detect NET after the classic image examinations were included in this study. Ga-68 Octreotide scans plus FDG-PET and MRI were performed. The exclusive criteria were lactating or pregnancy, fasting sugar higher than 200 mg%, and GFR less than 30 ml/min. Their clinical data were recorded for comparison. Results: The results showed four of the patients were found to have NET lesions from their Ga-68 Dotatoc scans, another one had a lesion on FDG-PET. Three of the patients with positive Ga68 Dotatoc scan received surgery and the NETs were confirmed by pathological examination. The detection rate was 33.3%. Five of eight patients (63%) who failed to have their tumors detected had a history of PPI intake, while the positive patients had no PPI intake. Conclusion: Ga-68 Dotatoc scan plus FDG PET can be used for detection of NET, when the patients had elevated chromogranin A and their classic images failed to detect the tumors. The low Ga-68 Dotatoc scan rate may be due to PPI intake of patients. Keywords: gep-net, ga-68 dotatoc scan.

Evaluation of the Added Value of Diffusion-Weighted Imaging to Conventional MRI in Pancreatic Neuroendocrine Tumors and Comparison with 68Ga-DOTANOC PET/CT

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Introduction: Pancreatic neuroendocrine tumors (pNETs) are often difficult to detect because of small size and have variable prognosis related to grading and staging. Aim(s): To investigate the added value of DWI in pNETs evaluation and to compare MRI results with those of 68GaDOTANOC PET/CT. Materials and Methods: MRI (morphological/DWI) and 68GaDOTANOC PET/CT in 25 patients/30 pNETs were retrospectively evaluated. Per-patient and per-lesion detection rates (pDR, lDR) were calculated. ADC values were compared among: – pNET, surrounding and normal pancreas (control group); – tumors different grading and staging groups. Results: Non-experienced radiologist: morphological MRI had a better DR than DWMRI (pDR:76% v. 60%; lDR:72% v. 60%); combined evaluation had 76% pDR and 73% lDR. Experienced radiologist: morphological MRI and DWMRI had the same DR (pDR:88% v. IDR:87%); combined evaluation showed 92%pDR and 90%lDR. Nuclear physician: 68Ga-DOTANOC PET/CT had 88% pDR and 80% lDR. Comparing PET/CT and MRI no statistically significant differences in detection rate were found. Consensus reading (morphological/DW-MRI/PET/CT) improved pDR and IDR (100%). ADC mean values: pNETs’ was significantly lower compared to surrounding and normal parenchyma (p < 0.01); no statistically significant difference was found among different grading and staging groups. Conclusion: Conventional MRI, DWMRI and 68GaDOTANOC PET/CT can be alternative tools in pNET detection. However, the consensus reading of the three techniques seems the best approach. Keywords: neuroendocrine tumors, mri, dwi, pet.

Comparison of Diagnostic Methods in the Evaluation of Pancreatic and Duodenal Gastrinomas

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Introduction: Gastrinomas are neuroendocrine tumors, mainly located in the duodenum or the pancreas, that secrete gastrin and cause a clinical syndrome known as ZES. Aim(s): To enhance the effectiveness of diagnosis and reduce the time and effort in reaching the correct diagnosis. Materials and Methods: We evaluated the sensitivity of the most important tumor markers (CgA, gastrin and NSE), as well as the main Imaging modalities used for diagnosis e.g. (USG, CT, MRI, SRS and EUS) in 29 patients with pancreatic gastrinomas and 27 patients with duodenal gastrinomas, confirmed by immunohistochemistry and time in reaching diagnosis. Results: The mean age of patients with gastrinoma was found to be 56.4 y. CgA sensitivity was found to be 92.4% in localized gastrinomas and 94.7% in metastatic gastrinomas, while Gastrin was 85.7%/89.5%, respectively, NSE 26.8%/57.9% and HIAA 8.9%/10.5%. While localization sensitivity was found to be 92.4% in localized gastrinomas and 94.7% in metastatic gastrinomas, while Gastrin was 85.7%/89.5%, respectively, NSE 26.8%/57.9% and HIAA 8.9%/10.5%. While localization sensitivity of pancreatic gastrinoma: EUS 89.7%; SRS 51.07%; US 3.7%, MRI 51.9%, CT 55%. Conclusion: The average time needed for diagnosis from the early signs and symptoms was 5.4±1.2 years. The most sensitive tumor marker has been shown to be Chromogranin A (CgA) (with 92% sensitivity) followed by gastrin (86%) as a specific marker, while NSE has minimal importance for the diagnosis. As for imaging methods,
endoscopic ultrasonography was the most sensitive. **Keywords:** neuroendocrine tumors, gastrinoma, effectiveness of tumor markers, imaging diagnostic methods, clinical features.

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**Analysis of Somatostatin-Receptor 2A (SSTR2A) Immunohistochemistry, RT-qPCR and In-Vivo-PET/CT Data in Patients with Pancreatic Neuroendocrine Neoplasm**


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**Introduction:** Ga-68 somatostatin receptor (SSTR) PET/CT is one of the most sensitive imaging methods for pancreatic neuroendocrine tumors. **Aim(s):** We analyzed if the receptor density predicted by the semi-quantitative parameters generated from the static PET/CT (standard uptake values – SUVmax/SUVmean) correlate with ex-vivo SSTR2A immunohistochemistry (IHC) and RT-qPCR gene expression data. **Materials and Methods:** Twenty-three pancreatic neuroendocrine tumor specimens (14 primary tumors, nine metastases) of 15 patients were evaluated. PET/CT was performed preoperatively in all patients. SSTR2A and Ki-67 expression was quantified immunohistochemically using the Immunoreactive Score (IRS), according to Remmelle and Stegner as well as by means of RT-qPCR. **Results:** SUVmax showed a wide variability in primary and metastatic specimens. SSTR2A IRS correlated significantly with SUVmax (p = 0.03; C: 0.44) and SUV mean (p = 0.05; C: 0.53). SUVmax and SUVmean also displayed an association with the PCR data (SUVmax p = 0.042; C: 0.64; SUVmean p < 0.001; C: 0.85). A relationship was also found between Ki-67 IHC and RT-qPCR data (p = 0.01; C: 0.77). Additionally, a trend towards a correlation between SSTR2A IRS and RT-qPCR values was seen (p = 0.07; C: 0.57). **Conclusion:** SUVmax and SUVmean are reliable parameters for in-vivo quantification of SSTR expression. As expected, SSTR2A protein expression tends to correlate with its gene expression. Both IHC and RT-qPCR are reliable methods for SSTR2A and Ki-67 quantification. **Keywords:** molecular imaging, somatostatin receptor, pancreatic tumor.

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### 17

**Comparison of Different Diagnostic Methods for the Assessment of Progression in Patients with Neuroendocrine Tumors (NET)**


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**Introduction:** Different imaging and laboratory methods are used to evaluate patients with NET. **Aim(s):** To compare the accordance of different imaging techniques and a biomarker in patients with metastatic NET. **Materials and Methods:** Retrospective analysis of 17 NET patients data, covering MRT/CT, somatostatin receptor scintigraphy, DOPA-PET and Chromogranin A. **Results:** Thirty-two follow-up visits that served as a basis for the evaluation of accordances could be identified. Visits were grouped into time categories of six months each to compare appropriate examination intervals. Only the categories 2 (7–12 mos) and 3 (13–18 mos) contained enough cases for statistical analysis with 16 and 11 cases, respectively. Overall, progression was found in 41 (36%) and partial remission/stable disease in 72 (64%). The agreement evaluation of MRT/CT with SRS shows Cohen’s Kappa (CK) values of 0.30 and 0.29 (fair) for the time categories 2 and 3. Agreement of DP in the same time categories was 0.42 (moderate) and 0.00. CK for CgA showed results of 0.05 and 0.04, showing only accidental match with MRT/CT. **Conclusion:** SRS showed the best agreement with MRT/CT in the investigated time categories. DP showed the best agreement for the 7–12 month category, but there was no agreement beside an accidental match for the 13–18 month time category. For CgA, no agreement except an accidental match was found. In summary, accordance of different diagnostic tools in metastatic NET is limited. **Keywords:** neuroendocrine tumor, dopa-pet, somatostatin receptor scintigraphy, progression.

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### 18

**Novel Succinate Dehydrogenase Subunit B Intrinsic Mutation in an Australian Kindred with Variable Clinical and Imaging Phenotype Necessitating Different Treatment Modalities Including 131-I MIBG and 177-Lutetium DOTATATE**

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**Introduction:** SDH B mutation has variable functional imaging phenotype challenging in terms of diagnosis, treatment modalities and follow-up. **Aim(s):** To describe a kindred with a novel SDH B mutation (c.286+2T>G). **Materials and Methods:** Case series. **Results:** Mutation has thus far been confirmed in 17 family members, aged 11 to 63, with four individuals exhibiting clinical disease. The proband, at the age of 19, had adrenalectomy for localized pheochromocytoma then had metastatic recurrence at age...
Abstracts

**Video Capsule Endoscopy as a Tool to Detect Small Bowel Neuroendocrine Tumors**
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**Introduction:** Recent studies suggest that video capsule endoscopy (CE) should be implemented in diagnostic work-up in patients with suspected small bowel tumors. Small bowel is the primary site in 80–85% of patients with intestinal neuroendocrine tumors (NET). In 10–15% of patients diagnosed with metastasized NET, the localization of the primary tumors remains obscure. **Aim(s):** Evaluate the efficacy of CE in small bowel NET detection in this setting. **Materials and Methods:** Between January 2010 and October 2013, 10 patients with metastasized NET and unknown primary tumor localization were referred to our institution. CT, MRI and PET/CT were carried out and failed to detect the primary tumor site. All patients underwent CE using a PillCam® SB2 capsule and the videos were read using Rapidv5 software (Given Imaging). Patients with univocal findings were considered for surgery. **Results:** In 6/10 patients (60%), CE revealed a small bowel tumor. All six patients (mean age 56 years (range 40–71 years) underwent surgery. All six were found to have a small bowel tumor. Histology confirmed a NET (grade 1 to 2) and lymph node metastases. Of the four remaining patients, two had normal findings on CE while two had a polyoid lesion and ulcers in the terminal ileum on CE and a double-balloon enteroscopy was done with no evidence of NET on biopsy. **Conclusion:** Video capsule endoscopy is a very useful tool in the diagnostic work-up of NET patients. It should be used in cases where standard imaging failed to localize the primary tumor site. **Keywords:** net, unknown primary, capsule endoscopy.

**Superior Mesenteric Vein Stenting for Management of Complications of Mesenteric Desmoplasia in Midgut Neuroendocrine Tumors**
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**Introduction:** Mesenteric fibrosis is a cause of morbidity and mortality in patients with midgut neuroendocrine tumors (mNETs). It may cause occlusion of the superior mesenteric vein (SMV), which can be associated with development of ascites and mesenteric and small bowel varices (SBVs) leading to occult gastrointestinal (GI) bleeding. **Aim(s):** To investigate the role of SMV stents in management of ascites and SBVs in mNET patients. **Materials and Methods:** Five patients (three male, two female) were included. All patients had GI mNETs, and evidence of inoperable mesenteric disease, desmoplasia and SMV occlusion. **Results:** Three patients presented with occult GI bleeding and two patients with ascites. Two out of three patients with GI bleeding, had obvious SBVs. Following stent insertion all patients had normalization of venous circulation on venography. All patients who presented with GI bleeding and one patient with ascites had no signs of relapse to date (follow-up range: 5–19 m). Three out of five patients, despite initial resolution of symptoms, relapsed within 20 days (mean time) after stent insertion. In-stent thrombosis was proven radiologically in these patients with computed tomography and they all re-presented clinically with ascites. **Conclusion:** SMV stents can control some of the symptoms associated with mesenteric desmoplasia. Stent failure is most likely to thrombosis and the role of anticoagulation needs to be defined with further studies and longer follow-up. **Keywords:** mesenteric desmoplasia, smv, stent.

**Tumor Perfusion Changes During Everolimus (E) Treatment: Preliminary Results from Perfusion-CT (P-CT) Study**
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**Introduction:** Criteria other than RECIST are not validated for evaluation of response during treatment in pancreatic neuroendocrine tumors (pNETs). Preliminary evidence favors antiangiogenic properties of E. **Aim(s):** To evaluate in a prospective study P-CT changes in pNET liver metastasis (LM) during E. **Materials and Methods:** We evaluated eight LM from three patients with G1-2 pNETs. P-CT was performed at baseline (T0), after two (T1) and four (T2) months of E on a 64-row multidetector CT scan. A single ROI was drawn within each LM on the main axial slice. Perfusion (PF), Time to Peak (TTP), Peak Enhancement Intensity (PEI) and Blood Volume (BV) were calculated. **Results:** All LM remained dimensionally stable, except for one LM with a reduction >30% at T1. At T0, all LM had high PF.
and PEI, consistent with hypervascularization of G1–2 pNETs. BV discriminated among two different patterns of perfusional changes in response to E: significant progressive increase (T2 v. T0 +5.4±1.1 ml/100 g; n = 3 LM) v. initial increase (T1 v. T0; +64.2±11.64 ml/100 g; n = 5 LM) and subsequent reduction (T2 v. T1; −73.5±3.3 ml/100 g). No clear patterns were identified for PF, TTP and PEI.

Conclusion: BV changes seem to be the earliest, more significant modifications among P-CT values during E treatment in pNETs. BV could reflect early vascular changes in tumor circulation. Longer follow-up is needed to evaluate the role of BV as an early predictive parameter and further studies are claimed to understand physiopathology of vascular response to E. Keywords: everolimus, pnet, p-ct.

112 Molecular Imaging of Somatostatin Receptors with 68Ga-DOTATOC-PET in Patients with Meningioma

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Introduction: In vitro studies showed that meningioma cells may express somatostatin receptors (SSTRs), which bears the possibility of receptor-mediated radionuclide therapy in patients with meningioma. Aim(s): To evaluate the application of 68Ga-DOTATOC-PET in patients with meningioma and the correlation between the expression of SSTRs in meningioma and gender, age of patients and tumor size. Materials and Methods: Twenty-five patients (14 f, 11 m, age 22–80 years) with meningioma were investigated with 68Ga-DOTATOC-PET (150 MBq, i.v.). Software-based coregistration of PET with MRI and/or CT was performed using Hybrid Viewer from Hermes Medical Solutions. Expression of SSTRs was classified in 4 grades [0, no uptake; 1, faint uptake; 2, moderate uptake; 3, high uptake (equal or higher than pituitary uptake)]. The tumor size (range 0.7–6.0 cm) was established on recent (<48 hr) MRI and/or CT data. Results: Grade 1 was found in two patients, grade 2 in six patients, and grade 3 in the remaining 17 patients. No false negative result was observed with 68Ga-DOTATOC-PET. No correlation was found between SSTRs expression and gender, age of the patient, or tumor size. Image fusion was very useful for differentiation of meningioma from non-menigioma lesions (i.e. scars). Conclusion: Most meningiomas show a high expression of SSTRs. Assessment of the receptor expression status with 68Ga-DOTATOC-PET has to be conducted on an individual basis in order to evaluate the eligibility of each patient to receptor-mediated radionuclide therapy. Keywords: 68ga-dotatoc, pet, meningioma, sstrs.

113 Assessment of Neuroendocrine Tumors’ Heterogeneity with Combination of Molecular Imaging Studies

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Introduction: Neuroendocrine tumors (NET) are heterogeneous neoplasms. The choice of the appropriate molecular imaging study for assessment of disease extent usually depends on tumor grade. Aim(s): To assess the value of combination of molecular imaging when a heterogeneous cell population is suspected or established. Materials and Methods: Patients with different-grade NET lesions, confirmed with biopsies and existing simultaneously, were identified. All patients had two molecular imaging studies Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) and Gallium-68 octreotate PET (Ga-68 DOTATATE) around the same period. Results: Five patients were included. In three patients, metastatic lesions (ovary in one and liver in two patients) showed different uptake in the two molecular imaging studies. More advanced grades, in comparison to the primary, were eventually identified. The ovarian metastasis was resected and the other two patients received chemotherapy. In the remaining two patients who had already known different grades between primary and metastatic lesions, combination of the above-noted molecular imaging revealed unexpected tumor lesions in different sites, and both patients were treated more aggressively with systemic chemotherapy. Conclusion: In cases of heterogeneous NET population, combination of molecular imaging contributes to accurate assessment of tumor load with possible implications to patients’ management. Keywords: neuroendocrine tumor, histology, functional imaging.

114 Role of Somatostatin-Receptor Scintigraphy with SPECT-CT in Diagnosis, Staging and Follow-Up of Patients with Neuroendocrine Tumors (NETs)

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Introduction: SPECT-CT study improves the certainty and accuracy of SPECT images. Aim(s): To evaluate the diagnostic impact of SPECT-CT somatostatin-receptor scintigraphy using 99mTc-Tektrotody in patients with NETs. Materials and Methods: Seventy-five pts with various NETs were studied; eight were with metastatic
lesions from tumors of unknown primary origin (UPO). SPECT-CT studies of the neck and chest and/or abdomen were performed 2–4 hr post i.v. inj. of 99mTc-Tektrotyd. Results: In four out of eight pts with UPO, primary tumor was discovered – MTC, mesenterial NETs and pulmonary NET. For correct N-/M-staging somatostatin scintigraphy was carried out in 35 pts. Loco-regional lymphadenopathy, distant liver, bone and/or pulmonary metastatic lesions, overexpressing somatostatin receptors were imaged in 28 pts, in three of them uptake was very low significant of insufficient expression of receptors. Four pts were true negative for secondary lesions. In the other 32 pts, SPECT-CT studies were used to determine therapeutic response post complex treatment. Functional imaging results were compared to CgA or Calcitonin. 1. Complete therapeutic response was obtained in three pts. 2. Partial response – in 12 pts. 3. Stable disease – in five pts. Persistence of one or more lesions and/or the maintenance of tumor marker level above the normal limits – CgA. 4. Progressive disease – in 25 pts. Conclusion: SPECT-CT 99mTc-Tektrotyd is a potential new tool for staging and follow-up of patients with NET. Keywords: spect-ct, tec-264.

I15
The Role of Combined 68Ga-DOTATOC and 18F-FDG PET/CT in Patients with Pancreatic Neuroendocrine Tumors

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Introduction: The value of combined (68)Ga-DOTATOC (68Ga) and (18)F-FDG (18FDG) PET/CT in diagnosis and staging of pancreatic NET is still unclear. Aim(s): To evaluate the accuracy of combined 68Ga and 18FDG PET/CT in pancreatic NET. Materials and Methods: Between January 2012 and December 2013, 35 consecutive patients with cytological and/or histological proven diagnosis of pancreatic NET (PNET) underwent combined 68Ga and 18FDG PET/CT in the same day. Results: Overall, seven PNETs (20%) were classified as stage I, two (6%) as stage II, two (6%) as stage III and 24 (69%) as stage IV. Surgical resection was performed in eight (23%) patients. 68Ga imaging achieved disease detection in 34 out of 35 and 18FDG PET/CT in 25 of 35 (71%). These results corresponded to sensitivities of 98% for 68Ga versus 68% for 18FDG PET/CT. Patients with NET-G1/NET-G2 had 68Ga positive and 18FDG negative in 10 cases (33%) whereas both 68Ga and 18FDG PET were positive in 20 (67%). Patients with NEC-G3 were both 68Ga and 18FDG PET/CT positive in four cases and only 18FDG positive in one case. The median Ki-67 was six for 68Ga PET positive tumors and 10 for tumors with both 68Ga and 18FDG PET/CT positive (P = 0.029). Fifteen of 24 patients (62.5%) with both 68Ga and 18FDG PET/CT positive had >5 liver metastases compared with three patients (30%) with only 68Ga PET positive (P = 0.084). Conclusion: The combination of 68Ga and 18FDG PET/CT has a good sensitivity in the diagnosis of pancreatic NET. 18FDG PET seems to be more accurate for high grade PNET. The uptake of both tracers in patients with multiple metastases could indicate heterogeneity for tumor grading. Keywords: pancreatic neuroendocrine tumor, pet, 68ga-dotatoc, 18fdg.

I16
Normal Tissue Perfusion Changes During Everolimus Treatment: Preliminary Results from a Functional Vascular Study


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Introduction: Everolimus (E) acts on cancer progression, even inhibiting tumor angiogenesis. Both tumor vasculature and a normal one could undergo everolimus effect. Aim(s): To analyze short-term changes in vascular function caused by E in patients with pNETs. Materials and Methods: In four patients with advanced E-treated pNETs, at baseline (B), after one month (T1) and 2 months (T2), we evaluated: central blood pressures (CBP), Augmentation Index (Alx) and Pulse Wave Velocity (PWV) using Sphygmocor as markers of arterial stiffness and arteriolar resistance, microcircular perfusion flow (PF) and vasodilatation response to ischemia (VDRi) using Laser-Doppler Flowmetry as a marker of endothelial function. Results: At T1, we observed a significant increase in PF (13.32±3.45 v. 27±4 PU) and an hemodynamic response with reduction of Alx (30±3 v. 26±4%) and CBP. Simultaneously, we found a significant reduction in VDRi (2.90±1 v. 1.56±0.17 ratio). At T2, we found a significant rise of Alx (32.75±5.50%), PWV (12.39±1 v. 15.67±0.9 m/s) and finally of CBP with a complete restoration of PF B value. Conclusion: We observed early endothelial dysfunction during E treatment. Vasodilatation of peripheral vessels were followed by compensatory mechanisms involving modifications of peripheral resistance and arterial stiffness for adequate peripheral perfusion pressure. Further studies could allow a better understanding of everolimus effects on vascular biology and their potential role as early predictive markers of response. Keywords: everolimus, endothelial dysfunction.

I17
The Analysis of Immunohistochemistry Staining, Neuron Specific Enolase (NSE) Level and Somatostatin Receptor Scintigraphy of Gastroenteropancreatic Neuroendocrine Neoplasm Cases

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Introduction: 99mTc-HYNIC-TYR3-OCTREOTIDE somatostatin receptor (SSR) scintigraphy has been used to diagnose gastroenteropancreatic neuroendocrine neoplasms (GEP-NEN). Keywords: gastroenteropancreatic neuroendocrine neoplasms.
Aim(s): To evaluate the value of neuroendocrine biomarkers in the diagnosis of GEP-NEN and the relationship between 99mTc-HYNIC-TYR3-OCTREOTIDE SSR scintigraphy and tumor differentiation. Materials and Methods: Seventy-seven GEP-NEN patients were included. The neuroendocrine properties of the tumors were determined by IHC of Syn and CgA. Plasma neurospecific enolase (NSE) levels were measured, and all the patients had 99mTc-HYNIC-TYR3-OCTREOTIDE somatostatin receptor scintigraphy results. Results: Syn and CgA positive rates were 90.4% (66/73) and 65.7% (44/67), and Syn was statistically higher than CgA (P < 0.01). Plasma NSE levels were significantly higher in 70.5% (31/44) GEP-NEN patients (16.02 ng/ml–5713 ng/ml), 64.9% (50/77) GEP-NEN represented avid uptake in SSR scintigraphy. The imaging positive rate in well-differentiated group (G1/G2) was 85.7% (24/28), which was 51.4% (18/35) in the poorly differentiated group (G3) and was 0% (0/6) in mixed adenoneuroendocrine carcinoma (MANEC) group. Poorly differentiated GEP-NEN had a lower imaging positive rate (P < 0.01). Conclusion: Syn positive was higher than CgA. Plasma NSE level became another useful marker in GEP-NEN. SSR scintigraphy results were correlated with tumor differentiation. Keywords: gastroenteropancreatic neuroendocrine neoplasm, nse, ssr scintigraphy.

Medical Treatment – Chemotherapy

J1
Topotecan in Pretreated Metastatic Neuroendocrine Carcinoma

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Introduction: Therapeutic options for metastatic poorly differentiated neuroendocrine carcinoma (NEC) after prior platinum-based chemotherapy are limited. Topotecan is an approved second line chemotherapy for small cell lung cancer (SCLC). NEC is often considered to show a biological behavior similar to SCLC. Aim(s): To analyze the efficacy of topotecan in pretreated metastatic NEC patients. Materials and Methods: We performed a retrospective analysis of all patients treated with topotecan for metastatic NEC at our center between April 2008 and July 2013 (n = 16). Results: All patients received at least a platinum and etoposide containing regimen as prior chemotherapy. Median proliferation rate (Ki-67) was 80%. As best response to topotecan, three patients showed stable disease, one patient a partial remission, resulting in a disease control rate of 25%. Of the remaining 12 patients, five (31%) showed progressive disease, four (25%) died before radiologic response could be evaluated and three (19%) were lost to follow-up. Median progression-free and overall survival after start of topotecan was 2.0 and 3.1 months, respectively. Conclusion: Topotecan shows only mild antitumor activity in metastatic NEC. Disease control rate is lower than reported for SCLC. It is also lower than for other chemotherapy regimens studied in NEC like temozolomide containing schemes and FOLFIRI. However, the NECs in our analysis had a higher median proliferation rate than in these previous studies. Keywords: neuroendocrine carcinoma, chemotherapy, topotecan.

J2
Ki-67 Index as a Biomarker of Response to Cytotoxic Chemotherapy

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Introduction: Chemotherapy (CT) is widely used for neuroendocrine tumors (NET) but there are no validated biomarkers to predict response. The Ki-67 proliferation index has been proposed as a means of selecting patients for CT but robust data are lacking. Aim(s): We investigated the relationship between response and Ki-67, and sought to define a cut-off for patient stratification. Materials and Methods: We reviewed data from 152 patients treated with 5-fluorouracil, cisplatin and streptozocin (FCiSt). Tumors were graded according to Ki-67 index: low ≤5%, intermediate 5–20% and high >20%. Radiological response was assessed by RECIST and survival calculated from start of chemotherapy to death. To explore the utility of Ki-67 as a marker of response, we calculated the likelihood ratio and performed receiver operating characteristic (ROC) analysis. Results: One-hundred and sixteen patients were evaluable for both response and Ki-67; 23% had low Ki-67, 34% intermediate and 43% high; 50% were pancreatic NETs (PNET). Median overall survival was 21.2 months. Overall response rate to CT was 26% (30% in PNET v. 22% in non-PNET). Response rate increased with grade; 19% in low grade, 28% in intermediate and 39% in high (p = 0.06). However, maximum likelihood ratio was 1.5 at Ki-67=35%, and the area under the ROC curve was 0.60. As previously reported, a high Ki-67 was an adverse prognostic factor for overall survival. Conclusion: Ki-67 alone is an unreliable means to select patients for CT. Improved methods to stratify patients for systemic therapy are required. Keywords: chemotherapy, ki-67.
**J3**

**Streptozocin/5-Fluorouracil (STZ/5FU) Chemotherapy in G1-G2 Pancreatic Neuroendocrine Tumors (pNETs): Single Institution Experience**

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**Introduction:** STZ is the only FDA-approved antihistatic drug for well-/moderately-differentiated NETs. To date, no clear therapeutic sequence is defined for medical treatment of advanced pNETs. **Aim(s):** To evaluate STZ/5FU chemotherapy regimen in selected pNETs. **Materials and Methods:** Progressive and advanced G1-G2 pNETs patients were considered eligible for treatment. STZ/5FU schedule was: 500 mg/m² for both drugs day 1–5 every six weeks. Four to six cycles were planned. The patients were considered evaluable for response once undergoing a minimum of two cycles. Response to treatment was evaluated every two cycles, according to RECIST v1.1 criteria. Toxicity was evaluated according to CTC v4.0. **Results:** In the last 12 months, we enrolled seven patients with advanced G1-G2 pNETs. Main clinical features of the patients enrolled are: no pretreatment other than SSA, FDG-PET positivity in 86% of them, progressive disease under SSA. Response Rate (RR) was 57%. Median PFS and OS are not yet reached. Fourteen per cent of G3-G4 hematological toxicity was observed. **Conclusion:** In SSA-only pretreated, FDG-PET positive-enriched, G1-G2 pNETs patients, STZ/5FU is an effective cytoreductive therapeutic option. STZ/5FU could be a reasonable first line option in FDG-positive patients with symptomatic disease burden or whenever significant tumor shrinkage is pursued. **Keywords:** streptozocin, 5-fluorouracil, pNETs.

**J4**

**STZ-Based Chemotherapy is Associated with Durable Response Rate in Pancreatic NET as 1st or 2nd Line Treatment**

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**Introduction:** The role of chemotherapy for pancreatic neuroendocrine tumors (pNETs) is controversially discussed. Objective response rates (RR) with streptozocin (STZ)-based chemotherapy are variable. Novel targeted drugs have recently been approved. **Aim(s):** To evaluate the efficacy of STZ+5-Fluorouracil (5-FU) in a large pNET cohort. **Materials and Methods:** Data from 97 patients (pts) with advanced pNET were analysed retrospectively. Imaging was reviewed (RECIST criteria) by an experienced radiologist. **Results:** Median age at start of therapy was 60.2 years. 77.3% were non-functional pNETs. 12.4% had G1, 78.4% G2 and 6.2% G3 neoplasms. Mean number of therapy cycles was six. Treatment was discontinued due to toxicity in 16 pts. Objective RR was 44.3%. 39.2% showed stable disease, 16.5% disease progression as best response. In Kaplan-Meier analysis, median time to tumor progression (TTP) was 19.6 months (95% CI, 13.7–25.5) and overall survival 54.8 months (95% CI, 32.8–76.7). Fifty per cent had SD at 1-year-follow up (n = 78). In multivariate Cox regression including Ki-67, liver tumor burden and therapy line only Ki-67 (≥15%) was a significant predictor for TTP (HR, 3.4; P < 0.001). **Conclusion:** STZ+5-FU was associated with a considerable objective RR, which is higher than those observed with targeted drugs. Efficacy of treatment was more durable in pts with Ki-67 index ≤15%. These findings along with good tolerability strengthen the value of this chemotherapy for the management of pts with unresectable pNETs. **Keywords:** pancreatic net, ki-67, chemotherapy, streptozocin.

**J5**

**Experience of Temozolomide Mono- and Combination Therapy in Advanced Neuroendocrine Tumors (NETs) in Russia**

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**Introduction:** Temozolomide (T) demonstrated promising activity in NETs in numerous phase 2 studies worldwide. But there is not enough data about its efficacy in the Russian population. **Aim(s):** To evaluate efficacy and tolerability of T mono- and combination therapy in advanced NETs. **Materials and Methods:** Twenty-seven patients (pts) with advanced NETs (10 pancreatic NETs, seven GI NETs, three bronchial carcinoids, two kidney NETs, one mediastinal and three NETs without primary) were treated with T in monotherapy (five pts) or combination regimens, which included T+nitrosourea derivatives (10 pts), T+irinotecan (seven pts), T+capecitabine (four pts) and combination with cisplatin (one pt). Primary tumor site was resected in 14 patients. Most of the patients received long-acting octreotide. Ten pts were chemotherapy-naive. The median time from initial diagnosis till treatment initiation was seven months. The mean age was 57 years (26–78), 12 females, 15 males. Tumor differentiation was as follows: Grade 1 in one patient (3.7%), Grade 2 in 24 patients (89%) and Grade 3 in two patients (7.3%). **Results:** Main toxicity events included thrombocytopenia (three pts), fatigue (three pts), nausea/vomiting (four pts). T dose was reduced in two pts. Median PFS and OS are not yet reached. Forty per cent of pts had SD at 1-year-follow up (n = 78). In multivariate Cox regression including Ki-67, liver tumor burden and therapy line only Ki-67 (≥15%) was a significant predictor for TTP (HR, 3.4; P < 0.001). Conclusion: STZ+5-FU was associated with a considerable objective RR, which is higher than those observed with targeted drugs. Efficacy of treatment was more durable in pts with Ki-67 index ≤15%. These findings along with good tolerability strengthen the value of this chemotherapy for the management of pts with unresectable pNETs. **Keywords:** streptozocin, 5-fluorouracil, pNETs.
**J6**

5-FU-Based Chemotherapy in Pancreatic Neuroendocrine Neoplasms: Predictive and Prognostic Markers for Treatment and Survival

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**Introduction:** Chemotherapy with 5-FU and Streptozotocin (STZ) represents a standard of care for patients with metastatic pancreatic neuroendocrine neoplasms (PNENs). However, data to identify predictive and prognostic markers are limited. **Aim(s):** Evaluation of clinicopathological characteristics and possible predictive and prognostic markers of patients with PNENs. **Materials and Methods:** We retrospectively analyzed 41 patients with PNEN who were treated at the University Hospital Marburg between 2000 and 2013. Dihydropyrimidin-Dehydrogenase (DPD) and Thymidylate-Synthase (TS) expression was correlated with treatment response in 19 patients who had available tumor tissue and response data. The median overall survival (OS) and progression-free survival (PFS) were calculated using Kaplan-Meier and Cox regression methods, respectively. **Results:** The median OS in patients receiving STZ/5-FU/Doc was 28 months with a median PFS of 15 months. Objective response rate (ORR) and disease control rate (DCR) were 34% and 72%, respectively. Univariate analysis revealed Ki-67 >10%, primary tumor resection and PS as independent risk factors for shorter OS. Furthermore, Ki-67 and PS were seen as independent risk factors for shorter PFS, as well as biochemical response, DCR and radiological response as independent risk factors for longer PFS. **Conclusion:** STZ-based chemotherapy is an effective treatment option in patients with well-differentiated neuroendocrine neoplasms. Ki-67 >10% and PS ≥ 1 were independent prognostic markers of OS and PFS in these population. **Keywords:** streptozotocin, nen, 5-fluourouracil, doc.

**J7**

Streptozotocin-Based Chemotherapy is Still Alive in Patients with Neuroendocrine Neoplasms: Predictive and Prognostic Markers for Treatment und Survival


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**Introduction:** Chemotherapy with Streptozotocin (STZ) and 5-FU or Doxorubicin (Doc) represents a standard of care for patients with well-differentiated metastatic neuroendocrine neoplasms, especially for the pancreas (PNENs). However, data to identify predictive and prognostic markers are limited. **Aim(s):** Evaluation of clinicopathological characteristics and possible predictive and prognostic markers of patients receiving this combination. **Materials and Methods:** We retrospectively analyzed 77 patients who were treated at the University Hospital Marburg between 1995 and 2013. The median overall survival (OS) and progression-free survival (PFS) were calculated using Kaplan-Meier and Cox regression methods, respectively. **Results:** The median OS in patients receiving STZ/5-FU/Doc was 28 months with a median PFS of 15 months. Objective response rate (ORR) and disease control rate (DCR) were 34% and 72%, respectively. Univariate analysis revealed Ki-67 >10%, primary tumor resection and PS as independent risk factors for shorter OS. Furthermore, Ki-67 and PS were seen as independent risk factors for shorter PFS, as well as biochemical response, DCR and radiological response as independent risk factors for longer PFS. **Conclusion:** STZ-based chemotherapy is an effective treatment option in patients with well-differentiated neuroendocrine neoplasms. Ki-67 >10% and PS ≥ 1 were independent prognostic markers of OS and PFS in these population. **Keywords:** streptozotocin, nen, 5-fluourouracil, doc.


**J9**

**Capcitabine (Cp) and Somatostatine Analog (SSA) Suitable Treatment for Progressing G1-G2 Neuroendocrine Tumors (WD NET)**


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**Introduction:** Results from phase II and non-randomized trials with metronomic 5-FU in combination with SSA in well-differentiated (WD) NET are limited, and considered investigational. **Aim(s):** We evaluate our experience in metastatic WD NET patients (pts) treated with Cp and SSA metronomic regimen. **Materials and Methods:** From October 2005 to December 2013, 30 WD NET pts with progressive disease after failure of SSA and/or CT, Everolimus, PRRT were treated with Cp and SSA. The primary tumor site was pancreas (P) in 12 pts, gastrointestinal tract (GI) in eight pts, lung (L) in five pts, and unknown (U) in five pts. Pts received Cp 1000 mg/mq/bidie os days 1-14 and SSA (octreotide LAR 30 mg 1 fl im q28 or lanreotide LAR 120 mg 1 fl im q28). Treatment efficacy was evaluated by response rate according to RECIST criteria and in terms of PFS. Safety and tolerability were evaluated by assessing the onset of adverse events and treatment feasibility. **Results:** One (3%) pt had a PR, 16 pts (54%) showed SD, 13 (43%) pts showed PD; median PFS was 4.9 months (1.43–42.7+), three pts are still in treatment. In GI-NET median PFS was 15.7 m (1.96–42.7+), in P NET was 4.55 m (1.96–32.2), in L NET was 4.16 m (1.43–6.6), in U NET was 4.53 m (1.5–12.8). At a median follow-up of 50 m, median OS was 4.53 m (1.5–12.8). Among the 27 cases included in this study, no difference in basal CgA level was observed in terms of gender, primary tumor site, tumor grade (WHO classification), liver metastasis, number of metastatic site, and line of chemotherapy with serial CgA monitoring. Overall response rate (RR) by RECIST criteria was six of 27 cases (22.2%) and biochemical RR eight of 27 cases (29.6%). The concordance rates of RR between RECIST criteria and biochemical criteria were 70%. There was a significant difference for progression-free survival (PFS) between responders and non-responders for biochemical criteria (p = 0.05). **Conclusion:** This study revealed that the changes in CgA level were associated with in a 2-part study (retrospective and prospective part). **Materials and Methods:** Patients with GEP-NETS treated with STZ were included. The primary endpoint was the percentage of patients who had a decrease of estimated Glomerular Filtration Rate (eGFR) of at least 25% (MDRD formula) compared to baseline. We report here the results of the retrospective part of the study. **Results:** Among 110 patients included, 108 were evaluable (mean age 56.3±12.3 yrs, 65% men, mean eGFR 94±25 ml/min, 65% locally advanced tumor, 93% metastatic). Ninety-seven patients received IV STZ only, 10 intra-arterial STZ (chemoembolisation) and one had both. Median number of cycles was four (1–17) for IV STZ. Mean eGFR remained roughly stable during treatment. Thirty-eight (37.6%) and 14 (17%) had eGFR decrease ≥25% compared to baseline respectively at some point during therapy and at the end of treatment. None had grade 4 renal toxicity, no patient required haemodialysis. Age, baseline eGFR and cumulative dose of STZ were not associated with renal impairment in univariate analysis. Disease control was obtained in 78% of patients, and two patients died during the study. **Conclusion:** Renal function remained stable under STZ therapy and renal toxicity was not a major cause of treatment discontinuation. **Keywords:** digestible neuroendocrine tumors, streptozotocin, nephrotoxicity, chemotherapy.

**J10**

**Renal Effects of Streptozocin: Preliminary Results of the STREPTOTOX Study**

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**Introduction:** Based on old studies, Streptozocin (STZ) is known to have some renal toxicity. **Aim(s):** We investigated the renal effects of STZ with current dosing regimens and renal surveillance

**J11**

**The Role of Plasma Chromogranin A as Assessment of Treatment Response in Grade 1–3 Non-Functioning Gastroenteropancreatic (GEP) Neuroendocrine Tumors**

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**Introduction:** Chromogranin A (CgA) is considered to be of value not only in diagnosis but also in monitoring the disease response to treatment. However, only a few studies have been published on this issue. **Aim(s):** We investigated to evaluate whether biochemical response using plasma CgA level is in reliable concordance with the clinical response in grade 1–3 nonfunctioning gastroenteropancreatic neuroendocrine tumors (GEP-NETS) irrespective of chemotherapeutic agents. **Materials and Methods:** A total of 27 cases in 18 patients were enrolled in this study between March 2011 and September 2013. Twenty-seven cases were evaluated clinically and radiologically while serial CgA tests were also estimated during treatment. **Results:** Among the 27 cases included in this study, no difference in basal CgA level was observed in terms of gender, primary tumor site, tumor grade (WHO classification), liver metastasis, number of metastatic site, and line of chemotherapy with serial CgA monitoring. Overall response rate (RR) by RECIST criteria was six of 27 cases (22.2%) and biochemical RR eight of 27 cases (29.6%). The concordance rates of RR between RECIST criteria and biochemical criteria were 70%. There was a significant difference for progression-free survival (PFS) between responders and non-responders for biochemical criteria (p = 0.05). **Conclusion:** This study revealed that the changes in CgA level were associated with...
treatment responses and tumor progression in grade 1–3 GEP-NETs irrespective of chemotherapeutic agents. **Keywords:** cga, gastroenteropancreatic neuroendocrine tumor.

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**J12**

**PET+10 Study: Efficacy of Platin/Etoposide Combination in Well-Differentiated Pancreatic Neuroendocrine Tumors with Ki-67 ≥10%**

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**Introduction:** Platin-etoposide (PE), the gold standard regimen for poorly differentiated neuroendocrine carcinomas, might be effective in well-differentiated pancreatic neuroendocrine tumors (WD-PNETs) with a high Ki-67 proliferation index. **Aim(s):** To compare the efficacy of PE to other regimens, especially doxorubicin/streptozocin (D-STZ) in patients with Ki-67 ≥10%. **Materials and Methods:** Retrospective, multicenter study, within the French study group of endocrine tumors (GTE). All patients with proven WD-PNETs and Ki-67 ≥10% treated by chemotherapy between 2000 and 2012 were included. Survival curves (progression-free survival: PFS and overall survival: OS) were estimated by the Kaplan-Meier method and compared using log-rank tests (PE v. other regimens). **Results:** Eighty-nine patients (48 men), mean age 54, were included; 73 had metastases (82%), including 71 with liver metastases. Ki-67 ranged from 10 to 20% in 72% of cases. Frontline chemotherapy regimens were: PE (n = 18), D-STZ (n = 36), 5FU-STZ (n = 8) and 5FU-epiadiamycin-dacarbazine (n = 4). There was no significant difference in age, sex, presence of metastases at diagnosis, surgery of primary tumor and Ki-67 index across groups (PE v. other regimens). Median PFS was 6.7 months in the PE group v. 7.5 months with other associations (p = 0.79). Median OS was 26.9 and 32.2 years, respectively (p = 0.50). **Conclusion:** These data show no survival difference between PE and other chemotherapy associations, especially D-STZ regimen, in advanced WD-PNETs with Ki-67 ≥10%. **Keywords:** platin/etoposide, pnets, ki-67.

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**Medical Treatment – SMS Analogues, Interferon**

**K1**

**Somatostatin Analogs (SSA) in Patients with Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia: A Case Series**

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**Introduction:** Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare lung disease associated with proliferation of neuroendocrine cells in the lung. Although typically con-
sidered a benign condition, DIPNECH causes chronic, progressive cough and dyspnea. There have been no treatments described in the literature. **Aim(s):** To assess changes in symptoms and pulmonary function tests (PFTs) in response to somatostatin analog (SSA) treatment. **Materials and Methods:** Patients with DIPNECH were treated with SSAs at the Moffitt and Hadassah Medical Centers. Sixteen of the patients were treated with depot octreotide (LAN) or lanreotide (LAN) at the Moffitt and Hadassah Medical Centers. The charts were reviewed to assess changes in symptoms and PFTs. **Results:** Eighteen patient charts were reviewed which included 17 females and one male, ages 54–78, who presented with clinicopathologic evidence of DIPNECH. Sixteen of the patients complained of chronic cough and dyspnea; two were asymptomatic. Most of the patients had received previous treatment with steroids and/or inhalers without symptomatic improvement. The patients were started on treatment with depot octreotide or lanreotide every four weeks. Since initiation of therapy, fourteen of the sixteen symptomatic patients have noticed a subjective improvement in their cough and dyspnea. Additionally, seven of the eight patients in whom PFTs were checked showed improvement in FEV1. **Conclusion:** SSAs improve chronic respiratory symptoms and PFTs in patients with DIPNECH. **Keywords:** dipnech, octreotide, lanreotide.

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**K2**

**Progression-Free Survival (PFS) and Tumor Growth with Lanreotide Autogel (LAN) in Patients (Pts) with Enteropancreatic NETs: Results from CLARINET, a Randomized, Double-Blind, Placebo (Pbo)-Controlled Study**

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**Introduction:** Prospective data on antiproliferative effects of somatostatin analogs are lacking in grade 2 and non-midgut tumors. **Aim(s):** To evaluate the antiproliferative efficacy and tolerability of Pasireotide LAR as a first-line agent in low-intermediate grade NETs. **Materials and Methods:** We performed a phase II trial of first-line pasireotide LAR 60 mg in patients with metastatic G1-G2 NETs. Prior systemic therapy, including octreotide and lanreotide, was not permitted. The primary endpoint was PFS. SSTR subtype analysis was performed on archival tissue. **Results:** Twenty-nine patients were enrolled, of whom 28 patients were assessable for response. Primary sites included small intestine (14 pts), pancreas (6), rectum (2), unknown (4) and other (3). Thirteen patients had G1 and 16 patients had G2 tumors. Best response was stable disease in 17 patients (60%), progressive disease in 10 patients (36%) and partial response in one patient (4%). Median PFS was 12.2 months (95% CI 7.7–17.5). Although well tolerated, pasireotide treatment was associated with a 79% rate of hyperglycemia. Four patients (14%) developed grade 3 hyperglycemia. Six patients were started on insulin during the trial period, and at least two have remained on long-term insulin therapy after discontinuation of pasireotide. **Conclusion:** Although the median PFS of 12.2 months in a heterogeneous population of NET patients is encouraging, the high rate of hyperglycemia requiring intervention represents a significant concern. **Keywords:** net, pasireotide, first-line.

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**K3**

**Phase II Clinical Trial of Pasireotide LAR in Patients with Metastatic Neuroendocrine Tumors**

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**Introduction:** Pasireotide LAR is a novel SSA with avid binding to SSTR 1, 2, 3 and 5. It has never been investigated in treatment-naive patients. **Aim(s):** To evaluate the antiproliferative efficacy and tolerability of Pasireotide LAR as a first-line agent in low-intermediate grade NETs. **Materials and Methods:** We performed a phase II trial of first-line pasireotide LAR 60 mg in patients with metastatic G1-G2 NETs. Prior systemic therapy, including octreotide and lanreotide, was not permitted. The primary endpoint was PFS. SSTR subtype analysis was performed on archival tissue. **Results:** Twenty-nine patients were enrolled, of whom 28 patients were assessable for response. Primary sites included small intestine (14 pts), pancreas (6), rectum (2), unknown (4) and other (3). Thirteen patients had G1 and 16 patients had G2 tumors. Best response was stable disease in 17 patients (60%), progressive disease in 10 patients (36%) and partial response in one patient (4%). Median PFS was 12.2 months (95% CI 7.7–17.5). Although well tolerated, pasireotide treatment was associated with a 79% rate of hyperglycemia. Four patients (14%) developed grade 3 hyperglycemia. Six patients were started on insulin during the trial period, and at least two have remained on long-term insulin therapy after discontinuation of pasireotide. **Conclusion:** Although the median PFS of 12.2 months in a heterogeneous population of NET patients is encouraging, the high rate of hyperglycemia requiring intervention represents a significant concern. **Keywords:** net, pasireotide, first-line.
Anti-Tumor Efficacy of Somatostatin Analogues (SSAs) in Patients with Neuroendocrine Tumors (NETs) According to Ki-67 Score: A Multicentric Study from ELIOS (Educational Learning Investigational Observational Study)


Introduction: SSAs have been demonstrated to have antiproliferative effects in ileal NETs. The 2010 WHO NET classification provides a grading score which can be helpful in predicting tumor response to SSA. Aim(s): To evaluate the efficacy of long-acting SSA in NET pts according to Ki-67 score. Materials and Methods: An observational Italian multicentric study was designed to collect data on NET pts under treatment with SSA. The observational data were collected through an e-CRF and stored in a centralized computer database. Both retrospective data of pts in treatment with SSA from 2005 and prospective data of pts treated with SSA from March 2012 to November 2012 were included. Study population included 280 pts who have had a histological diagnosis of NET (77 thoracic, 80 pancreatic, 83 gastro-intestinal, 40 unknown primary tumors). Among these, 134 have been treated with octreotide LAR or lanreotide autogel. These form the basis of the statistical analysis. Results: An objective tumor response was observed in 13% of patients, 33% in G1-G2 vs. 20% in G3. Objective tumor response was significantly higher in G1 (18%) than in G2 (11%). Objective tumor response was significantly different between G1 and G2. However, clinical benefit (including both objective response and stability) was significantly higher in G1 than G2 (p < 0.05), as well as in GEP than in either thoracic or unknown primary NETs (p < 0.05). Conclusion: Therapy with SSA is a remarkable antiproliferative therapeutic option not only in NET G1 but also in NET G2. Keywords: net, ssa, g1, g2, who classification.

Somatostatin Analogues for Preventing Carcinoid Crisis

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Introduction: Carcinoid crisis is a life-threatening syndrome of neuroendocrine tumors (NETs) and is characterized by dramatic blood pressure fluctuation, arrhythmias, and bronchospasm. Somatostatin analogues (SSTA) have been recommended for prophylactic administration before provocative procedures. Aim(s): To review efficacy of SSTA for preventing carcinoid crisis. Materials and Methods: PubMed, Cochrane Library, EMBASE and Chinese databases (1952–2013) were searched using the terms ‘carcinoid crisis’; ‘somatostatin’; ‘octreotide’; ‘lanreotide’ and ‘pasireotide’. Results: Ninety-one unique patients (54% male, age 10–84 y, median 50 y) were identified. The most common primary sites of NETs for carcinoid crisis were small intestine and respiratory tract. Carcinoid crisis without liver metastasis occurred in 9.9% of cases. The triggering factors for carcinoid crisis included anesthesia/surgery (54.9%), interventional therapy (16.5%), radionuclide therapy (7.7%), non-invasive examination (6.6%), spontaneous (5.5%), biopsy (4.4%) and medication (4.4%). Carcinoid crisis appeared without previous carcinoid syndrome nor elevation of 5-hydroxyindoleacetic acid (5-HIAA) in 6.6%. Carcinoid crisis occurred without previous carcinoid syndrome nor elevation of 5-hydroxyindoleacetic acid (5-HIAA) in 6.6%, but in 91% had previously had a carcinoid crisis. Methods: Supported by Ipsen. Keywords: carcinoid crisis, neuroendocrine tumors, somatostatin.

ELECT: A Phase 3 Study of Efficacy and Safety of Lanreotide Autogel (LAN) Treatment for Carcinoid Syndrome (CS) in Patients (Pts) with Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

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Methods: Eligible pts had histologically-confirmed NET and a history of CS, and were SSA naïve or responsive to octreotide LAR ≤30 mg/4 wks or short-acting SC ≤600 µg/day. Design: a 16 wk randomized double-blind phase (LAN 120 mg [n = 59] v. placebo [n = 56] every 4 wks), and a 32 wk open-label LAN extension. Pts had access to octreotide SC as rescue for breakthrough symptoms. Primary endpoint: % of days rescue used during double-blind phase. Study was designed to have 90% power to detect a 30% treatment difference. Double-blind phase results only are presented. Results: Of the study population, 83 (72%) had symptoms for ≥1 yr, and 51 (44%) had no prior SSA use. Mean [95% CI] % of days rescue medication use was significantly lower with LAN (34% [25.42%]) v. placebo (49% [40.57%]), absolute difference –15% (~27–3%), p = 0.02; however, the pre-defined difference was not met. Complete/partial success (<3 days use) rather than failure (>3 days use) was more likely with LAN than placebo (OR 2.4; 95% CI 1.1–5.3; p = 0.04). Treatment related AEs: 15 (26%) LAN pts v. 11 (19%) placebo pts; few were serious (0 vs. 1 [2%]) or led to study withdrawal (0 vs. 1 [2%]); and most were GI disorders (9 [16%] v. 5 [9%]). Conclusion: LAN significantly reduced need for short-acting SSA use with a favorable safety/tolerability profile, confirming its positive benefit-risk profile. Supported by Ipsen. Keywords: symptom control.
**K7**

**Somatostatin Analogues for Carcinoid Syndrome**

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**Introduction:** Carcinoid syndrome is a significant clinical problem in neuroendocrine tumors (NETs). Somatostatin analogues (SSA) have been the mainstay management for carcinoid syndrome. **Aim(s):** To assess the efficacy of SSA for carcinoid syndrome. **Materials and Methods:** The Cochrane Library, MEDLINE, EMBASE, Chinese Biomedical Database, and China National Knowledge Infrastructure database were searched until September 2013 for identifying the randomized trials. **Results:** A total of 77 patients were included. There was a statistically significant benefit of octreotide compared to placebo in controlling flush (Mean difference (MD) –12.00; 95% CI –14.14 to –9.86) and diarrhea (MD –3.00; 95% CI –5.74 to –0.26). No difference between octreotide LAR and placebo for flush control (RR 0.41; 95% CI 0.15 to 1.09) and for diarrhea (RR 0.78; 95% CI 0.40 to 1.48) were observed. There was no statistically significant improvement of using octreotide v. lanreotide for flush control (RR 0.40; 95% CI 0.15 to 1.09) and for diarrhea (RR 0.78; 95% CI 0.41 to 1.48) were observed. There was no statistically significant improvement of using using octreotide v. lanreotide for flush control (RR 0.90; 95% CI 0.55 to 1.49), for diarrhea (RR 2.5; 95% CI 0.54 to 11.54) and for biochemical response (MD –3.00; 95% CI –52.97 to 46.97). **Conclusion:** Octreotide is effective for carcinoid syndrome. Octreotide LAR is not useful in the complete remission of flush and diarrhea for treatment-naive patients. No difference was revealed between octreotide and lanreotide. There is no evidence from randomized clinical trials comparing other forms of SSA. **Keywords:** carcinoid syndrome, neuroendocrine tumors, somatostatin analogues.

**K8**

**Efficacy of Lanreotide Autogel in MEN1-Related Gastrinoma: A Case Series**

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**Introduction:** GEP NETs, especially gastrinomas, occur in 40–70% of MEN1 patients and represent the main cause of death in these patients. **Aim(s):** To investigate the efficacy of lanreotide autogel (ATG) in the treatment of MEN1-related gastrinomas. **Materials and Methods:** We report a monocentric series of seven MEN1 patients (3 M, 4 F) treated with lanreotide ATG (120 mg/4 weeks) for a mean period of 62.1 months. Plasma gastrin levels have been measured at diagnosis, three months after starting lanreotide and then every six months. Five of the seven patients underwent surgery at least three months after starting lanreotide treatment, while two patients refused surgical treatment. **Results:** Mean plasma gastrin levels at diagnosis were 5562 pg/ml (1300–17178 pg/ml; n.v. 30–115) and fell, after three months of treatment, to 117.1 pg/ml (53–241 pg/ml; mean reduction 78.9%). Five patients underwent surgery and three of these had persistent hypergastrinemia. In these patients, the treatment with lanreotide was resumed with normalization of gastrin plasma levels and disease stabilization. Two patients refused surgery: during follow up gastrin levels remained controlled with no evidence of disease progression. **Conclusion:** Lanreotide ATG proved efficacy in the biochemical control of hypergastrinemia with normalization of plasma gastrin levels in 70% of patients and a mean reduction of 78.9% after the first three months of treatment. Moreover, lanreotide demonstrated efficacy in the long-term control of disease and allowed tumor stabilization in all patients. **Keywords:** men1, ssa, gastrin.

**K9**

**Association between Dose of Octreotide and Tumor Control in Gastroenteropancreatic Neuroendocrine Tumors**

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**Introduction:** Gastroenteropancreatic neuroendocrine tumors (NETs) represent a heterogeneous group of tumors. Octreotide is used in the symptom control of NETs. The PROMID study demonstrated a benefit of octreotide on disease stabilization in midgut NETs, but a survival analysis was not possible due to insufficient events. **Aim(s):** To determine if dose of octreotide correlates with outcomes. **Materials and Methods:** We reviewed all patients who were diagnosed between 1987–2013 and treated with octreotide at the BC Cancer Agency. We compared overall survival in patients who received low v. high dose octreotide. **Results:** A total of 170 patients were included. The mean age was 60 years. Tumors commonly originated from the midgut (47%) or pancreas (21%). In this cohort, 81% had metastatic disease among whom 87% had hepatic involvement. Carcinoid syndrome was prevalent with 72% of patients presenting with diarrhea, flushing, or tricuspid regurgitation. Octreotide was initiated with the intent of symptom management (71%), disease stabilization (23%), or tumor marker control (6%). The mean dose per 28-day cycle was 27 mg. After accounting for confounders, patients who received high dose (>27 mg) experienced significantly longer median survival when compared to those who received low dose (<27 mg) octreotide (82 v.39 months, respectively, p < 0.0001). **Conclusion:** Our findings suggest that octreotide may confer survival benefits. Further prospective studies are needed to validate the impact of high dose octreotide on outcomes. **Keywords:** gi, net, octreotide.
SSA Therapy for Patients with Bronchial Carcinoids (BC) in the Community Setting


Introduction: SSA show antitumoral effect in GEP-NETs in 2 phase III trials, PROMID and CLARINET. However, patients (pts) with BC were not included in these studies. Aim(s): Explore efficacy and safety of SSA in pts with BC. Materials and Methods: Retrospective analysis of 22 pts with metastatic BC treated with SSA monotherapy at seven Spanish hospitals between 2000-2013. Results: Seventy-seven per cent were females. Median Ki-67 index was 5% (1–25). Liver was the most frequently involved organ, 13 pts (59%). Octreoscan was positive in 82%. Median systemic treatment lines were three. All received SSA depot formulation monotherapy, either octreotide (9) or lanreotide (13), mainly as 1st line, 68%. Twenty-seven per cent showed clinical improvement and 78% radiological response, according to RECIST criteria and in terms of time to tumor progression (TTP). Safety and tolerability were evaluated by assessing the onset of adverse events and treatment feasibility. Results: Thirteen pts (primary tumor was lung, pancreas (p), midgut, colon, and unknown (u) respectively in 3, 3, 4, 1 and 2 pts) were treated with Octreotide Lanreotide in first line and second line. Nine pts (primary tumor was p, mi, and u respectively in 2, 4 and 3 pts) were treated with La in first line and Oc in second line. In first line treatment, considering all 22 pt, median TTP was 17.52 months (range 1.93–105.13), with 16 SD, four PR and two PD. In second line treatment, median TTP was 14.9 months (range 1.60–160.43) with 20 SD and 2 PD. Four pts are still in treatment. No pts complained of any severe adverse reactions. Conclusion: The results of our study suggest that a second SSA is effective in tumor progression control of WD NET even after first line treatment with other SSA. Keywords: octreotide, lanreotide.

Impact of Long-Acting Octreotide in Patients with Early-Stage MEN1-Related Duodeno-Pancreatic Neuroendocrine Tumors


Introduction: Somatostatin analogues (SSA) represent one of the main therapeutic options in patients affected by functioning well-differentiated neuroendocrine tumors (NETs). There are no studies specifically focusing on NETs associated with Multiple Endocrine Neoplasia type 1 (MEN1). Aim(s): To evaluate the efficacy of the long-acting SSA octreotide in MEN1 patients with early-stage duodeno-pancreatic NETs. Materials and Methods: Forty MEN1 patients were retrospectively evaluated. Twenty patients with evidence of one or more MEN1-related duodeno-pancreatic NETs <20 mm in size (age range 26–61 yrs) were treated with octreotide LAR as first-line therapy. Treatment duration ranged 12–75 months. At the baseline radiological evaluation, multiple duodeno-pancreatic NETs (range 1–8, size 3–18 mm) were detected. Results: An objective tumor response was observed in 10%, stable disease in 80% and progression of disease in 10% of cases. In six patients with abnormally increased CgA, gastrin and/or insulin serum concentrations, a significant clinical and hormonal response occurred in 100% of cases and was stable along the time. Conclusion: Therapy with SSA is highly safe and effective in patients with early-stage MEN1-related duodeno-pancreatic NETs, resulting in long-time suppression of tumor progression.

Metastatic G1-G2 Neuroendocrine Tumors (WDNET) Treated with Sequences of Different Somatostatine Analogs (SSA)-Lanreotide LAR (La), Octreotide LAR (Oc): A Single Center Experience


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Introduction: PROMID and CLARINET trials demonstrate an improvement in PFS of SSA v. placebo in WDNET. Aim(s): We evaluate retrospectively the efficacy, safety, and tolerability of the sequences of these two different SSA in WDNET observed in our Institute between 1999 and 2013. Materials and Methods: Patients (pt) affected by WD NET were given Oc 30 mg/month or La 120 mg/month by intramuscular injection as first line treatment. At disease progression, pts were given a second line treatment with the other SSA. For each line of treatment, efficacy was evaluated by response rate according to RECIST criteria and in terms of time to tumor progression (TTP). Safety and tolerability were evaluated by assessing the onset of adverse events and treatment feasibility. Results: Thirteen pts (primary tumor was lung, pancreas (p), midgut (mi), colon, and unknown (u) respectively in 3, 3, 4, 1 and 2 pts) were treated with Oc in first line and La in second line. Nine pts (primary tumor was p, mi, and u respectively in 2, 4 and 3 pts) were treated with La in first line and Oc in second line. In first line treatment, considering all 22 pt, median TTP was 17.52 months (range 1.93–105.13), with 16 SD, four PR and two PD. In second line treatment, median TTP was 14.9 months (range 1.60–160.43) with 20 SD e 2 PD. Four pts are still in treatment. No pts complained of any severe adverse reactions. Conclusion: The results of our study suggest that a second SSA is effective in tumor progression control of WD NET even after first line treatment with other SSA. Keywords: octreotide, lanreotide.
Abstracts

K13
SYMNET: A Study of Patient-Reported Outcomes (PROs) Associated with Lanreotide Autogel (LAN) for the Control of Carcinoid Syndrome (CS) Symptoms in Gastroenteropancreatic Neuroendocrine Tumor (GEP-NET) Patients (Pts)

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Introduction: Somatostatin analogs can reduce incidence/severity of CS symptoms but their impact on pt satisfaction needs further investigation. Aim(s): To assess PROs during LAN treatment of CS in NET pts. Materials and Methods: At routine visit, CS-related diarrhea pts treated with LAN for >3 mos completed PRO questionnaires on satisfaction and symptoms associated with CS control. Investigators assessed pt characteristics as predictors for satisfaction. Results: Two-hundred and seventy-three pts were enrolled (56% male, 57% aged >60 yrs, 66% small bowel primary tumors, and 80% liver metastases). Prior to study, 66% had surgery and 23% other anti-tumor therapy within 3 mos. Mean time since diagnosis was 4.4 yrs. Mean LAN treatment duration was 21.7 mos and median dose 120 mg on study day. Most pts were satisfied with diarrhea (76%) and flushing control (73%). More pts indicated no/minimal/mild diarrhea at study visit v. before treatment (75 v. 33%). Most (79%) pts reported diarrhea improved on LAN. Investigators identified clinically relevant decrease in stool frequency since treatment initiation (median: 4–2 episodes/d). Statistically significant decreases (McNemar paired tests, p < 0.001) occurred in nos. with urgency (73–41%), leakage (21–9%) and associated pain (37–4%). Predictors of satisfaction with diarrhea control were initial stool leakage and non-small bowel primary localization. Conclusion: NET pts report favorable symptom control with LAN, consistent with investigator medical assessments. Pt satisfaction with symptom control on LAN may be supported by associated factors. Keywords: pro.

K14
Efficacy of Octreotide LAR (OCT) in Patients (pts) with Advanced Neuroendocrine Tumors (NET): A Subgroup Analysis of Phase III RADIANT-2 Study with Updated Overall Survival (OS)

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Introduction: OCT has shown antitumor activity and significantly prolonged time to tumor progression vs PBO in pts with metastatic midgut NET (PROMID). Aim(s): To assess efficacy of OCT (30 mg q28d) in PBO+OCT arm of phase III RADIANT-2 study (a subgroup analysis). Materials and Methods: Progression-free survival (PFS; central review; cutoff Apr 2, 2010) and OS (cutoff Jun 13, 2013) were estimated using Kaplan-Meier method stratified by prior somatostatin analogue (SSA) use and primary tumor site. Results: Two-hundred and thirteen pts were randomized to PBO+OCT; 47 were SSA naive, 166 had prior SSA therapy. In SSA naive pts, 32% had primary foregut tumors, 51% had midgut tumors, 4% had hindgut tumors and 13% had tumors of unknown primary. Among pts with prior SSA, 10% had foregut tumors, 72% had midgut tumors, 11% had hindgut tumors and 7% had tumors of unknown primary. Median PFS (95% CI) was 13.6 (8.2–22.7) months for SSA naive pts and 11.1 (8.4–14.2) months for pts who had prior SSA. Analysis of PFS by tumor site will also be presented. Median OS (95% CI): 50.6 (36.4–68.8) months for SSA naïve pts and 33.0 (24.5–43.7) months for pts with prior SSA. Conclusion: In this subgroup analysis, OCT was associated with a somewhat longer PFS in SSA naive pts. Unlike PROMID pts, the RADIANT-2 PBO+OCT study pts all had progressive disease at baseline, and nearly half had non-midgut primary tumors. Data from present analysis offer additional evidence of the antitumor efficacy of OCT in a heterogeneous population of NET pts. Keywords: neuroendocrine tumors, octreotide lar, PFS.
Medical Treatment – Targeted Therapies

L1
Clinical Impact of Everolimus Cumulative Dose on Pancreatic Neuroendocrine Tumors (pNETs) Outcome


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Introduction: Everolimus is approved for advanced pancreatic neuroendocrine tumors (pNETs). Aim(s): To evaluate the effect of cumulative dose (CD) on survival in patients (pts) treated with everolimus for advanced pNETs. Materials and Methods: Twelve pts with advanced pNETs were treated with everolimus. Pts were stratified into two groups with CD <1500 mg (Group A) vs. CD≥1500 mg (Group B). ROC curve analysis was performed to determine the 1500 mg cut-off value. Overall survival (OS) was estimated using Kaplan-Meier method. Results: M/F was 4/8, median age was 64 years (range 47–69). Histological grading was: G1=50%, G2=50%. Groups A and B were homogeneous and the pts received everolimus for at least three months. Despite response rate and grade 3-4 toxicity was comparable in the two groups, group A experienced more dose modifications (delays or reductions according to medical decisions and pts’ will), if compared with group B. Median OS was 13.92 months in Group A while it was not reached in Group B (p = 0.033). Conclusion: To the best of our knowledge, this is the first study investigating the prognostic role of everolimus CD. This should be taken into account treating pts with advanced pNETs, thus making every effort to continue everolimus consumption in responsive pts up to at least 1500 mg, despite delays or temporary interruptions. On the basis of our findings, a national study has been started in order to confirm the results on a larger series of pts. Keywords: pancreatic neuroendocrine tumor, targeted therapy, mtor inhibitors, everolimus, cumulative dose.

L2
Predictive Factors for Progression Free Survival (PFS) in Patients with Advanced Pancreatic Neuroendocrine Tumors (PNET) Treated with Sunitinib


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Introduction: Sunitinib and everolimus were approved for treatment of progressive PNET based on phase III trial data. However, features that may influence outcome with these antitargets have not been well-established. Aim(s): To identify possible predictive factors (ECOG, Ki-67, hepatic tumor load, surgery, line of treatment) for PFS in pNET patients (pts) treated with Sunitinib. Materials and Methods: Twenty-two pts treated with Sunitinib 37.5 mg/d until progression in a single university hospital between Nov 2010 - Nov 2013 were analyzed. Pts had a metastatic, non-functioning G1-2 pNETs. Results: Pt characteristics: ECOG 2 only one pt, 58% were female and median age was 54 yo (39–69). Ki-67 were 1–2% in 36%; ≥3 in 31%; 6–10% in 18%; 11–19% in 15%. Twenty-one of 22 pts had liver metastases and 76% had low hepatic tumor load, <25%. Sixteen per cent underwent surgery and 31% had received prior systemic therapies. Disease control was 85% with objective response in 18%. Median PFS were 13 months (95% CI, 3–31). All pts continued sunitinib until progression. Dose reduction was required in 24%, due to GI toxicity in 15% and haematological toxicity in 9%. Statistical significance was obtained only for the parameter ‘line of therapy’. Thus, pts treated with sunitinib in first-line tended to have a better PFS. PFS was independent of ECOG, Ki-67, hepatic tumor load and surgery. Conclusion: These data suggest that sunitinib has a more favorable PFS when it is administered in first-line and continued until progression. Keywords: sunitinib, pancreatic neuroendocrine tumor, prior treatment, predictive factor.

L3
Systemic Therapy in Advanced Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET) and Ki Index 5–10%


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Introduction: Phase III trials of sunitinib, everolimus and octreotide lar confirmed that these drugs improved progression-free survival (PFS) in well-differentiated PNET, low/intermediate grade pNET and well-differentiated midgut NETs, respectively. CLARINET...
is the 1st phase III study that showed PFS benefit of SSA, lanreotide, in both P- and midgut NET and in Ki-67 5–10%. **Aim(s):** To assess the systemic treatment of Ki-67 5–10% metastatic GEP-NET. **Materials and Methods:** Two-hundred and seventeen pts with metastatic GEPNET were attended in a Spanish Medical Oncology Department from 2005–2012. Twenty of these 217 (9%) which had Ki-67 5–10% GEPNET were analysed. **Results:** First-line systemic therapy approaches in Ki-67 5–10% pNET were: SSA in 56%, chemotherapy (CT), streptozotocin-based regimens, in 35%, everolimus in 6% and sunitinib in 3%. From 2011, systemic treatment in PNET Ki-67 5–10% shows an increased administration of antitargets: SSA in 47%, everolimus in 29%, sunitinib in 26% and CT in 8%. Features of pts and tumors treated with SSA: ECOG 82%, median age 67 yo and low hepatic tumor load 78%. Features of those treated with antitarget: ECOG 67% median age 52 yo and high hepatic tumor load 31%. First line therapy in Ki-67 5–10% GEPNET were: SSA in 96%, everolimus in 2% and CT in 2%. **Conclusion:** Prior to 2011, SSA and from that, antitargets were most used first line systemic therapy in Ki-67 5–10% pNET in our series. Further studies should analyze the treatment sequence now that there are three effective alternatives in this setting. **Keywords:** ki-67, pancreatic neuroendocrine tumor, systemic therapy.

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**L5**

**Phase 1 Expansion Study of an Oral TORC1/TORC2 Kinase Inhibitor (CC-223) in Non-Pancreatic Neuroendocrine Tumors (NET)**


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**Introduction:** Clinical efficacy of everolimus, an allosteric TORC1-selective inhibitor, has been established in pancreatic NET. CC-223 is an ATP-competitive inhibitor of the mTOR kinase, inhibiting both TORC1 and TORC2. **Aim(s):** To evaluate clinical activity of CC-223 in NET. **Materials and Methods:** After establishing MTD, subjects with non-pancreatic NET on somatostatin analogues (SSA) and progressing within 12 months were enrolled in an expansion cohort of CC-223 at 45 mg QD in 28-day cycles. **Results:** Results for 23 subjects are reported. Sixty-one per cent had metastatic midgut NET and 13/20 had refractory carcinoid syndrome despite SSA. Related AEs were diarrhoea, fatigue and stomatitis (70% each), rash (63%), nausea (43%) and pruritus (39%). One case of serious drug-related renal insufficiency was reported. Dose reduction was required in 78% of subjects. Inhibition of TORC1 and TORC2 was confirmed in blood cells and correlated with drug exposure. Nine out of 10 subjects with carcinoid-related flushing reported improved SD and symptomatic improvement using the starting dose of 30 mg is ongoing. **Keywords:** torc-1 cc-223.
**L6**

**Real-World Study on Everolimus in Advanced, Progressive Neuroendocrine Tumors**

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**Introduction:** Everolimus (EVE) is a valid therapeutic option for neuroendocrine tumors (NETs). However, data in the ‘real-world’ setting outside regulatory trials are scant. **Aim(s):** To determine EVE tolerability and efficacy, in relationship with previous treatments, in a compassionate-use program. **Materials and Methods:** One-hundred and sixty-nine advanced progressive NETs treated with EVE evaluated: 85 pancreatic (pNETs), and 84 non-pancreatic (non-pNETs). Previous treatments were: somatostatin analogs 92.9%, PRRT 50.3%, pre-treated with PRRT and chemotherapy, a 12-fold increased risk for severe toxicity occurred in pts pre-treated with chemotherapy and PRRT. This finding prompts caution when using EVE in these pts, and suggests that it should be considered before chemotherapy and PRRT in the therapeutic algorithm of NETs. **Keywords:** everolimus, compassionate use.

**Results:** 85.2% of pts had adverse events (AEs), which were severe (Grade 3–4) in 46.1%. Most frequent severe AEs were: pneumonitis (8.3%), thrombocytopenia (7.7%), anemia (5.3%), renal failure (3.5%). In pts pre-treated with PRRT and chemotherapy, a 12-fold increased risk for severe toxicity was observed, Grade 3–4 AEs being reported in 86.8% (v. 34.3% in other pts, p < 0.0001). 63.3% of pts required temporary EVE discontinuation due to toxicity. Overall, 27.8% of patients died during a median follow-up of 12 months. Median PFS and OS were 12 months and 32 months, respectively. Similar PFS and OS were during a median follow-up of 12 months. Median PFS and OS were reported in pNETs and non-pNETs. **Conclusion:** In the ‘real-world’ setting, EVE is safe and effective for the treatment of NETs. Higher severe toxicity occurred in pts pre-treated with chemotherapy and PRRT. This finding prompts caution when using EVE in these pts, and suggests that it should be considered before chemotherapy and PRRT in the therapeutic algorithm of NETs. **Keywords:** everolimus, qol, net.

**L7**

**Health-Related Quality-of-Life (HRQoL) in Patients (pts) with Advanced Neuroendocrine Tumors (NET) Treated with Everolimus (EVE): Results from an Open-Label, Phase IIIb, Multicenter, Expanded Access Program (EAP)**

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**Introduction:** NET is associated with a considerable HRQoL burden. **Aim(s):** To assess the effect of EVE treatment on pt-reported outcomes with validated instruments. **Materials and Methods:** Pts with advanced NET (N = 246), WHO PS 0–2, treated with EVE (10 mg/d) were included in EAP until disease progression, unacceptable toxicity, discontinuation, death, until commercial availability of EVE or May 2012, whichever came first. HRQoL was assessed with EORTC QLQ-C30, EORTC QLQ-GINET21 and EQ-5D instruments at baseline, for three 28-day cycles and then at every three cycles (84-day) until end of treatment (EOT). For QLQ-C30 and QLQ-GINET21, a change of >10 points from baseline to EOT was considered clinically significant. **Results:** Pts with pancreatic NET (pNET; n = 126) had no clinically significant changes in QLQ-C30 global health status (mean [±SD] change from baseline: –3.9 [±21.0]; n = 86), functioning, or symptom scores. Pts with non-pNET (n = 120) had worsening QLQ-C30 global health status (–13.0 [±28.1]; n = 69), functioning (physical, role, social), and symptom (fatigue, pain, loss of appetite) scores. No clinically significant changes in QLQ-GINET21 scores were seen, except for body image in non-pNET pts. Overall health status on EQ-5D VAS scores remained stable in pts with pNET. Mean utility score remained unchanged at EOT compared to baseline for pNET and non-pNET pts. Safety was consistent with earlier reports. **Conclusion:** EVE maintained HRQoL in pts with pNET. Non-pNET pts had a worsening in some HRQoL scores. **Keywords:** everolimus, qol, net.
Abstracts

M2

Patient-Reported Symptom Experiences Following Participation in a Study of Telotristat Etiprate for Patients with Neuroendocrine Tumors and Diarrhea Not Adequately Controlled on Octreotide


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Introduction: Telotristat etiprate (LX1606), an oral tryptophan hydroxylase (TPH) inhibitor, was recently evaluated in a dose-escalation (DE) study in patients (pts) with carcinoid tumors and diarrhea not adequately controlled on octreotide. Aim(s): The current study was designed to characterize the symptom experiences of those pts.

Materials and Methods: Consenting pts participated in semi-structured, 1-on-1, qualitative interviews to record symptoms and the recollection of changes in symptoms experienced while participating in the DE study. After the interviews, pts completed the EORTC-QLQ-C30 and GI.NET-21 questionnaires.

Results: Among 23 pts who participated in the four-week DE study, 11 consented to the current study (LX1606 n = 9; placebo n = 2). The median time from DE study end to interview was 31 months. Four pts were receiving LX1606 as part of an open-label study at the time of their interview. Symptoms reported included: diarrhea, abdominal pain (100% each), flushing, fatigue/tiredness (82% each); >50% of pts also reported sleep interruptions, irregular heartbeat, or abdominal cramping (distinct from abdominal pain). Nine pts reported symptom changes during their participation in the dose-escalation study; all reported improvements most commonly in diarrhea (82%), abdominal pain (45%), flushing and abdominal cramping (36% each); no pts reported symptom worsening.

Conclusion: Several pts reported improvements in gastrointestinal symptoms, fatigue, and other symptoms during study participation. Keywords: carcinoid, interview, symptom improvement.
M3

Outcome of Malignant Insulinomas (MI) in the Community Setting
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Introduction: MI is a rare and difficult to handle functional pancreatic neuroendocrine tumor with a variety of therapeutic alternatives. Aim(s): To analyze the characteristics and multidisciplinary management of MI. Materials and Methods: Seventeen patients (pts) with MI attended in seven Spanish University Hospitals between 1995 and 2013 were analyzed. Results: Forty-one per cent were males. Median age was 50 yo. Most common location for primary tumor was pancreatic tail (53%) and all pts had liver metastasis. Average primary tumor size was 5.1 cm. Tumor grades were G1 (23%) and G2 (59%). Octreoscan® was positive in 88%. Forty-seven per cent underwent surgery of primary tumors and/or metastases. Other treatments included EBRT (12%), TACE (24%), RFA (6%), PRRT (12%) and liver transplantation (12%). Median systemic treatment lines were three. Sixteen pts received somatostatin analogs, with clinical improvement (CI) in 56% and radiological partial response (PR) or stabilization (SD) in 6% and 65%, respectively. Chemotherapy was indicated in 12 pts (70%) with CI in 83% and PR in 33% of pts. At least one targeted therapy was used in all pts with a 77% of CI, 23% PR and 59% SD. Diazoxide and corticosteroids were needed in 70% and 35% of pts, respectively. Median overall survival was 67.3 months. Conclusion: Several treatment options are available for MI management. A balance between antiproliferative and symptomatic therapies is essential to maintaining quality of life and survival. Well-designed clinical trials are needed to establish the best treatment sequence. Keywords: insulinoma, pnet, functional tumors.

M4

Role of Metformin on Recurrence-Free Survival (RFS) in Neuroendocrine Tumors (NET)
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Introduction: Recent data suggest metformin (Met) has antineoplastic properties in different type of cancer. Effects of Met have never been investigated in NET. Aim(s): To determine the role of Met on RFS in NET patients (pts). Materials and Methods: A retrospective analysis was conducted comparing NET pts with recent diagnosis (<1 yr) of diabetes mellitus, with HbA1c ≤7%, treated with Met (group A) to non-diabetic NET pts without Met (group B) with comparable clinical and pathological characteristics. RFS was evaluated by Kaplan-Meier analysis. Results: We analysed data from 12 pts in group A (five F, seven M; mean age 62 yrs, follow-up since diagnosis: four –173 mo and 24 pts in group B (13 F, 11 M; mean age 57 yrs, follow-up: 6–149 m). G1 and G2 NET were five and seven in group A, and 12 and 12 each in group B. Primary NET was in bronchi (one group A, two group B), gastrointestinal tract (four group A, eight group B), pancreas (seven group A, 14 group B). Five pts in group A and seven in group B had liver metastases at diagnosis. Recurrence rate was lower in group A than in group B (8% v. 42%). Median RFS was not reached in group A, it was 86 mo in group B (95% CI:19–153, p < 0.05). There were no statistically significant differences in RFS between the two groups according to grading, metastases, NET therapies, other anti-diabetic drugs in association with Met. Conclusion: Metformin therapy seems to be associated with improved RFS in diabetic NET pts. Prospective studies are needed to better define the anti-neoplastic role of metformin in NET. Keywords: prognosis, metformin, rfs, survival.

M5

Transarterial (Chemo)embolization for Patients with Liver Metastasis of Neuroendocrine Tumors
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Introduction: Neuroendocrine Tumors (NETs) are slowly growing tumors with an indolent course. NETs often present with liver metastasis, and most of these tumors are inoperable at the time of presentation. Transarterial (chemo)embolization [TA(C)E] is widely available to manage liver metastasis of NET. Aim(s): To evaluate the efficacy and adverse events in patients with NET treated with TA(C)E. Materials and Methods: Forty-three patients with metastatic neuroendocrine tumors who underwent TA(C)E between December 1999 and June 2013 in National Cancer Center Hospital and National Cancer Center Hospital East were included in this retrospective study. We assessed the tumor response, disease control rate, progression-free survival, and adverse events of TA(C)E. Results: Median age was 59 years, and 23 (53%) patients were male. ECOG PS was 0-1 in all patients. The primary cancer sites were pancreas (67%), gastrointestinal tract (26%), and unknown (7%). Response rate and disease control rate for the treated lesions by TA(C)E were 56% and 95%, respectively. Median progression-free survival (PFS) was 16.5 months. The significant correlation was not seen between baseline characteristics and median PFS. As the adverse events, liver abscesses was observed in two patients, biloma in two patients, and acute renal failure in one patient, but the other adverse events were well-tolerated. Conclusion: TA(C)E was highly effective and feasible in NET patients presented with liver metastasis. Keywords: neuroendocrine tumor, tace, tae.
M6
Complete Mesenterial Venous Obstruction – A Clinical Syndrome Unique to Neuroendocrine Neoplasms of the Small Bowel
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Introduction: Neuroendocrine neoplasms of the small bowel are mostly advanced or metastasized at diagnosis. Metastases typically occur in the mesenteric root and liver. Aim(s): We report clinical presentation and interdisciplinary management of cachexia and malnutrition caused by complete mesenteric venous occlusion due to mesenteric lymph node metastases. Materials and Methods: Between 12/2011 and 09/2012, three patients with obstructing lymph node metastases in the mesenteric root were diagnosed due to malnutrition and typical thickening of the small bowel with ascites, which was caused by dual obstruction of superior and inferior mesenteric veins without development of extra-splanchnic circulation. These patients showed no signs of liver metastases. In the same period, control patients with obstructing lymph node metastases in the mesenteric root were diagnosed due to malnutrition and typical thickening of the small bowel with ascites, which was caused by dual obstruction of superior and inferior mesenteric veins without development of extra-splanchnic circulation. These patients showed no signs of liver metastases. Results: Two male patients and one female patient were 58 years old at diagnosis. All patients were treated by peptide receptor radiotherapy in our center. Body mass index was 19.89 kg/m² at diagnosis. Interdisciplinary management included stenting of mesenteric veins, peptide receptor radiotherapy and parenteral nutrition. Sole mesenteric venous obstruction could be successfully treated by mesenteric stenting without parenteral nutrition. Conclusion: Malnutrition due to complete mesenteric venous obstruction requires multidisciplinary management. Unless weight loss is not stopped, prognosis is still grim in these patients. Keywords: net.

M7
Retrospective Study of MIBG Therapy for Phaeochromocytoma (PH) and Paraganglioma (PG): The Christie Experience
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Introduction: PH & PG are rare neuroendocrine tumors treated with MIBG but protocols are not standardized and reported results are variable. Aim(s): Outcomes after MIBG therapy vary as there is no set protocol as to the dose or number of cycles given. We report results of seven pts receiving MIBG therapy for metastatic PH/PG. Materials and Methods: Retrospectively study: seven pts receiving MIBG [M/F 6/1 median age 31 yr] with metastatic PH (n = 4) or PG (n = 3) to evaluate efficacy tolerability & overall survival. Response assessed using clinical benefit biochemical markers and radiology. Results: Median number of metastatic sites three (range 1–4) and included lymph nodes (n = 5), lung (n = 6), liver (n = 2), and bone (n = 5). Previous treatment included surgery (n = 3), chemotherapy (n = 3), and RT (n = 3). Five out of seven pts symptomatic. Four out of seven had SDHB gene mutation but RET/MEN2 and VHL mutations not identified in five cases tested. Sixteen cycles of therapy delivered (range 1–3 per pt). Median MIBG dose 5000 MBq (range 3700–7500). Five out of seven raised catecholamines before MIBG and four responded (two normalized 80% OR). Six cases had overall radiological response (87%, 2 CR, 2 PR, 2 SD & 1 PD). Five out of seven pts symptomatic. Four pt developed renal dysfunction and one had myelosuppression. Three pts alive (three died and one lost to FU). Survival from diagnosis was between 1–19 yrs and between 1–11 yrs from first MIBG therapy. It was not possible to analyze predictors of response or survival. Conclusion: MIBG therapy is relatively well-tolerated and effective. It is possible to achieve benefit even in pts with metastasis. Keywords: mibg.

M8
Phase 1 and Phase 2 Clinical Trials Investigating Targets Against the Molecular Hallmarks of Gastroenteropancreatic Neuroendocrine Tumors
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Introduction: Recently there have been many advances in the diagnosis and treatment of gastroenteropancreatic neuroendocrine tumors (GEP NETs), accompanied by significant improvements in our understanding of GEP NET biology. A number of well-established or novel molecular hallmarks are involved in GEP NET tumorigenesis and may help in identifying potential diagnostic or therapeutic targets. Aim(s): To characterize the current state-of-the-art of GEP NET clinical research, which may inform future patient care. Materials and Methods: We reviewed the current Phase 1 and Phase 2 clinical trials that investigate targets against GEP NET molecular hallmarks (www.clinicaltrials.gov). Results: We have identified 43 open trials (32 Phase 2, 5 Phase 1, 4 Phase 1/2 trials, and 2 trials without a defined phase). The majority of trials target a G-protein-coupled receptor (n = 26), alone or in combination with other molecular tar-
Effects of Sunitinib in Combination with Octreotide LAR for Patients with Advanced Pancreatic Neuroendocrine Tumor which Failed Sunitinib or Octreotide LAR Alone

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Introduction: Aim(s): To observe the efficacy and side effects of sunitinib in combination with octreotide LAR for patients with advanced pancreatic neuroendocrine tumor (pNET) which failed Sunitinib or octreotide LAR alone.

Materials and Methods: From May 2010 to October 2013, three patients got sunitinib 37.5 mg/d (Group A) and two patients got octreotide LAR 20 mg/4 w (Group B), respectively. After progression on single agent, the five patients got combination therapy of the two drugs. The mean age was 53.2 years (48–62 years). Four patients were male and one female. Two had G1 pNET, three had G2. Three patients had their primary tumor resected. Somatostatin receptor scintigraphy of all patients revealed tracer-uptake lesions.

Results: In group A, one patient was classified as G1 pNET and two were G2. One had PR and two had SD on sunitinib. The TTP was 3.5, 9.5 and 24.5 months. In group B, one patient revealed PR (G2 pNET), the other was SD (G1 pNET). Their TTP was 6.0 and 9.0 months, respectively. When patients got combination therapy, two patients had PR, three had SD. Their TTP were from seven months to longer than 37.5 months. Toxicities include three grade 1 hypertension, one grade 2 GI bleeding, one grade 2 rash, one grade 2 diarrhea, one grade 2 angina and one grade 2 thrombocytopenia. No more toxicities were observed when the combination therapy was given.

Conclusion: From the above experience, we could see the combination therapy had some effects on the pNET patient who failed sunitinib or octreotide LAR alone.

Keywords: pnet, sunitinib, octreotide lar, combination, efficacy.

Telotristat Etiprate (TE) in a Cohort of Carcinoid Heart Disease Patients in Two Phase 2 Trials

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Introduction: Serotonin is a key mediator of carcinoid syndrome (CS). High levels of urinary 5-hydroxyindoleacetic acid (u5-HIAA, a serotonin metabolite) have also been linked with carcinoid heart disease (CaHD). Telotristat etiprate (TE), a novel, oral inhibitor of serotonin synthesis, is in Phase 3 development for the treatment of CS. Aim(s): There is limited information on the potential benefits of serotonin reduction in patients (pts) with CaHD.

Materials and Methods: We retrospectively reviewed data on all pts who received TE in Phase 2 trials for CS. In pts with prior history of CaHD, we assessed baseline characteristics, reductions in u5-HIAA, adverse events (AEs), and procedures while on TE. Results: Five (13%) of the 38 enrolled pts had a history of CaHD and were evaluable. All had elevated baseline u5-HIAA levels (mean 144 mg/24 hrs, range 10–282), despite use of somatostatin analogs (SSAs) (5/5) and prior tumor-directed therapies (4/5). In all pts, levels of u5-HIAA decreased over time (mean maximum reduction 82%, range 78–86%). As of Oct 2013, mean duration of TE exposure was 71 wks (range: 12–164); two pts remained in the study, with >128 wks exposure at the highest dose of TE (500 mg tid), including one pt who received a pulmonary valve replacement ~ two years ago. There were four SAEs (including two heart valve surgeries), none of which were considered drug-related.

Conclusion: In five pts with CaHD, u5-HIAA levels decreased substantially while on TE. Additional studies are warranted. Keywords: carcinoid, heart disease, serotonin, telotristat.
PRRT-Ablative Therapies-Endoscopic Treatment

N1
Peptide Receptor Radionuclide Therapy for Progressive and Metastatic Neuroendocrine Tumors: Analysis of Efficacy in 1,000 Patients from a Single Center


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Introduction: Peptide receptor radionuclide therapy (PRRT) is beneficial in well-differentiated neuroendocrine tumors (NETs). Aim(s): To assess the efficacy of PRRT in NETs. Materials and Methods: Retrospective analysis was performed using a database in 1,000 patients (age 4–85 years) with metastatic and/or progressive NETs, undergoing 1–9 cycles of PRRT at our center, using Lu-177 (n = 331), Y-90 (n = 170) or both (n = 499). Median total administered activity was 17.5 GBq. They were followed up for up to 132 months after the 1st cycle of PRRT. Well-differentiated NETs (G1-2) accounted for 54%. Most patients (95.6%) had undergone at least one previous therapy (surgery 86.8%, medical therapy 55%, ablative therapy 14.2% and radiotherapy 3.4%). Results: The median overall survival (OS) of all patients from the start of PRRT was 52 months (mo). Median OS according to radionuclide used: Y-90 24 mo, Lu-177 55 mo, both 64 mo; according to the grade of tumor: G1 87 mo, G2 55 mo, G3 28 mo, unknown 50 mo; and according to origin of primary tumors: pancreas 45 mo, small intestine 77 mo, unknown primary 55 mo, lung 36 mo. Median progression-free survival (PFS) measured from the last therapy cycle was 22 mo, comparable for pancreatic (23 mo) and small intestinal (25 mo) NETs. Conclusion: PRRT lends a significant benefit in OS in metastasized and/or progressive G1-2 NETs as compared to other treatment modalities and regardless of previous therapy. Combination of Lu-177 and Y-90 (duo) based PRRT may be more effective than either radionuclide alone. Keywords: prrt.

N2
An Analysis of Toxicity after Peptide Receptor Radionuclide Therapy (PRRT) in 807 Patients: Determination of the Limited Predictive Role of Clinical Factors


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Introduction: PRRT with 90Y-octreotide (Y) and 177Lu-octreotate (Lu) is well-tolerated. Aim(s): To identify clinical parameters predictive of long-term renal and hematological toxicity. Materials and Methods: Eight-hundred and seven patients from IEO-Milan (1997–2013). Seven-hundred and ninety-three (98%) with Lu, Y or both (Lu: 34.4%, Y: 44.4%, Lu+Y: 19.5%), 2% combinations of PRRT + other agents. Follow-up: 30 months (1–180). Parameters included renal and marrow risk factors. Analysis: multiple regression, modeling. Results: Y (33.6%) and Y+Lu (23.6%) showed greater nephrotoxicity than Lu alone (13.1%, p < 0.0001). Nephrotoxicity (any grade) occurred in 279 (34.6%), only 42% modeled by clinical data (F = 73, p = 2x10–90) and was severe in 1.5%. Hb toxicity, age and hypertension were relevant. Persistent toxicity occurred in 196 (24.3%), 33% modeled by clinical data (F = 57, p = 5x10–66). Hb toxicity (co-efficient 0.16, p = 2x10–5) and Y therapy (+Lu, co-efficient 0.22–0.26, p < 0.001) were relevant. Persistent toxicity was associated with shorter PRRT (mean 387 v. 658 days, p < 0.004). MDS occurred in 2.6% (29% modeled by clinical data: F = 56, p = 5x10–58). PLT toxicity (2±1.2 v. 0.6±0.8, p < 0.0001) and longer PRRT (22.6±24 months v. 15.5±9, p = 0.01) were relevant. AL occurred in 1.1% (22% modeled by clinical data: F = 48, p = 2x10–43). Only MDS was relevant (co-efficient: 0.29, p = 4x10–42). Conclusion: PRRT with Lu is safe in ~98%. Known risk factors provide only a limited (<45%) risk estimate. Unidentified individual susceptibilities to radiation-associated disease (genetic) likely exist. Keywords: net, prrt, risk, toxicity.

N3
Delayed Haematological Toxicity in Patients Treated with 177Lu-octreotate Peptide Receptor Radiotherapy (PRRT) for Metastatic Neuroendocrine Tumors (NETs)


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Introduction: PRRT is associated with a high tumor control rate and early toxicity seems acceptable (haematological grade 3–4 toxicity: 11.3%). Long-term monitoring of haematological toxicity is unavailable. Aim(s): To evaluate delayed haematological toxicity after PRRT for metastatic NETs. Materials and Methods: Twenty
 pts treated with 177-Lu PRRT between 2005 and 2013 for a progressive metastatic digestive NET (four courses every eight weeks, 7.9 GBq/injection) had prolonged follow-up with blood cell tests. 

**Results:** Fourteen pts had been previously pretreated with alkylating agent. In four pts, PRRT was incomplete due to grade 1–4 thrombocytopenia. Delayed grade 3–4 haematological toxicity was observed in six pts (30%). This included sustained (six and 18 months, respectively) pancytopenia in two pts, myelodysplastic syndrome (MDS) at the end of treatment persisting for eight years in one pt, refractory anaemia with blast excess, MDS with monosomy seven and acute myeloid leukemia in one pt each, occurring 30–78 months after treatment. The three last patients had previously received an alkylating agent and one had tumoral bone marrow infiltration. Nine pts (45%) died during follow-up, including three from haematological complications and six from NET evolution. **Conclusion:** Sustained and/or delayed haematological toxicity is frequent and might be severe after PRRT for NET, namely in pts previously pretreated with chemotherapy. The indication and dosage of PRRT should consider age and previous treatments. Sustained monitoring of blood tests is mandatory. 

**Keywords:** metastatic net, prrt, haematological toxicity.

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**N4 Hematological Toxicity of Combined Lutetium-177 Octreotate Radiopptide-Chemotherapy of Gastroenteropancreatic Neuroendocrine Tumors Followed Long-Term**

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**Introduction:** Combination radiopptide therapy (PRRT) with radiosensitizing chemotherapy of gastroenteropancreatic neuroendocrine tumors (GEP NETs) may improve efficacy, but has the potential to increase myelotoxicity. **Aim(s):** In a prospective clinical study of GEP NET patients treated with Lutetium-177 octreotate PRRT in combination with capecitabine and temozolomide, we characterized the incidence and degree of hematological toxicity. 

**Materials and Methods:** Well-differentiated progressive metastatic GEP-NETS in 65 patients were treated with four cycles of 7.8 GBq 177Lu-octreotate, 1650 mg/m² capecitabine (n = 28) and 1500 mg/m² capecitabine with 200 mg/m² temozolomide (n = 37), and monitored for hematological toxicity over a 5-year period. **Results:** Short-term, self-limitet hematological toxicity grade 3/4 comprised anemia 3.5% and thrombocytopenia 3.5% in the 28-patient cohort of patients treated with 177Lu-octreotate and capecitabine. The incidence of grade 3/4 myelosuppression in 37 patients after 177Lu-octreotate/capecitabine/temozolomide was 10.8% for anemia and 2.7%, respectively, for thrombocytopenia and neutropenia. Long-term follow-up was a median 60 months and 36 months, respectively. Two patients in the 177Lu-octreotate/capecitabine/temozolomide cohort developed MDS with complex bone marrow cytogenetics on assessment.

**Conclusion:** The modest reversible hematological toxicity of PRRT of GEP NETs is not significantly increased by the combination of 177 Lu and radiosensitizing chemotherapy with capecitabine and temozolomide. **Keywords:** prrt, gep-net.

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**N5 Comparison of Radiolabeled Somatostatin Analogues and (131) I-MIBG Treatment for the Management of Patients with Metastatic/Progressive Phaeochromocytomas and Paragangliomas**

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**Introduction:** Radionuclide therapy has been used to treat patients with progressive/metastatic paragangliomas (PGGs) and pheochromocytomas (PCCs). To date, there is no study comparing (131)I-MIBG and peptide receptor radionuclide treatment (PRRT) in those patients. **Aim(s):** To compare the effectiveness of those modalities in progressive PCCs and PGGs. 

**Materials and Methods:** All patients had progressive tumors, despite previous treatments. Overall survival (OS), progression-free survival (PFS), event-free survival (EFS) and response to treatment were calculated. Renal and hematomatological toxicity were documented. **Results:** Twenty-two patients underwent either (131)I-MIBG, (90)Y-(DOTATATE) or (177)Lu-(DOTATATE). A total of 30 treatments were administered (17 treatments with (131)I-MIBG, two with (177)Lu-(DOTATATE) and 11 with (90)Y-(DOTATATE). Patients treated with PRRT had increased PFS and better response to treatment compared to those who had (131)I-MIBG(p < 0.05). However, differences in OS were marginaly non-significant (p = 0.09). There was no difference in major toxicities between groups. When stratifying patients with PGGs OS, PFS, EFS and response to treatment were significantly higher in the PRRT treatment group. **Conclusion:** PRRT treatment seems to be more effective than (131)I-MIBG therapy in the management of patients with progressive/malignant PGGs and PCCs. This conclusion seems to be more prominent in patients with PGGs. **Keywords:** paraganglioma, pheochromocytoma, (131)I-mibg, prrt.

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**N6 Transarterial Chemoembolization for Unresectable Liver Neuroendocrine Metastases**

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**Introduction:** Most patients with neuroendocrine tumors (NETs) present with liver involvement at the time of diagnosis. Trans-catheter arterial chemoembolization (TACE) is a method of treatment of non-resectable liver metastases. **Aim(s):** To evaluate the clinical outcome: Overall survival (OS) and Progression Free Survival (PFS). 

**Materials and Methods:** We analyzed 40 patients...
who underwent 177 TACE procedures during 2003–2013. Kaplan–Meier method was used to calculate OS and PFS. Results: NET originated from the pancreas (n = 8), small bowel (n = 17), lung (n = 8), stomach (n = 1) and unknown primary localization (n = 5). Almost all patients had received medical treatment, including octreotide (90%), interferon-alfa (30%), chemotherapy (30%), and peptide-receptor-radiouclide therapy-PRRT (15%). Primary tumor was operated in 27 patients (67.5%), and nine patients had liver resection (22.5%). Ki-67 analysis was performed in 38 cases, of which nine were classified as G1 and 28 as G2 NETs. Median OS for all NETs was 49 months with 5-year survival of 41.2%. The 5-year OS rates for patients with pancreatic, intestinal, pulmonary and unknown primary were 41.7%, 47.6%, 40% and 0%, respectively. Median PFS for all patients was 38 months. The 47% patients with intestinal and 41% patients with pulmonary tumor had 5-year duration of PFS, but none with pancreatic or unknown origin. Conclusion: The OS after TACE for all NETs is approximately four years, and median PFS is about 38 months. Keywords: liver chemoembolization, neuroendocrine tumor.

N7
AHCC Extract which Potentially Can Attenuate Immunological Toxicity in Patients with Neuroendocrine Tumors after Treatment with the Radioisotope Preparation (90Y-DOTA-TATE): An Initial Report
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Introduction: Active hexose correlated compound (AHCC) is an alpha-glucan nutritional supplement made from the mycelia of Lentinula edodes mushroom. Human clinical studies have shown that AHCC significantly improves immune response, increases normal NK cell activity and enhances macrophage and T-cell activity. Aim(s): To assess the efficacy of AHCC to protect the immunological system in neuroendocrine tumor (NET) patients after 90Y-DOTA-TATE therapy. Materials and Methods: We evaluated three patients with confirmed NETs. Patients were treated with four doses of 90Y-DOTA-TATE (3.7 GBq/m²/dose) in 8–10 week intervals (median dose 14.8 GBq/m² per patient). Control computed tomography and PET/CT with somatostatin analog 68Ga-DOTA-TATE were conducted three months after the last dose of 90Y-DOTA-TATE. Patients took AHCC in the amount of 3 × 2 g daily, 40 min before meals. Immunological toxicity has been compared with nine patients summarised by Sierra study. In the Italian group, the average dose of 90Y-DOTA-TOC was 5.5 GBq per patient. Results: Three months after the last dose of 90Y-DOTA-ATE, the following was found: the Lymph B (CD19+) and Lymph T (CD3+) cells decreased by 31% and 67%, respectively, in the Italian group and 30% and 4.9%, respectively, in our group. The NK cells (CD56+) decreased by 57% in the Italian group and increased by 18.84% in our group. Conclusion: AHCC is a promising extract that can alleviate the immunological toxicity after 90Y-DOTA therapy. Further studies are needed to confirm these results. Keywords: ahcc, net, prrt.

Surgical Treatment

01
Resection at Diagnosis of the Primary Pancreatic Neuroendocrine Tumor in Patients with Unresectable Liver Metastases. A Possible New Approach for a Multimodal Treatment
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Introduction: Pancreatic neuroendocrine tumors (PNETs) present in more than 50% of cases with liver metastases as the only systemic localization. Liver metastases are unresectable in 80% of cases at diagnosis. In the context of metastatic disease, the benefit of primary tumor removal in terms of survival is controversial. Aim(s): To assess the prognostic factors and the potential benefit of primary tumor resection at diagnosis on long-term survival in patients with PNET and synchronous unresectable liver metastases. Materials and Methods: A single-centre series of PNETs presenting with synchronous hepatic unresectable metastases and treated within a framework of a multidisciplinary team was retrospectively analysed. Results: At the time of diagnosis, 12 patients out of 43 (27.9%) underwent primary tumor resection. In the operated and unoperated patients, the 5-year disease-specific survival was 81.8% and 49.7%, respectively (P = 0.027). At multivariate analysis, patients with primary tumor removed had a statistically significant improved survival compared to patients who did not (HR: 0.18; 95% CI 0.05–0.66; P = 0.010). Other significant factors associated with improved survival at multivariate analysis were lower age, lower Ki-67 index, and liver tumor burden <25%. Conclusion: Resection of the primary tumor was associated with an improved survival. Its indication and timing should be discussed within a multidisciplinary team. Keywords: pancreatic neuroendocrine tumor, synchronous liver metastases, debulking, resection, prognostic factors, survival.

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Abstracts
**O2**

**Surgery after Peptide Receptor Radionuclide Therapy (PRRT) in Patients with Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)**

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**Introduction**: There are a few case reports on surgery after peptide receptor radionuclide therapy (PRRT). **Aim(s)**: To analyze the results of surgery in patients affected by abdominal neuroendocrine tumor (NET) localizations who previously underwent PRRT to test the feasibility of this sequential treatment. **Materials and Methods**: We extracted from the institutional tumor registry those patients with histologically confirmed diagnosis of abdominal localizations from NET who underwent surgery after PRRT. **Results**: Eleven of 181 patients, who previously underwent PRRT with 90Y-DOTATOC or 177Lu-DOTATATE, were submitted to surgical resection, after discussion within a multidisciplinary team. Nine patients presented with liver metastases. Six distal pancreatectomies, two extended right colectomies, one ileal resection and two ovariecitoses were performed. Liver resection was performed in four of these patients. Perioperative mortality was nil. Morbidity was 9% (one patient). After a median follow-up of 21 months following surgery (range: 2–164 months), five patients experienced disease progression after a median of four months (range: two to 10 months). **Conclusion**: Surgery after PRRT for metastatic NETs with abdominal localizations is feasible and safe. It should be a part of a global therapeutic strategy for patients with low-grade enteropancreatic neuroendocrine tumors and its timing should be discussed within a multidisciplinary team. **Keywords**: neuroendocrine tumors, peptide receptor radionuclide therapy, surgery, survival, progression-free survival.

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**O3**

**Toward a Preoperative Classification of Mesenteric Lymph Node Metastases for Better Selection of Carcinoid Tumors Before Radical Surgery**

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**Introduction**: Surgery for small bowel carcinoid (SBC) and lymph node (LN) metastases, when technically possible, represents the best therapy. However, surgical challenge is (i) not to recuse patients for false unresectable mesenteric artery invasion, and/or (ii) to avoid extensive small bowel resection. **Aim(s)**: We hypothesized that the length of bowel resection would not reflect the quality of lymphadenectomy. Then, we proposed a 4-stage preoperative CT-scan (or MRI) classification that could predict complete resectability of SBC and LN. **Materials and Methods**: Consecutive patients operated on a 3-year period were retrospectively analysed. The liaison between number of resected LN and resection length of SB were performed in highly selected patients who fulfilled inclusion criteria by an ANOVA. Preoperative imaging was reviewed blindly by two independent observers and data correlated to intraoperative findings by weighted Kappa coefficient. **Results**: Sixty consecutive patients were analysed. There was no correlation between SB length (63 cm±46) and mean LN number (18.6±11) (p = 0.56). There was a good concordance between pre- and intra-operative findings (WK = 0.86, IC95% 0.73–0.98). Patients with stage I, II, IIIa were found to be easily resectable. **Conclusion**: These preliminary data predicting the length and quality of SB resection based on a novel preoperative classification should be prospectively evaluated in a large setting. **Keywords**: carcinoid tumor, surgical procedures.

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**O4**

**Laparoscopic Antrectomy: A Safe and Definitive Treatment in Managing Type 1 Gastric Carcinoids**

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**Introduction**: Various type 1 gastric carcinoid (T1GC) treatments exist, including esophagastroduodenoscopy (EGD) observation, polypectomy, and antrectomy, but studies comparing treatment outcomes have been limited. **Aim(s)**: This study assessed the risk-benefit ratio for these treatments to find the most effective way to manage T1GC, reduce follow-up, and maintain the highest patient quality of life. **Materials and Methods**: A retrospective review of 52 T1GC patients (ages 30–88; 75% female) who presented to The Mount Sinai Medical Center between 2004–2012 and underwent one of the abovementioned procedures was conducted. Patient demographics, procedures, recurrence, and outcomes were analyzed using SPSS v20 software. **Results**: Twenty patients received antrectomy, 16 EGD surveillance, and 16 EGD with polypectomy. Average number of EGDs needed per follow-up year was significantly lower for antrectomy patients than for polypectomy or EGD surveillance patients (0.41 v. 1.038 v. 1.380, p = 0.002). Average number of EGDs needing post-antrectomy was significantly lower than total number of nonsurgical options (1.35 v. 2.88, p = 0.019). Antrectomy patients had also a lower recurrence risk than polypectomy patients (10% v. 44%, p = 0.049), despite a longer average follow-up time (6.17 v. 4.39 years, p = 0.009). **Conclusion**: By safely and effectively treating T1GC with lower recurrence risk and less post-intervention monitoring necessary, antrectomy allows patients to avoid the pain and discomfort of repeated EGD surveillance. **Keywords**: antrectomy, gastric carcinoid.
Characteristics and Determinants of Long-Term Outcome for Resectable Sporadic Non-Functional Pancreatic Neuroendocrine Tumors (NF-PNETs): Updated 16-year Experience from Two Large Chinese Centers


Introduction: Non-functional pancreatic neuroendocrine tumors (NF-PNETs) are increasingly recognized with unique biology. Aim(s): To assess characteristics and determinants of long-term survival for NF-PNETs. Materials and Methods: Two-hundred and four pts were analyzed retrospectively from Jan 1998 to Jun 2013. Results: The percentages of ENETS TNM I, II, III and IV were 11%, 53%, 25% and 11%, respectively. The G1, G2 and G3 pts accounted for 44%, 41% and 15%. Morphologically, well-, intermediate- and poorly-differentiated pts were 71%, 9% and 20%. Surgery comprised pancreatic resection (95%) and biopsy (5%). The 5-y OS rate was 80%. Among 194 pts with R0 resection, the relapse rate was 21% and median relapse time was 18 mo. Ki-67 >5% and >2%, poor differentiation, distant metastasis, LN metastasis, tumor necrosis, tumor >4 cm, major vascular invasion and neural invasion were dismal predictors. When categorizing grade according to the increased Ki-67 cutoff value of 5% between G1 and G2, G1 were 70% and G2 were 15%. Moreover, the 5-y OS for new G1 and G2 were 93% and 57%, and it was seen that grade was predictive of survival (P = 0.001). Multivariate analysis showed poor differentiation (P = 0.001, HR = 2.4), Ki-67 >2% (P = 0.030, HR = 9.2), and Ki-67 >5% (P = 0.035, HR = 2.8) were independent predictors. Conclusion: Sporadic NF-PNETs showed heterogeneous characteristics and determinants. NF-PNETs could relapse after R0 resection. An increased Ki-67 cutoff value of 5% between G1 and G2 could be more valuable in predicting outcome. Ki-67 and poor differentiation were two key predictors. Keywords: esophageal stricture, zes, hypergastrinemia.

Zollinger-Ellison Syndrome: The Esophageal Stricture as a Rare and Severe Complication

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Introduction: Zollinger-Ellison Syndrome (ZES) is caused by tumoral hyperscretion of gastrin, inducing gastric hyperchlorhydria and complicated peptic ulcer disease. Esophageal strictures are rare in ZES, due to early PPI treatment. Aim(s): To evaluate clinical presentation, treatment, histology and prognosis. Materials and Methods: From 2004 to 2013, we observed three patients with ZES with severe esophageal strictures (out of 20 observed). Endoscopy and barium esophagram performed to detect the esophageal strictures and establish their severity and extension. ZES established by fasting serum gastrin or secretin provocative test, and gastric acid studies. Octreoscan scintigraphy performed for detecting tumor localization. Results: Two patients presented duodenal and jejunal perforation, the third patient had severe esophagitis before developing absout dysphagia. Tumor localization determined in two patients (duodenum/pancreatic head) and the histological examination confirmed the presence of gastrinoma. Esophagectomy plus total gastrectomy performed in two patients, the other had therapy with somatostatin-analogues with benefit. One patient died a few weeks after diagnosis because of advanced disease. Conclusion: ZES must be suspected in patients presenting with complications of peptic disease and hypergastrinemia or symptoms related to excess of gastric acid, so PPI treatment and somatostatin-analogues administration may be started as soon as possible to avoid severe esophageal complications. Keywords: esophageal stricture, zes, hypergastrinemia.
O8 Surgical Management of the Patients with Liver Metastases of Pancreatic Neuroendocrine Tumors
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Introduction: Most pancreatic neuroendocrine tumors (PNET) grow slowly but around 60% of the patients have distant metastases. Although new drugs have recently emerged, surgical resection is still one of the key modalities for curing the tumor. Aim(s): To elucidate the tumor categories which get the most benefit from surgical resection of the metastases, we examine the efficacy of the surgical resection of the PNET distant metastases on survival. Materials and Methods: From 1992 to 2012, 121 PNET patients were treated at our hospital. Of these, there were 16 patients who had recurrences after curative resection and 22 patients with distant metastasis at their first admission. We analyzed the progression-free survival as well as overall survival of the resected patients. Results: Thirty five out of 38 patients (92%) had liver metastasis. When we compared the primary tumor resected group with non-resected group, the primary tumor resected group have apparently better survival (p = 0.0407). When we compared the debulking surgery group of the distant metastatic sites and non-debulking surgery group, no survival benefit was observed. However, when we stratified the groups based on WHO categories, the overall survival of the debulking surgery group was apparently improved in G2 PNET patients. (p = 0.0287). Conclusion: In controlling the distant metastasis of the PNET, resection of the primary tumor seems recommended and WHO G2 but not G1 or G2 patients benefit the most by surgical resection of the distant metastases. Keywords: pnet, distant metastases, resection.

O9 Incidental Pathological Finding of Pancreatic Non-Functioning Neuroendocrine Tumors
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Introduction: Little is known about the incidental finding of non-functioning NETs (Neuroendocrine Tumors) during pancreatic surgery performed for other reasons or during pathological examination of the surgical sample. Aim(s): To evaluate histology and staging of NETs, expression of NE markers, prognosis and main associated pancreatic disease. Materials and Methods: From 1997 to 2013, 157 non-functioning NETs observed in our Center. Sixteen incidental pathological findings in patients operated for other pancreatic diseases (average 64 years, range 44–85 yrs; 10 M/6 F). Results: All asymptomatic without evidence of NETs at preoperative imaging. Surgery: five pancreato-duodenectomy, one median pancreatectomy, seven distal pancreatectomy, three other pancreatic resections. Main pancreatic diseases: four chronic pancreatitis, one MCA (Mucinous Cystic Adenoma), three other diseases. Well differentiated NETs in all cases. Median size 0.5 cm (range 0.1–1.4 cm). Staging: T1 G1. Expression of NE markers: 3/16 NE serum markers available (one high chromogranin A); 11/16 immunohistochemistry available: five glucagon, three pancreatic polypeptide, three chromogranin-synaptophysin positive. Follow-up: nine dead (five disease progression), seven alive and asymptomatic. Conclusion: In our series, 10.2% of NETs observed in 15 years are incidental pathological findings. They are benign non-functioning NETs and do not affect the prognosis of the main pancreatic disease, reason of surgery. Keywords: neuroendocrine tumors, pancreatic cancer, incidental tumor.
O11
Vipomas: Report of Three Cases in Ten Years

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Introduction: VIPoma is a rare neuroendocrine tumor (NET) with an incidence of one in 10 million per year. Most cases arise within the pancreas, with others reported in the lungs, colon, liver, adrenals, and neuroglandia. Aim(s): We report three cases of VIPomas (two pancreatic and a jejunal one) observed in our Center in a period of 10 years. Materials and Methods: From January 2000 to December 2009, three cases (M:F 2:1; mean age 67.7 years) of VIPomas were observed in our Center (out of 164 Gastroenteropancreatic tumors). All patients were symptomatic (watery diarrhea) and with a high serum VIP. In one patient, a jejunal resection and hepatic metastasectomy were performed. In the second patient, a distal pancreatectomy and hepatic metastasectomy were performed. Both patients had a SST-analogue treatment after surgery. The last patient had a SST-analogue treatment after surgery. The last patient had a relief of symptoms after surgery. In all cases, histology showed a NET with immunohistochemistry positive for VIP. All patients had a relief of symptoms after surgery. Two patients died of disease progression at 59 and 63 months after surgery. One patient is alive without disease at 53 months after surgery. Conclusion: Surgery is the treatment of choice for VIPomas. A complete resection of the primary tumor improves the prognosis. Even with metastatic disease, surgery for tumor debulking represents the first-line treatment. Keywords: vipoma, neuroendocrine tumors, pancreatic resections.

O12
Recurrent Carcinoid Valvulopathy after Bioprosthetic Valve Surgery

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Introduction: Carcinoid heart disease (CHD) typically affects right-sided cardiac structures causing leaflet thickening, retraction and valve dysfunction requiring surgery. Aim(s): Evaluate early prosthetic dysfunction after valve replacement (VR) with tissue valves. Materials and Methods: From Jan 2001 to Nov 2013, 27 consecutive patients with carcinoid syndrome, liver metastases and CHD had tricuspid or/pulmonic valve replacement with tissue valves. Retrospective analysis of prospectively collected clinical, laboratory and echo data was performed. We could not assess recurrence in six patients due to perioperative mortality (n=3; 11%), valve replacement in 2013 (N=2), lost follow-up (n=1). Results: Eleven patients (52%) had prosthetic dysfunction (9 TV and PV dysfunction, 2 TV only). 2 patients underwent tricuspid and pulmonary valvuloplasty and 2 tricuspid and pulmonary VR with mechanical valves. Pathology confirmed carcinoid etiology. Others were not optimal for intervention due to poor survival expectancy or no indication for surgery. Recurrent valvulopathy appeared within a mean time of 24 months after surgery. There was no difference in levels of serotonin, urinary 5HIAA before and after surgery between patients that suffered recurrence and those that did not. Patients with recurrence had higher chromogranin A after cardiac surgery. Conclusion: There’s a high incidence (52%) of CHD recurrence, likely due to serotonin. If this can’t be controlled, mechanical valves should be considered. Keywords: valves, recurrent carcinoid disease, serotonin.

Non Digestive NETs (Bronchial, MTC, Pheochromocytoma)

P1
Expression of IGF/mTOR Pathway Components in Human Pheochromocytomas and In Vitro Inhibition of PC12 Rat Pheochromocytoma Cell Growth by mTOR Inhibitors Alone and in Combination with the Dual IGFI-R/INS-R Antagonist OSI-906

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Introduction: Dysregulation of the mTOR and IGF pathways have been suggested to be involved in the pathogenesis of pheochromocytomas (PCC). mTOR inhibitors, such as sirolimus (S) and everolimus (E), as well as IGFI-R antagonists such as OSI-906, could be new a treatment for malignant PCC. Aim(s): To evaluate expression of IGF/mTOR pathway components in PCC and to investigate whether IGF/mTOR pathway blockade has antiproliferative effects on PCC cells. Materials and Methods: The mRNA expression of: IGFI, IGFIIR, IGFI-Receiver [IGF-R], Insulin-Receiver[IR]A, IRB, IGFIIR, IGFI-Binding-Proteins [BP] 1, 2, 3 and 6, mTOR, 4EBP1 and p70S6K (qPCR) was evaluated in 24 human PCC. The dose- and time-dependent effect of S, E and OSI-906 were able to suppress PC12 growth in a dose- and time-dependent manner. mTOR inhibitors inhibited PC12 proliferation, but S was more potent than E. OSI-906 strongly inhibited PC12 growth in a dose- and OSI-906 alone or in combination with mTOR inhibitors as a potential new treatment option in progressive PCCs patients. Keywords: igf, mtor, everolimus, osi-906, pheochromocytoma, pc12, adrenal, neuroendocrine, tumor.
P2
Succinate Dehydrogenase Subunit B (SDHB) Immunohistochemistry Should Not Replace Clinical Genetic Testing for SDHx Mutations in Patients with Pheochromocytoma and Paraganglioma
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Introduction: Mutations in any of the subunits of the succinate dehydrogenase (SDH) complex predispose to PCC/PGL. Knowing the germline mutation is important for surveillance for recurrence, metastatic disease or more primary tumors and for screening affected family members. Expression of SDHB protein by immunohistochemistry (IHC) has been proposed as a surrogate marker for SDHx mutation status, with absent or decreased expression of SDHB suggesting the presence of a germline SDH mutation or disruption of the SDH complex by mutation in another subunit. Aim(s): To evaluate the effectiveness of SDHB IHC in predicting SDHx germline mutation status. Materials and Methods: We performed a retrospective review of the pathology reports between 2011–13 which included SDHB IHC on PCC/PGLs from patients with clinical genetic testing who either tested positive for SDHx germline mutation or had no identified mutation. Results: A total of 19 patients (20 tumors) were identified (10 with no mutation, three SDHB, one SDHC, four SDHD and one SDHD VUS, likely pathogenic based on in silico analysis, tumor multiplicity and positive family history). SDHB staining was called as negative, weak, or moderate to strong cytoplasmic positivity. SDHB IHC results were concordant with SDHx mutation status in 11 of 20 cases. Conclusion: Therefore, we conclude there is not a strong correlation between SDHx mutation and SDHB IHC. In our experience, SDHB IHC does not predict the presence of SDHx mutations and should not replace clinical genetic testing. Keywords: pheo, succinate dehydrogenase.

P3
Immunohistochemical and Genomic Evidence for the Expression of Somatostatin Receptors 1–5 and Dopamine Receptor 2 in Lung Carcinoids
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Introduction: Expression of somatostatin receptors (SSTRs) and dopamine receptor 2 (DR2) in neuroendocrine tumors is of clinical importance, as they represent potential targets for diagnosis and treatment. Aim(s): To examine the expression of the five SSTR subtypes and DR2 subtype in lung carcinoids (LCs) by means of immunohistochemistry (IHC) and real time polymerase chain reaction (RT-PCR). Materials and Methods: A retrospective study of 119 LCs from 106 patients [typical carcinoids (TCs) \(n = 100\), and atypical carcinoids (ACs) \(n = 19\)] was conducted. The expression of all five SSTR subtypes and DR2 was evaluated by IHC and correlated to clinocopathological data. In a subgroup of cases, receptor expression was further analyzed using RT-PCR. SSTR expression was also correlated to Octreoscan data. Results: SSTR2A was the receptor type most frequently expressed (67%), followed by SSTR1 (63%), SSTR5 (40%) and SSTR3 (20%), whereas SSTR4 was negative. DR2 was expressed in 74% and co-expressed with SSTR1 in 56%, SSTR2A in 54%, SSTR3 in 19% and SSTR5 in 37% of the tumors, respectively. Receptor expression was largely attributed to increased gene transcription as shown by RT-PCR. Concordance between SRS and IHC data was substantial regarding only SSTR2A subtype. Conclusion: SSTR1, SSTR2A and to a lesser extent SSTR5 and SSTR3 are avidly expressed in LCs, and co-expressed with DR2 in a significant number of these tumors, a knowledge that could provide the rationale for treatment with agents that target these receptors. Keywords: lung, carcinoid, somatostatin.

P4
Immunohistochemical Expression of Connective Tissue Growth Factor and Insulin-like Growth Factor-1 in Lung Carcinoids
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Introduction: Several studies have shown altered expression of Insulin-like Growth Factor-1 (IGF-1) and its receptor (IGF-1R) in different types of cancers. Connective Tissue Growth Factor (CTGF) is triggered by Serotonin (5-HT) and Hypoxia Induced Factor 1 (HIF-1) and has been associated with tumor expansion and desmoplastic reaction in carcinoid tumors. Aim(s): To examine CTGF, HIF-1, 5-HT IGF1- and IGF1R expression in Lung Carcinoids (LC). Materials and Methods: Retrospective immunohistochemical study of 121 LC [103 Typical(TC) and 18 Atypical(AC)] obtained from 104 patients (60 Female) with a mean age of 52 yrs (16–82). Tumors were considered positive if immunoreactivity (IR) appeared in the majority of tumor cells. Urine 5-hydroxyindoleacetic acid (U-5HIAA) was determined in 29 patients. Results: All studied parameters were expressed in the majority of tumors (CTGF, HIF-1, IGF-1 and IGF-1R in 70%, 76%, 76% and 67% of the cases, respectively) and were more frequent in TC, although this was significant only for HIF-1 (82 v. 44%). HIF-1 and CTGF were co-expressed in 58% of the tumors and IGF-1 with IGF-1R in 64%. Tumor size and metastases were not associated with higher expression of any of the studied parameters. 5-HT IR was negligible. Three patients had elevated U-5HIAA and all their tumors expressed CTGF but only one HIF-1. Conclusion: LC express in abundance IGF-1 and CTGF. IGF-1 is frequently co-expressed with...
Abstracts

were randomly selected for qRT-PCR analysis. Twenty serial paraffin slides each from the TC, AC and SCLC using specific antibodies and three semiquantitative scores for evaluation. SSTR expression data significantly correlated with the IHC. With both methods, SSTR1, 3, 4 and 5 expression in BP-NEN to provide an additional diagnostic cut-off and to stratify subsequent imaging of BP-NEN. The differential SSTR expression in BP-NEN may be used not only in the diagnosis and treatment of GEP-NEN, but also in the diagnosis and treatment of NET. Ga-68 SMS-R PET/CT is the imaging method of choice for the detection of non-producing neuroendocrine tumors, although 19–28% of patients have an increased dopamine production. The high sensitivity of 18F-DOPA PET also shows that these tumors might be able to synthesize catecholamines. Aim(s): To demonstrate the presence of catecholamine synthesizing enzymes, tyrosine hydroxylase (TH), aromatic L-amino acid decarboxylase (AADC) and dopamine beta hydroxylase (DBH). Materials and Methods: HNPGL tissue (n = 29) was immunohistochemically stained for TH, AADC and DBH. Information on gene mutations, lab results (metanephrine (MN), normetanephrine (NMN) and 3-methoxytyramine (3-MT)), and imaging were collected from the medical records. Catecholamine excess was defined as MN, NMN and/or 3-MT levels above the upper reference limit. Results: Six patients had a mutation in the succinate dehydrogenase (SDH) gene (5 SDHB, 1 SDHD), in 11 patients genetic analysis was not performed. Twenty-eight (97%) tumor tissues stained positive for AADC, 12 (41%) for TH, and five (17%) for DBH. 18F-DOPA PET was performed in eight patients, seven had focal uptake. The tissue of these seven patients stained positive for AADC. Five (19%) patients had catecholamine excess; MN (2), NMN (2), 3-MT (2). The tissue of these five patients all stained for AADC, 12 (41%) for TH, and five (17%) for DBH. Conclusion: Catecholamine synthesizing enzymes, in particular AADC, are expressed in the majority of HNPGL tissues. Since AADC catalyzes L-DOPA into dopamine, a sensitive dopamine assay might be useful as a tumor marker. Keywords: paraganglioma, dopamine.

P5

Immunohistochemical and qRT-PCR-Based Evaluation of Somatostatin Receptor 1 to 5 Expression in 92 Patients with Bronchopulmonary Neuroendocrine Neoplasms

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Introduction: Little is known about the somatostatin receptor (SSTR) status in bronchopulmonary neuroendocrine neoplasms (BP-NEN), comprising typical carcinoids (TC), atypical carcinoids (AC), small cell lung cancer (SCLC) and large cell neuroendocrine lung carcinomas (LCNEC). Aim(s): To investigate the SSTR1, 2A, 3, 4 and 5 expression in BP-NEN to provide an additional diagnosis and treatment option. Materials and Methods: A total of 242 formalin-fixed, paraffin-embedded specimens from 26 TC, 30 AC, 35 SCLC and 1 LCNEC were examined by immunohistochemistry (IHC) using specific antibodies and three semiquantitative scores for evaluation. Twenty serial paraffin slides each from the TC, AC and SCLC were randomly selected for qRT-PCR analysis. Results: In different expression patterns, SSTR could be detected in most tumor sections, both at protein and mRNA level. However, intra- and interindividual variations were observed. With the exception of SSTR4, qRT-PCR data significantly correlated with the IHC. With both methods, SSTR1, 3 and 2A were detected most frequently. Significant SSTR expression differences between the entities and grading levels were observed. Conclusion: As an example of individualised medicine, SSTR can be used not only in the diagnosis and treatment of NET, but also in the diagnosis and treatment of NET. Conventional proliferation rate (Ki-67) level is used for the grading of NET. Ga-68 SMS-R PET/CT is the imaging method of choice for the detection of non-producing neuroendocrine tumors, although 19–28% of patients have an increased dopamine production. The high sensitivity of 18F-DOPA PET also shows that these tumors might be able to synthesize catecholamines. Aim(s): To demonstrate the presence of catecholamine synthesizing enzymes, tyrosine hydroxylase (TH), aromatic L-amino acid decarboxylase (AADC) and dopamine beta hydroxylase (DBH). Materials and Methods: HNPGL tissue (n = 29) was immunohistochemically stained for TH, AADC and DBH. Information on gene mutations, lab results (metanephrine (MN), normetanephrine (NMN) and 3-methoxytyramine (3-MT)), and imaging were collected from the medical records. Catecholamine excess was defined as MN, NMN and/or 3-MT levels above the upper reference limit. Results: Six patients had a mutation in the succinate dehydrogenase (SDH) gene (5 SDHB, 1 SDHD), in 11 patients genetic analysis was not performed. Twenty-eight (97%) tumor tissues stained positive for AADC, 12 (41%) for TH, and five (17%) for DBH. 18F-DOPA PET was performed in eight patients, seven had focal uptake. The tissue of these seven patients stained positive for AADC. Five (19%) patients had catecholamine excess; MN (2), NMN (2), 3-MT (2). The tissue of these five patients all stained for AADC, one stained positive for DBH. Conclusion: Catecholamine synthesizing enzymes, in particular AADC, are expressed in the majority of HNPGL tissues. Since AADC catalyzes L-DOPA into dopamine, a sensitive dopamine assay might be useful as a tumor marker. Keywords: paraganglioma, dopamine.

Clinical Cases/Reports

Q1

Nuclear Imaging in Intermediate Grade Neuroendocrine Tumors

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Introduction: Early diagnosis and grading is essential to the treatment decision-making in neuroendocrine tumors. Conventionally, proliferation rate (Ki-67) level is used for the grading of NET. Ga-68 SMS-R PET/CT is the imaging method of choice for the detection of paraganglioma, dopamine.
of unknown primary neuroendocrine tumors. It is very sensitive in well-differentiated tumors (Ki-67 <2%). Poorly and undifferentiated tumors having Ki-67 greater than 20% are primarily responsible for false negativity of Ga-68 SMS-R PET/CT. In those patients, FDG-PET is performed to localize the site of the primary tumor. Aim(s): The data are scarce regarding the imaging modality of choice for intermediate grade (Ki-67 between 2 and 20%) NET. Our aim is to highlight the importance of FDG PET in grade 2 NET. Materials and Methods: Four patients with grade 2 NET (Ki-67 levels between 3% and 20%) of different primary locations (liver, pancreas and two mediastinal) underwent both Ga-PET and FDG-PET at the time of diagnosis. Results: We have noted low activity in Ga-PET scans (SUV max ranging between 1 and 10) compared to a discrepant very high activity on FDG PET (ranging between 5.89 and 17) for the four patients. Conclusion: FDG-PET scan provides vital information in patients with grade 2 NET. Keywords: neuroendocrine tumors, nuclear imaging, histopathology.

Q2

Sunitinib Induced Hypocalcaemia During Treatment of Pancreatic Neuroendocrine Tumors (pNETs)

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Introduction: Sunitinib is an oral multitargeted tyrosine kinase inhibitor used for pNET treatment. Aim(s): To investigate the prevalence of hypocalcemia during treatment. Materials and Methods: Three out of 12 patients with pNETs treated with sunitinib developed grade 1, 2 and 4 hypocalcemia. Results: A 51-year-old man with a stage IV, grade 1 pNET developed disease progression despite treatment with somatostatin analogues (SA); nine months after sunitinib was initiated he developed symptomatic grade 2 hypocalcemia (7.2 mg/dl) necessitating treatment discontinuation and calcium supplementation. A 53-year-old man with MEN-1 with stage IV, grade 1 pNET was treated with Whipple’s operation and SA. Following disease progression, he was initially treated with everolimus that was initiated. Six months later, he developed grade 1 hypocalcemia (8.2 mg/dl) that improved with dose reduction. A 58-year-old man with a long history of a stage IV, grade 2 pNET developed severe and refractory hypercalcemia due to PTHrP secretion by the tumor. Following disease progression he was treated with sunitinib and one month later he developed grade 4 hypocalcemia (<6 mg/dl). Following reinition of treatment, his previous refractory hypercalcemia became easily controlled. Conclusion: Hypocalcemia can occur relatively often with wide severity that may necessitate treatment modification. This potential side effect may be of therapeutic significance in patients with refractory hypercalcemia. Keywords: sunitinib, pnet, hypocalcaemia.

Q3

The Natural History of an Apparently Aggressive Gastric Neuroendocrine Neoplasm Type 1

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Introduction: Gastric neuroendocrine neoplasm type 1 (GNE1) is the most common GEP-NETs. GNE1 has traditionally been considered non-metastatic as compared to the large, solitary GNE3 that has high malignant potential. Aim(s): To confirm that prognosis remains relatively good even in apparently aggressive GNE1. Materials and Methods: We report the case of GNE1 that followed an unusual initially aggressive course as it developed metastases to both lymph nodes and liver. Results: A 46-year-old woman had a 3.5 cm GNE1 diagnosed with a Ki-67 1.5% and two metastatic hepatic foci and Ki-67 8%. She then had a subtotal gastrectomy, wide lymph node removal (one positive), resection of liver foci whereas was further treated with radiofrequency ablation. Due to the relative aggressive features of the tumor, the patient was considered to have a GNE3. Three years later, she was further evaluated. Because of her past medical history (pernicious anaemia, autoimmune thyroiditis, premature ovarian failure), the alternative diagnosis of GNE1 in the context of autoimmune gastritis was addressed. Antiparietal cell antibodies were found positive and revision of the pathology specimen reported marked diffuse linear hyperplasia of enterocromaffin-like cells in the vicinity of the resected tumor supporting the diagnosis of a GNE1. The patient remains well eleven years after her primary surgery. Conclusion: This case implies that precise diagnosis is of clinical utility since GNE1 has greater long-term survival and a much more favorable prognosis compared to GNE3. Keywords: gne1.
Q4
The Use of Endoluminal Stents to Overcome Vascular Obstruction Arising from Mesenteric and Retroperitoneal Neuroendocrine Metastases
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Introduction: Gastroenteropancreatic neuroendocrine tumors (GEP-NET) often metastasise to lymph nodes. Nodal metastases from neuroendocrine tumors in the distal small intestine commonly (>50%) develop in the mesentery and are often centred at the mesenteric root surrounding the major vessels supplying the bowel. Compression of these vessels, by the nodes or associated fibrosis, can lead to severe symptoms such as pain (secondary to bowel ischaemia), ascites (from superior mesenteric vein obstruction) and bowel perforation. In view of the often indolent nature of GEP-NET, symptoms from lymph node masses can persist for years, causing significant morbidity and early mortality. \textbf{Aim(s):} We present a case series of patients with significant symptoms arising from such vascular compression who have been treated by the insertion of endoluminal vascular stents. Three patients had rapidly reaccumulating ascites secondary to obstruction of the superior mesenteric vein. In each case, the ascites were resistant to medical control and required frequent paracentesis. One patient had constant pain in keeping with mesenteric angina. \textbf{Materials and Methods: Results:} The clinical and radiological features of each case will be presented along with information on the changes in symptoms arising after stenting and complications involved with these procedures. \textbf{Conclusion: Keywords:} gastroenteropancreatic neuroendocrine tumor, endoluminal stent, mesentery.

Q5
Pancreatic Neuroendocrine Tumor Presenting in Pregnancy with Severe Hypercalcemia
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Introduction: Malignant hypercalcemia secondary to pancreatic neuroendocrine tumor (pNET) is a rare occurrence with no standard management. We report a challenging case of pNET presenting during pregnancy and complicated by severe hypercalcemia. \textbf{Aim(s):} We discuss the mechanisms of hypercalcemia and the therapeutic interventions used. \textbf{Materials and Methods:} A 23-year-old woman presented at 26 weeks of gestation with persistent vomiting. MRI showed large pancreatic mass and innumerable liver lesions. Biopsy revealed well-differentiated NET having a Ki-67 of 15%. She commenced sandostatin LAR, however, presented four weeks later with severe hypercalcemia of 20 mg/dl (8.5–10.5 mg/dl). PTH was suppressed but PTHrP elevated. \textbf{Results:} Emergency management consisted of hemodialysis, cesarean section followed by embolisation of the right hepatic artery and bisphosphonate infusion. Calcium normalized in early postpartum but peaked again six weeks later. Gallium PET showed diffuse skeletal lytic lesions having low SUVmax. Bone biopsy showed metastatic pNET with a Ki-67 of 35%, liver lesions increased in size and aneurysmal arterial branches arising from the head of pancreas were noted. Treatment consisted of hepatic artery embolisation, gastroduodenal artery coiling, bisphosphonate, capecitabine and temozolomide. \textbf{Conclusion:} Malignant hypercalcemia of NETs is rare and challenging particularly in the setting of pregnancy. Systemic therapy and arterial embolisation may have therapeutic potential if surgery is unfeasible. \textbf{Keywords:} pregnancy, pnet, hypercalcemia, embolisation.

Q6
Primary Hepatic Neuroendocrine Tumors: Four Familial Case Series with Review of Literature
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Introduction: Non-multiple endocrine neoplasia (MEN) familial neuroendocrine tumors (NET) are very rare with only six families being described to date. Primary hepatic neuroendocrine tumors (PHNETs) are rare tumors with a particular sporadic diagnosis. Herein, we report a series of four members of one Lebanese family, diagnosed with primary hepatic neuroendocrine tumors. \textbf{Aim(s):} We present four well-documented cases of primary hepatic neuroendocrine tumors with review of the literature and a focus on genetic studies. \textbf{Materials and Methods:} We recently collected four Lebanese family members who were separately diagnosed with hepatic masses: the daughter at the age of 16 years and her mother at the age of 43 years, the maternal cousin at the age of 25 years and his mother at the age of 53 years. All four patients underwent partial hepatectomy at different times. \textbf{Results:} Histopathological examination and immunohistochemical staining of the resected specimens (excluding the cousin who refused to share his results) revealed similar tumors compatible with PHNET. We are currently collecting blood from affected and healthy members to be tested by genetic sequencing studies. \textbf{Conclusion:} PHNET is a rare clinical entity that poses a challenge for diagnosis and management. The above cited four familial cases are illuminating. To our best knowledge, this is the first report of familial PHNETs. We hope that the genetic studies we are conducting might help in depicting a common defect or pathway. \textbf{Keywords:} familial primary hepatic neuroendocrine tumors, genetic studies.
**Q7**

**Extrapulmonary Small Cell Neuroendocrine Carcinoma of the Colon in an 18-Year-Old Girl**

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**Introduction:** Extrapulmonary small cell carcinoma (EPSCC) is a very rare aggressive malignant tumor typical for older age. Prognosis of EPSCC remains very poor, with three years OS 38% and five years OS less than 13%. The median survival for GI localized EPSCC is only five months. Initial extent of disease is the most sensitive prognostic factor. **Aim(s):** Case study of a very rare tumor with extremely aggressive behavior in an unusually young patient.

**Materials and Methods:** Eighteen-year-old girl with one week history of abdominal pain was admitted to the hospital with acute hepato-renal failure and severe hypercalcaemia. US/MRI showed extreme hepatomegaly and multiple small nodules in liver parenchyma. Within 48 hours she suddenly developed hemorrhagic shock with intrabdominal bleeding. Laparotomy revealed spontaneous rupture of the right liver lobe. Days after surgery there were complications, including multiple organ failure and coagulopathy. Despite intensive care, the girl died only 20 days after the first symptoms occur. **Results:** Autopsy found the small ring-shaped primary lesion localized in the colon about 20 cm from the anus, massive metastatic involvement of the liver, abdominal LN and micrometastases in both lungs. Final histopathology confirmed widespread poorly differentiated small cell NEC. **Conclusion:** Presented case is unusual due to atypical young age without known risk factors. Primary silent small tumor was presented with massive metastatic spread and paraneoplastic PTHrP production. Pathogenesis remains unknown. **Keywords:** colon epscc, young age.

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**Q8**

**Pheochromocytoma and Paraganglioma in Pediatric Age**

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**Introduction:** Pheochromocytoma (PHE) and paraganglioma (PGL) are rare tumors of the adrenal medulla and extra-adrenal sympathetic chromaffin tissue. Nearly 30% of them are familiar or associated with genetic syndromes (VHL, MEN2, NF1, SDH mutation, Pacak-Zhuang). Only 20% PHE occur before 20 years of age. Incidence of pediatric PHE is 0.3:1 million. **Aim(s):** Fifteen years of experience at a single academic institution. Symptoms, clinical outcome, definition of risk factors and age-specific differences of PHE/
Q10

Hyperinsulinemic Hypoglycemia by an Ovarian Germ Cell Tumor

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Introduction: A 76-yr-old woman was admitted to our department for recurrent hot flushes, sweating and dizziness associated with fasting hypoglycemia. Physical examination revealed abdominal obesity and ascites. Aim(s): Materials and Methods: Fasting test was performed and at the fifth hour, the patient showed neuroglycopenia symptoms and blood samples revealed inappropriately elevated insulin and C-peptide levels. An abdominal US showed a 10 cm diameter isomorphic mass in the left adnexal region, CT confirmed the necrotic-colliquiative expansive lesion in left adnexal and described ascites. Blood tests showed abnormal levels of CgA, β-HCG, NSE and CA15.3. A 18FDG-PET described pathological uptake in left adnexal while Octreoscan® was negative. Results: The patient underwent istero-anectionectomy; she died a few days later because of septc complications. Hystological examination was consistent with ovarian germ cell tumor presenting extensive areas of neuroendocrine differentiation and areas of glandular type. We detected a significant amount of insulin in the medium of ovarian cancer cell culture. Remarkably, a complete inhibition of insulin secretion was observed in vitro at maximal doses of both Pasireotide and Everolimus with no effect on cell vitality. Conclusion: To the best of our knowledge, this is the first in vitro analysis showing an insulin secretion by an ovarian tumor, assessing also the effect of SSA and everolimus on tumor cells. Keywords: ovary, insulin, ssa, everolimus.

Q12

Hypoglycemic Syndrome Recurrence after Surgical Removal of a Pancreatic Neuroendocrine Adenoma

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Introduction: A 56-year-old woman was submitted to caudal pancreatectomy for an insulin-secreting adenoma suspected by MRI and fast test positivity at 38th hour. Intraoperative US excluded other pancreatic lesions but tissue analysis described a 8 mm neuroendocrine well-differentiated tumor and the surrounding pancreatic tissue exhibited characteristics of nesidioblastosis. Five months after surgery, she still reported episodes of hypoglycemia requiring diazoxide therapy and she was admitted to our department. Results: Fast test resulted again positive at 32nd hour (glucose 1.8 mmol/L, insulin 5.1 mU/L, C-peptide 0.8 ug/L and proinsulin 75 pmol/L) and a 18F-DOPA PET-TC demonstrated an increased tracer uptake in pancreatic head and uncinate process. We also showed an acute insulin response (425% of the basal value after 2’) to peripheral i.v. calcium infusion (CaAIR test). Conclusion: We describe a rare case of association between ‘insulinoma’ and b-cell hyperplasia, pointing out the importance of performing a correct preoperative diagnosis and an accurate instrumental investigation before surgery. In particular the F18-DOPA PET-TC would have been useful to suggesting the presence of b-cell hyperplasia, despite the presence of a nodular lesion. In our experience, CaAIR seems to be a useful tool for the diagnosis and follow up of endogenous hyperinsulinism, despite this, until today it has not been validated and standardized. Keywords: insulinoma, nesidioblastosis, hypoglycemia.
Q13
Success with Lutetium-177 DOTATATE Therapy in Cushing’s Syndrome Caused by Functional Pancreatic Neuroendocrine Tumor (pNET) with Ectopic Adrenocorticotropic Hormone (ACTH) Secretion Refractory to Concomitant Everolimus, Pasireotide and Metrapone

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Introduction: We report a case of a 59-year-old female presenting with florid ACTH-dependent Cushing’s syndrome complicated by pulmonary cryptococcal infection. Aim(s): Materials and Methods: Following a normal pituitary MRI, a CT demonstrated an inoperable pancreatic mass with regional lymphadenopathy. Para-aortic lymph node biopsy demonstrated low to intermediate grade pNET with positive immunohistochemical staining for ACTH and Ki-67 <5%. Indium-111 octreotide scintigraphy confirmed intense octreotide-avidity with moderate avidity on Fluorine-18 FDG PET (SUV max 3.8). Adrenalectomy was not technically feasible due to splenic vein thrombosis and abdominal varices. Everolimus and pasireotide were commenced along with escalating doses of metyrapone and spironolactone. She improved both clinically and biochemically but OCT demonstrated widespread progressive disease including new bilateral liver metastases and ECS. He was treated with k resulting in partial control of the ECS. Because of a high Ki-67 and the absence of SSTR at GaDOTATOC–PET, he was given three lines of chemotherapy (CHT), which resulted in disease progression. He subsequently underwent right AD to definitively relieve the ECS. A subsequent GaPET-DOTATOC showed the presence of SSTR and the pt started lanreotide treatment with E, resulting in SD documented at CT after 10 months. Results: Four cycles of 8GBq of Lutetium-177 DOTATATE were administered with a rapid clinical, biochemical and radiological response. The metrapone dose was able to be significantly reduced. Serial biochemical and imaging responses as well as additional post-treatment follow-up will be presented. Conclusion: Lutetium can be effective in metastatic pNET refractory to standard treatment. Keywords: pancreatic, neuroendocrine, tumor, acth, everolimus, pasireotide, lutetium.

Q14
Metastatic Pancreatic Neuroendocrine Tumors with Ectopic Cushing Syndrome: Could Everolimus Be a Safe Therapeutic Option?

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Introduction: Everolimus(E) has proved effective in prolonging PFS in advanced P-NETs. As E is a substrate of CYP3A4 co-administration with ketoconazole (k), a strong inhibitor of CYP3A4 used to control hypercortisolism, should be avoided. Aim(s): We present two pts affected by ectopic Cushing syndrome (ECS) due to metastatic P-NETs that have been treated with E after bilateral adrenalectomy (AD). Materials and Methods: A 61-year-old male underwent left pancreatectomy and AD for a P-NET (Ki-67 25%) associated with bilateral liver metastases and ECS. He was treated with k resulting in partial control of the ECS. Because of a high Ki-67 and the absence of SSTR at GaDOTATOC–PET, he was given three lines of chemotherapy (CHT), which resulted in disease progression. He subsequently underwent right AD to definitively relieve the ECS. A subsequent GaPET-DOTATOC showed the presence of SSTR and the pt started lanreotide treatment with E, resulting in SD documented at CT after 10 months. Results: A 49-year-old female showed ECS relapse 10 yrs after the removal of a P-NET (Ki-67 10%) followed by 3 TACE and PRRT for liver metastases. She underwent AD since ECS was not controlled by octreotide-LAR and k. As a liver metastasis biopsy showed a Ki-67 30%, she underwent two lines of CHT, which had no effect. Then she was treated with E for three months. Follow-up is ongoing. Conclusion: E can be used for tumor growth control in P-NETs and even moderately differentiated G3 and ECS after AD. The latter resolving hypercortisolism allows a safer use of E. Keywords: everolimus, pancreatic net, ectopic cushing syndrome.

Q15
Metachronous Functioning Syndromes in Sporadic Pancreatic Neuroendocrine Tumors (PNET)


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Introduction: A metachronous functioning syndrome (MFS) may develop during the evolution of PNET initially functioning or not. Aim(s): To describe a multicenter series of MFS occurring in sporadic PNET patients. Materials and Methods: Patients in
whom symptoms related to hypersecretion of insulin, gastrin, VIP or glucagon secondary occurred during follow-up were included. A central review of pathological material was performed, including Ki-67 and peptide immunostaining. Results: Fourteen patients (nine men, median age 49 years) were included. At initial presentation, two PNET were functioning (1 PTHrP, one insulinoma). Mean Ki-67 (SD) was 7.9±5.1%. Fifteen MFS were observed after a median delay of 47 (33–87) months: organic hypoglycemia (n = 5), Zollinger-Ellison syndrome (n = 1), Verner-Morrison syndrome (n = 5) and glucagonoma syndrome (n = 4). Plasma levels of specific peptides were increased in all cases, while initially normal in 89%. MFS occurred in a context of progression, stability and tumor response in 53, 40 and 7% of cases, respectively. A pathological specimen at time of MHS diagnosis was available in nine patients. Mean Ki-67 was 21.6±21.8%. Immunostaining of the peptide responsible for MFS was positive when assessed, and was retrospectively found in a small proportion of cells on pathological specimens obtained prior to MFS. Conclusion: MFS is frequently associated with increased Ki-67 and marks a turn in tumor evolution, as it seems to occur in a context of progression. Keywords: neuroendocrine tumors, pancreas, functioning syndrome, natural evolution.

Q16

French Cohort of Familial Midgut Carcinoid Tumors

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Introduction: Familial Midgut Carcinoid Tumors (FMCT) are a rare and poorly described entity defined by the occurrence of a midgut carcinoid tumor in at least two first-degree relatives. Aim(s): To describe a multicentre cohort of FMCT. Materials and Methods: Patients with an FMCT were included. After eliminating hypothesis of type 1 MEN, clinical characteristics were reviewed. A central pathological review was performed. Results: Eight families (17 patients) were identified (nine men, median age 58). A past history of other cancers existed in 29% of cases. Pedigrees suggested autosomal dominant transmission. Metastases (liver 94%) were present at diagnosis in 10 patients, or occurred later in four. A carcinoïd syndrome existed in 67%. Octreoscan® was positive when performed (n = 12). At pathological examination, morphological features were similar to that of sporadic carcinoid tumors. Tumor multiplicity (from 2 to 80) existed in 50% of cases. All MFCT were well-differentiated, with a Ki-67 <3% in 72% of cases. Serous invasion, lymphovascular emboli and lymph-node involvement were noted in 64, 77 and 93% of cases, respectively. Some features were frequently identical among the relatives of the same family, such as precise tumor localization in the ileum (95%) and multiplicity (83%). Conclusion: Several clinical and pathological features suggest that FMCT could be a distinct pattern of carcinoid tumors with hereditary transmission. A study is ongoing to identify the genetic abnormalities responsible for FMCT. Keywords: carcinoid tumor, family, heredity.

Q17

Primary Neuroendocrine Tumor of Extrahepatic Bile Duct


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Introduction: Biliary tract primary malignant tumors are rare neoplasms. Eighty-five per cent are cholangiocarcinomas, being in exceptional cases a neuroendocrine tumor. The absence of clinical suspicion involves a difficult preoperative diagnosis. Aim(s): Clinical case presentation, diagnosis and treatment. Materials and Methods: Review scientific literature and clinical case. Results: Female 54-year-old, intervened one year ago for scheduled laparoscopic cholecystectomy with normal histopathological study, was admitted in our center for suspicion of common bile duct stenosis. The presumptive diagnosis was iatrogenic postcholecystectomy. In colangioMRN and ERCP partial filling defect of common hepatic duct 2 cm in length, immediately distal to the bifurcation and a 1 cm nodule in the common bile duct with lymphadenopathies were observed. Tumor markers were normal, bilirubine was elevated. Chromogranin A was 99.4 ng/mL. Bile duct resection, lymphadenectomy of hepatic hilium and hepatic-jejunal anastomosis were performed. Intraoperative study reported a neuroendocrine tumor. The deferred study confirms the diagnosis of NET G2, pN0, free margins. Conclusion: Neuroendocrine tumors of the biliary tract are rare and comprise between 0.2–2% of all gastrointestinal neuroendocrine tumors. Low clinical suspicion generates a delay in diagnosis and treatment. Curative resection is the main prognostic factor and a biloexcision of the tumor should be performed. Keywords: primary bile duct tumor, neuroendocrine tumor, nonfunctioning neuroendocrine tumor.
Q18
Parathyroid Hormone-Related Peptide (PTHrP) Secretion by Metastatic Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET): Clinical Features, Diagnosis, Management, and Long-Term Follow-Up
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Introduction: There are a few large series of patients with parathyroid hormone (PTH)-related protein (PTHrP) secreting neuroendocrine tumors (NETs) causing severe hypercalcemia. Aim(s): To analyze the clinical, biochemical, radiological features, response to therapy and survival of patients with PTHrP-secretating NETs. Materials and Methods: Ten patients with PTHrP-secreting GEP-NETs treated between 1986–2013. MEN1 was excluded. Patients were assessed for progressive disease (PD) and response to therapy of hypercalcemia with three parameters: (1) radiological documentation of PD, (2) progression of clinical symptoms, (3) worsening of biochemical markers. Overall survival (OS) was analyzed using a KM curve. Results: Ten GEP-NET patients – six men and four women, median age: 50.4 years (range: 38.3–61.1) at diagnosis. Nine pancreatic (p)NETs, one unknown primary. Median follow-up: 57.2 months (range 11.6–204.5). Treatment regiments hypercalcemia: somatostatin analogs, bisphosphonates and glucocorticoids. Overall survival is shortened compared to large cohort studies. Conclusion: Hypercalcemia is a well-characterized paraneoplastic syndrome that could not be integrated by the stand neurological diagnostic pathway. Special laboratory analysis revealed a high titer of anti-Ri, a well-characterized antibody that is associated with paraneoplastic neurologic syndroms. A cortisone therapy for five days improved the neurological symptoms, which are currently completely decayed. Keywords: rectum, anti-ri, tace, pns.

Q19
Paraneoplastic Encephalitis in a Patient with Exceptionally Long Survival Despite a Hepatic Metastatic Neuroendocrine Rectum Neoplasm
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Introduction: We report the instructive case of a woman that was diagnosed with a neuroendocrine neoplasm (NEN) of the rectum with multiple liver metastases, who subsequently developed an anti-Ri positive paraneoplastic neurological syndrome (PNS). Aim(s): – Materials and Methods: We retrospectively analyzed the patient treated in our institution since 2002. Tumor tissue was explored via IHC concerning expression of CgA, Synaptophysin and Ki-67. Results: In 2002 we diagnosed a patient with multiple liver lesions, which histologically corresponded to a well-differentiated neuroendocrine neoplasm (G1, Ki-67 <1%). The primary tumor was found in the rectum having a size of 1cm and was removed in total via colonscopy. Due to extensive liver metastases, liver-specific transcatheter chemoembolization (TACE) was initiated. Ever since, she did not receive any cancer-specific therapy. Ten years after the diagnosis of the tumor, the patient emerged with unspecific neurological symptoms that were not integrated by the stand neurological diagnostic pathway. Special laboratory analysis revealed a high titer of anti-Ri, a well-characterized antibody that is associated with paraneoplastic neurologic syndroms. A cortisone therapy for five days improved the neurological symptoms, which are currently completely decayed. Conclusion: The clinical exceptionally long course of a hepatic metastatic hormone-negative rectum neoplasm, as well as the diagnosis of a paraneoplastic syndrome by anti-Ri antibodies, represent a rarity. Keywords: rectum, anti-ri, tace, pns.

Q20
Good Clinical Response to a Somatostatin Analog in a Patient with Metastatic Glucagonoma and Necrotic Migratory Erythema: 5-Year Follow-Up
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Introduction: Glucagonoma is a rare neuroendocrine tumor of the pancreas usually diagnosed in advanced stages or when necrotic migratory erythema occurs. Aim(s): To show the efficacy of the somatostatin analog therapy in a rare disease. Materials and Methods: Case report. Results: A 71-year-old woman with a 2-year history of generalized pruritus in the lower limbs associated with scaly and ulcerated skin lesions. Serum glucagon at the time was >1000 pg/ml, and necrotic migratory erythema was our first consideration. MRI of the abdomen showed a mass in the pancreatic head and neck with liver metastasis. A laparoscopic liver biopsy was performed in 2008, which revealed well-differentiated metastatic neuroendocrine carcinoma. The tumor was glucagon positive and Ki-67 <1%. Tumor was unresectable, and the patient refused cytoreductive surgery. We started 20 mg of octreotide LAR every 28 days via IHC concerning expression of CgA, Synaptophysin and Ki-67. Results: In 2002 we diagnosed a patient with multiple liver lesions, which histologically corresponded to a well-differentiated neuroendocrine neoplasm (G1, Ki-67 <1%). The primary tumor was found in the rectum having a size of 1cm and was removed in total via colonscopy. Due to extensive liver metastases, liver-specific transcatheter chemoembolization (TACE) was initiated. Ever since, she did not receive any cancer-specific therapy. Ten years after the diagnosis of the tumor, the patient emerged with unspecific neurological symptoms that could not be integrated by the stand neurological diagnostic pathway. Special laboratory analysis revealed a high titer of anti-Ri, a well-characterized antibody that is associated with paraneoplastic neurologic syndroms. A cortisone therapy for five days improved the neurological symptoms, which are currently completely decayed. Conclusion: The clinical exceptionally long course of a hepatic metastatic hormone-negative rectum neoplasm, as well as the diagnosis of a paraneoplastic syndrome by anti-Ri antibodies, represent a rarity. Keywords: rectum, anti-ri, tace, pns.
control and resolution of necrolytic migratory erythema associated with glucagonoma. **Keywords:** glucagonoma, necrolytic migratory erythema, octreotide.

### Q21


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**Introduction:** GEP-NETs are the most common types of NET, accounting for about 67.5% of total NET. But so far, there have been no related statistics of Chinese patients with GEP-NET. Here, we performed a retrospective study in South China to provide clinical characteristics of GEP-NET. **Aim(s):** Through statistical analysis of clinical data to guide clinicians toward a better understanding of neuroendocrine tumors. **Materials and Methods:** Total of 245 patients with GEP-NETS at Nanfang Hospital Affiliated to Southern Medical University, between August 2002 and October 2013, were retrospectively analysed. **Results:** Rectum was the most common site of the involvement (52.7%). Two-hundred and fourteen patients (87.3%) presented as non-functional with non-specific symptoms such as abdominal pain (42.4%). Thirty-one patients (12.7%) presented with functional tumors with symptoms such as diarrhea, persistent hypoglycemia. Two patients (0.82%) presented with carcinoid syndrome, such as facial flushing, diarrhea. Seventy-eight patients had CgA test and 83 had Syn, positive rates of CgA and Syn were 60.3% and 96.3%, respectively. About 37.7% patients had G1 tumors, 17.4% G2 and 44.9% G3. Thirty-five (0.82%) presented with carcinoid syndrome, such as facial flushing, diarrhea. Seventy-eight patients had CgA test and 83 had Syn, positive rates of CgA and Syn were 60.3% and 96.3%, respectively. About 37.7% patients had G1 tumors, 17.4% G2 and 44.9% G3. Thirty-five patients (14.3%) presented as metastasis, the rest (85.7%) were non-functional with non-specific symptoms such as abdominal pain. **Conclusion:** Non-functional tumors account for the majority of GEP-NET. Diagnosis depends on pathological classification. We still need to continue to follow-up to assess disease progression and survival in patients. **Keywords:** gep-net, clinical pathological characteristics, clinical manifestations.

### Q22

**Non-Functional Pancreatic Neuroendocrine Tumors (pNETs) with Transformation to Insulinoma: An Esoteric Presentation of a Rare Disease**

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**Introduction:** Most pNETs are usually non-functioning. Rarely, a non-functioning tumor can undergo biological transformation to a functioning tumor with subsequent changes in its clinical features. **Aim(s):** We present here two patients with longstanding pNETs who developed severe hyperinsulinemic hypoglycemia in parallel with tumor progression. **Materials and Methods: Results:** A 45-year-old woman presented with a well-differentiated G2 pNET with secondary hepatic lesions. The patient was treated with somatuline and radio-labeled somatostatin analogues (PRRT) with disease stabilization. She later presented with severe episodes of hypoglycemia and high levels of insulin and C-peptide. A second biopsy revealed proliferation index of 20%. Subsequent treatment with everolimus, streptozocin, DDP and 5-FU resulted in resolution of the hypoglycemia and marked regression of the hepatic lesions. The second case is a 63-year-old man diagnosed with a pNET with secondary hepatic lesions and celiac root lymphadenopathy. Biopsy showed a well-differentiated NET G2. The patient was treated with Somatuline and PRRT for eight years. Recently, the disease progressed and the patient developed recurrent episodes of severe hyperinsulinemic hypoglycemia. The patient was started on everolimus with resolution of the hypoglycemic episodes. **Conclusion:** These cases highlight the ability of pNETs to change their biological behavior in parallel with disease progression and demonstrates the efficacy of everolimus in control of both hypoglycemia and tumor progression. **Keywords:** pnet, everolimus.

### Q23

**Large Cell Neuroendocrine Carcinoma of the Gallbladder: A Case Report and Literature Review**


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**Introduction:** Primary large cell neuroendocrine carcinoma (LCNEC) of the gallbladder is rare. The standard treatment for gallbladder NEC with liver metastases has not been established, but combination chemotherapy with etoposide plus cisplatin (EP) is recommended for NEC patients with liver metastasis, regardless of the primary tumor site. **Aim(s):** We present a case of gallbladder LCNEC and review the literature. **Materials and Methods:** A 75-year-old man presented with abdominal fullness. CT revealed irregular thickening of the gallbladder wall, multiple liver masses, and enlarged lymph nodes. **Results:** Histological examination of a fine needle biopsy specimen of the liver tumor confirmed the diagnosis of LCNEC. The Ki-67 labeling index was more than 80%; the mitotic count was six mitoses/10 HPF. CT after three cycles of EP showed regression of the liver and lymph node metastases. CT after six cycles of EP showed an enlarged lymph node on the posterior surface of the pancreas head. The progression-free survival was 171 days. The patient was administered irinotecan plus cisplatin (IP) as second-line chemotherapy. CT after two cycles of IP showed progression of lymph node metastases. To our knowledge, only 15 cases of LCNEC of the gallbladder have been published to date. The prog-
nosis of most gallbladder LCNECs with metastases remains poor. **Conclusion:** Thus, although a combination of EP for LCNECs of the gallbladder achieved partial response, new treatment regimens need to be developed. **Keywords:** gallbladder, large cell neuroendocrine carcinoma, chemotherapy.

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**Q24**

**Simultaneous Duplicate Malignant Disease-Adenocarcinoma of the Colon and Disseminated Neuroendocrine Tumor**

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**Introduction:** Fifty-nine-year old man, under examination due to weight loss, enterorrhagia, general abdominal discomfort. Endoscopy detected tumorous infiltration 20 cm from the anus, bleeding. Histology: adenocarcinoma. CT abdomen detected liver lesion. The lesion was hypervascularized, and the CT picture was atypical for metastatic adenocarcinoma. CT chest: tumor lesion in the left lower segment, metastatic LN in mediastinum. According to the CT, the picture is atypical for metastases. **Aim(s):** Bronchoscopy: tumorous granulations in the region of B 10 left, histology: neuroendocrine tumor. Scintigraphy of the skeleton: pathological cumulation in the ribs and chest backbone. Tumor markers within normal levels. **Materials and Methods:** Because of the unclear findings in the liver and patient’s symptoms, resection of sigmoid tumor and liver revision was done. In the liver, multiple lesions were found and resected. Histology from liver metastases: neuroendocrine tumor. Scintigraphy of the skeleton: pathological cumulation in the ribs and chest backbone. Tumor markers within normal levels. **Results:** Therapy has been started with somatostatin analogs (octreotide), followed by clinical improvement and decrease of the CrA level. Long-lasting stabilization. **Conclusion:** Careful diagnostic procedures, and histological verification of the metastatic lesions resulted in diagnosis of duplicate tumorous disease and launched correct therapy with very promising results. **Keywords:** duplicate malignant disease.

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**Q25**

**Role of 68Ga-DOTATATE PET/TC (68Ga-PET-CT) for the Management of Patients with Neuroendocrine Tumors (NETs): Impact in Therapeutic Decisions of our Clinical Practice**

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**Introduction:** 68Ga-PET-CT has demonstrated a higher diagnostic accuracy than any other imaging procedures (CT/MRI/SRS). ARGENTUM group described their experience with 68Ga-PET-CT in eight patients with advanced Gastroenteropancreatic Neuroendocrine Tumors (ENETS 2011). Conclusion was that 68Ga-PET-CT enabled changes in the strategy of treatment in all cases. The impact of 68Ga-PET-CT on the therapeutic management in NETs is constantly under evaluation. **Aim(s):** To evaluate how 68Ga-PET-CT results affected therapeutic decisions. **Materials and Methods:** Medical records of NETs patients who underwent 68Ga-PET-CT were reviewed retrospectively between 2010–2013. The analysis included: general and site of metastasis in 18 of 22 (81.8%) patients with metastatic NETs. 68Ga-PET-CT did not modify disease stage, but detected a higher volume of disease in the primary tumor, but it was only found in five of them (55.5%). 68Ga-PET-CT results changed the initial therapeutic decision in 18 out of 30 (60%) patients. Nine patients underwent the study looking for the primary tumor, but it was only found in five of them (55.5%). 68Ga-PET-CT did not modify disease stage, but detected a higher volume of disease and site of metastasis in 18 of 22 (81.8%) patients with metastatic NETs. **Conclusion:** Therefore, 68Ga-PET-TC made an impact in therapeutic decision in more than half of the patients. **Keywords:** neuroendocrine tumors, 68ga-pet-ct, therapeutic management.

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**Q26**

**Periampullary and Pancreatic Neuroendocrine Neoplasms with Duodenal Stromal Gastrointestinal Tumors in Patients with Type 1 Neurofibromatosis: Two Case Reports**

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**Introduction:** We describe two cases of type neuroendocrine tumors (NETs) in patients with neurofibromatosis type 1 (NF1) associated with gastrointestinal stromal tumors (GISTs). **Aim(s):** Materials
A Case Report of a Pancreatic Neuroendocrine Tumor (pNET) with High Levels of 5-HIAA in Urine

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Introduction: A 79-year-old man presented with weakness and weight loss. Clinical examination revealed a palpable liver and CT scan a mass in the head of pancreas and multiple liver lesions. 

Aim(s): A biopsy showed a well-differentiated neuroendocrine carcinoma of the pancreas with Ki-67 5%. Materials and Methods: Laboratory tests showed high bilirubin, serum cromogranin A (CgA) 3940 ng/ml (19.4–98.1 ng/ml) and 24 h urinary 5-HIAA 27 mg (19.4–98.1 ng/ml). Somatostatin receptor scanning showed increased uptake in the head of the pancreas and liver. Results: Therapy with the mTOR inhibitor everolimus 10mg/daily was started. The treatment was well-tolerated but after four months there was clinical deterioration with further weight loss, weakness and diarrhea. A CT scan showed stable disease, central necrosis of the lesions and laboratory tests decreased levels of CgA 2000 ng/ml, 5-HIAA 8 mg and normal bilirubin. Following a short period of discontinuation of everolimus, his clinical status improved and treatment with the combination of the long-acting octreotide and everolimus was started. Two months later, a significant improvement of his clinical status and an excellent biochemical response (90% reduction of CgA) was noticed. 

Conclusion: Although functioning pNET occurs with a frequency of less than 1/100,000 people per year, pNETs secreting serotonin are extremely rare. Somatostatin analogues help control symptoms, as in our case, where by using them we managed to achieve a great improvement in the patient’s quality of life. Keywords: 5-hiaa, pancreas, pnet.

Q28

Neuroendocrine Tumor of the Appendix in Pregnancy

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Introduction: Despite the fact the appendix is one of the rarest anatomical locations of neuroendocrine tumors (NETs) in the digestive system, the appendicular neuroendocrine tumor (A-NET) remains one of the most common tumors of the appendix. Aim(s): We present a well-documented case of A-NET of the appendix in a pregnant female in order to demonstrate a rare tumor in an unusual clinical setting. Materials and Methods: A 24-year-old female with progressive 2nd pregnancy of 35 weeks was admitted to the hospital due to dull pain in the epigastrium. Progressive pain in the lower part of the abdomen was established by the visit of a surgeon, a diarrhea episode was also revealed, C-reactive protein level was progressively increased. The laboratory investigations demonstrated low haemoglobin level 117 g/L and increased white blood cell (WBC) count 12.9 x109/L. The indications for appendectomy were set up, and the operation was performed by the McBurney laparotomy approach. Results: By histology, apical appendicular NET was revealed, measuring 1 cm. The diagnosis was confirmed by positive expression of neuroendocrine markers synaptophysin and chromogranin A. The proliferation activity marker Ki-67 was negligible (0.3%). Conclusion: A-NET in pregnant female has similar clinical manifestations to acute appendicitis. Thus, clinicians should keep in mind the possibility of primary A-NET management suspected acute appendicitis during pregnancy. Keywords: pregnancy, appendix, neuroendocrine tumor.

Q29

Negative Urinary Fractionated Metanephrines and Elevated Urinary Vanillylmandelic Acid in a Patient with a Sympathetic Paravesical Paraganglioma

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Introduction: Paragangliomas have hereditary and sporadic presentations. Aim(s): There are few reports in the literature of paravesical paraganglioma. Materials and Methods: Case report.
**Results:** We report the case of a 50-year-old male with a 2.5 cm paravasical mass documented on abdominal CT. Biopsy was performed by urology and the patient developed hypertensive crisis during the biopsy. He denied family or personal history of hypertension, flushing, palpitations or syncope during miction. Immunohistochemistry documented intense and diffuse positivity for chromogranin and synaptophysin, focal reactivity for S100 protein and 1% Ki-67 index. With a conclusive histology of paraganglioma, we conducted several biochemical tests, obtaining normal results for urinary metanephrines: total metanephrines: 614 ug/24hrs (RV <900 ug/24 hrs), normetanephrine: 423 ug/24 hrs (RV <600 ug/24 hrs), metanephrine: 141 ug/24 hrs (RV <300 ug/24 hrs), chromogranin A and ionic calcium, but elevated urinary vanillylmandelic acid (28.2 mg/24hrs RV: <13.6 mg/24 hrs). A 18 Fluorodeoxyglucose positron emission tomography showed a single paravesical lesion. Presurgical treatment was started with prazosin, followed by metoprolol and amlodipine. Surgical resection was performed successfully and antihypertensive medication was discontinued. The patient remains asymptomatic and normotensive (unmedicated). Results of genetic testing are pending. **Conclusion:** Negative urinary fractionated metanephrines don’t exclude paraganglioma. **Keywords:** paraganglioma, pheochromocytoma, metanephrines, vanillylmandelic acid.

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**Q30**

**A Case of Adrenal Pheochromocytoma Rupture Treated with Transarterial Embolization (TAE)**

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**Introduction:** Spontaneous hemorrhage within a pheochromocytoma resulting in capsular rupture and hemorrhage is a rare condition, but also catastrophic and highly lethal event. An emergent operation for pheochromocytoma rupture is higher mortality than elective operation, and misdiagnosis and failure to control the hemorrhage lead directly to 100% mortality. **Aim(s):** To report a case of pheochromocytoma rupture successfully treated with trans arterial embolization (TAE) before laparotomy. **Materials and Methods:** Describe the patient’s profile and findings of examinations. **Results:** A 49 y/o woman presented to emergency with sudden abdominal pain. Prior to this event, she denied having had any episodes of hypertension. Her systolic BP was 235 mm Hg and pulse was 1800pms. An urgent CT scan revealed a retroperitoneal tumor with a large hemorrhage above the left kidney. An MRI study was also done resulting in no lipid components in the mass. She was diagnosed with an adrenal pheochromocytoma rupture. Ongoing hemorrhage was detected by a repeat CT scan. She was taken for TAE. It revealed an active bleeding at the left renal artery, which was embolized with a gel. Perioperative blood pressure was controlled with phenolamine during TAE. After TAE, no rebleeding occurred. Left adrenalectomy was performed after adequate preoperative preparations. The patient’s postoperative recovery was uneventful. **Conclusion:** TAE of pheochromocytoma is effective in managing hypertensive crisis. **Keywords:** pheochromocytoma, tae, hypertensive crisis.
EORTC Quality of Life Questionnaire Core-30, which is the most widely used cancer-specific QOL instrument. Patients were compared to an Austrian general population sample (N = 411) using non-parametric and variance-analytic methods (α-level 5%). Results: Data from 89 patients (46% male, age 61.5±10.7; foregut 33%, midgut 37%, hindgut 8%, CUP 15%, other 6%) were analysed. Within the patient group midgut tumor patients reported most problems with diarrhoea and CUP patients had the highest emotional burden. Progressive disease was associated with more dyspnoea, less constipation and less financial impact compared to clinically stable patients. No effect was found for time since diagnosis. Compared with the general population, patients showed impairments on all domains except for emotional functioning, pain, and constipation, independent of age and gender. Strongest effects were found for diarrhoea, fatigue, social functioning, and financial impact. Conclusion: QOL assessment provides valuable information about patients’ subjective symptom burden and daily functioning both for research and for the clinical management of NETs. Keywords: quality of life.

R3
Metastatic Type 1 Gastric Carcinoid- A Real Threat or Just a Myth?

Introduction: Neuroendocrine tumors (NETs) are rare, slow-growing neoplasia with variable clinical presentations. Due to their non-specific symptoms and a lack of diagnostic tools, late diagnosis is common. There is little research relating to NETs as experienced by both patients and family carers. Aim(s): This qualitative study examined experiences of patients with NETs and their family carers and how they managed to cope with the disease on a daily basis. Materials and Methods: Eight patients and eight family members from an oncology outpatient clinic and a support group were interviewed. Content analysis methodology was adopted for data analysis. Results: Sufferers were faced with a rare, life-threatening and chronic disease. In most cases, patients experienced various non-specific symptoms before receiving the diagnosis, which was perceived by them as being terminal. During an intensive period of initial treatment, patients and carers often met with doctors who had little clinical experience with NETs. As they became aware of the rare and distinct nature of NETs, they sought reliable information and a doctor experienced in the field. The quality of patients’ daily lives was largely unaffected as symptoms appeared only sporadically. Conclusion: Educating medical staff and the public about NETs should be continued in order to detect and treat NETs early and effectively. Patients should be transferred to treatment centers specializing in NETs. Supported by Novartis Pharma Schweiz AG. Keywords: neuroendocrine tumors, rare diseases, qualitative research.

R4
On the Benign Side of Malignancy: How Neuroendocrine Tumors are Experienced by Patients and Their Family Carers
Kall S., Spichiger E., Stoll H.

Introduction: Neuroendocrine tumors (NETs) are rare, slow-growing neoplasia with variable clinical presentations. Due to their non-specific symptoms and a lack of diagnostic tools, late diagnosis is common. There is little research relating to NETs as experienced by both patients and family carers. Aim(s): This qualitative study examined experiences of patients with NETs and their family carers and how they managed to cope with the disease on a daily basis. Materials and Methods: Eight patients and eight family members from an oncology outpatient clinic and a support group were interviewed. Content analysis methodology was adopted for data analysis. Results: Sufferers were faced with a rare, life-threatening and chronic disease. In most cases, patients experienced various non-specific symptoms before receiving the diagnosis, which was perceived by them as being terminal. During an intensive period of initial treatment, patients and carers often met with doctors who had little clinical experience with NETs. As they became aware of the rare and distinct nature of NETs, they sought reliable information and a doctor experienced in the field. The quality of patients’ daily lives was largely unaffected as symptoms appeared only sporadically. Conclusion: Educating medical staff and the public about NETs should be continued in order to detect and treat NETs early and effectively. Patients should be transferred to treatment centers specializing in NETs. Supported by Novartis Pharma Schweiz AG. Keywords: neuroendocrine tumors, rare diseases, qualitative research.
Differentiated carcinomas (G3 PD-NECs).

compared well-differentiated tumors (G3 WD-NETs) to poorly differentiated carcinomas (G3 PD-NECs). Materials and Methods: All G3 NENs referred between 2008 and 2013 were identified from a histopathology database. Clinical data analysed included Ki-67, imaging, response to treatment and overall survival (OS). Results: Eighty-one patients were identified. Forty had G3 WD-NETs and 41 G3 PD-NECs. Mean Ki-67 was higher in G3 PD-NECs (71%) compared to G3 WD-NETs (33%) (p < 0.01). Octreoscan/68-Ga-octreotate PET was positive in 83% (30/36) and 53% (8/15) in G3 WD-NETs and G3 PD-NECs, whilst FDG PET was positive in 50% (6/12) and 82% (9/11), respectively. Objective response (OR) to chemotherapy, as first line was 36% in both G3-WD NETs (10/28) and G3 PD-NECs (13/36). Mean time to progression was 9.9 months (m) in G3 WD-NETs, and 6.6 m in G3-PD-NECs. Peptide Receptor Radionuclide Treatment (PRRT), as second line, resulted in OR in 37.5% (3/8) and disease stabilization in 25% (2/8) of G3 WD-NETs. Median OS was 17.5 m in G3 WD-NETs, and 11 m in G3-PD-NECs. Conclusion: G3 WD-NETs and G3 PD-NECs demonstrate different characteristics in Ki-67, uptake in functional imaging, treatment response and overall survival, which may have implications in patient management. Keywords: ki-67, g3 nens.

R6
DAXX and ATRX Loss Defines Chromosomal Instability and Poor Outcome in Pancreatic NET


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Introduction: Chromosomal Instability (CIN) has been reported in pancreatic neuroendocrine tumors (pNETs) with poor outcome. However, no specific genetic background has been associated with CIN. Whole exome sequencing revealed mutations in DAXX (Death domain associated protein gene) and ATRX (ATR-X gene) in 40% of pNETs. DAXX and ATRX mutations in pNETs are associated with Alternative Lengthening of Telomeres (ALT) activation. Aim(s): To assess whether DAXX/ATRX loss and consequent ALT activation is related to CIN in pNETs and if DAXX/ATRX loss defines a clinically relevant molecular subtype. Materials and Methods: We performed DAXX and ATRX IHC and Telomeric FISH on two different pNET cell lines comprising a total of 243 well-differentiated primary pNET. Of these, follow-up data was available for 149 patients. We correlated loss of DAXX/ATRX expression and ALT activation with CGH (Comparative Genomic Hybridization) array data, as well as with clinicopathological characteristics, tumor relapse and survival data. Results: We show that DAXX/ATRX protein loss and ALT activation associates with CIN in pNETs. Furthermore, loss of DAXX/ATRX expression correlates with tumor stage and metastasis and predicts both shortened relapse-free survival and decreased tumor-specific survival. Conclusion: These results indicate that DAXX/ATRX negative tumors represent a specific biological subtype of pNETs with distinct molecular characteristics, and pave the way to the identification of new potential targets leading to CIN in pNETs. Keywords: pnet, daxx, atrx, alt, cin.

R7
Adrenal Tumors in Patients with Pancreatic Neuroendocrine Tumors

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Introduction: The coexistence of adrenal tumors (AT) in patients with pancreatic neuroendocrine tumors (PNETs) has not been extensively studied. Aim(s): To investigate prevalence and clinical significance in these patients. Materials and Methods: We retrospectively studied 75 patients with PNETs treated at our department between 2004 and 2012, pNETs were classified as proposed by ENETS. The nature of AT was evaluated pathohistologically when possible, or by CT/MRI characteristics indicative for benign/malignant lesion. AT functionality was assessed in all patients. Statistical analysis was performed by SPSS software. Results: The prevalence of ATs was 25% (26 patients). The involvement was unilateral in 69.2% and bilateral in 30.8% of patients. Seven patients (26.9%) had MEN-1 syndrome. Metastatic nature was pathohistologically verified or was indicative by CT/MRI characteristics in the majority of cases (53.8%, 14 patients), three of which (21.4%) had MEN-1. Twelve patients (16%) had benign AT, none of them functionally active. Adrenal involvement did not correlate with tumor grade (p = 0.238) and stage (p = 0.250). Overall survival of patients with coexistent AT was 118.7 months (95% CI 79.5–157.8), which was not significantly different than OS of patients without AT (x² = 0.510, p = 0.475). Conclusion: ATs in patients with PNETs are more frequent than in the general population. Lesions are mostly metastatic, including some patients with MEN-1. Clinical relevance of AT in patients with PNETs remains to be evaluated. Keywords: pnet, adrenal, tumor.
Evaluation of Patients (pts) with Neuroendocrine Tumors at First Cardiological Consultation with Echocardiographic (Echo) Method. Argentum Group

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Introduction: The incidence of carcinoid tumors is approximately 1 in 75,000 of the population of whom 50% develop carcinoid syndrome. Once carcinoid syndrome has developed, approximately 50% of these patients develop carcinoid heart disease which typically causes abnormalities in the right side of the heart. Aim(s): Assessed by Echo method and clinical factors, those pts with valvular and right ventricular involvement at the time of derivation to the Cardiooncologist Centralized Department for pts with metastatic neuroendocrine tumors. Materials and Methods: Study cohort, prospective, centralized in a single department evaluation of echocardiography in 48 patients with NETs, using the score of Echo, for the assessment of valvular damage as well as the function of the right ventricle. Patients with indication for surgery were determined at the time of referral. Results: Forty-seven pts. were included. Median age 58 y (33–85), median 5HIAA 45 mg/24 hs (5–2350). Chromogranin A 28.5 (3–3260). Score at admission to cardiology 9 (6–25). Indication of cardiac surgery at admission six pts (12.8%), no indication in 41 (87.2%), m 5HIAA was 350 mg/24 hs in a first group of pts. Follow-up 56 m. Conclusion: The 5HIAA was the most sensitive marker in detecting more severe heart conditions and identified patients with indication for interventional surgery. Six of forty-seven (12.8%) pts had indication for surgery in the first query. The most frequent pathology was double valvular affectation. Keywords: carcinoid, heart disease, 5-hiaa, neuroendocrine tumors.
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